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Handbook for Children with Germ Cell Tumors

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from the
Cancer Committee

of the
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Attending physicians, residents, fellows, students and providers using this handbook in the treatment of pediatric patients should recognize that this text is not meant to be a replacement for discourse or consultations with the attending and consulting staff. Management strategies and styles discussed within this text are neither binding nor definitive and should not be treated as a collection of protocols.

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INTRODUCTION

This handbook intends to describe the management of children and adolescents with germ cell tumors. It is based on current literature and accepted practice, and is managed and updated by the APSA Cancer Committee. It is designed to consolidate the most current and up to date material you need to know when treating your patient. Successful management of pediatric germ cell tumors is highly dependent on adherence to sound surgical principles, which can vary depending on the nature and location of these tumors.

This handbook begins with a "One Minute Review" which is designed for use immediately before an operation or clinical consultation. Immediately to follow are more descriptive sections concerning staging, risk groups, and surgical management, including tips for management of tumors based on location and in other special situations.

Suggestions for improvement are welcome and encouraged.

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ONE-MINUTE REVIEW-TESTICULAR TUMORS

PREOP: Obtain serum markers AFP, β-hCG. Abdominal CT and chest imaging obtained to assess retroperitoneal lymph nodes and metastatic disease when malignancy suspected.

SURGERY: Perform radical orchiectomy with control of cord structures at the internal ring and delivery of the testicle via inguinal incision. High ligation of the cord structures at the internal ring. Avoid capsule disruption. Consider testicular-sparing approach for prepubertal boys with likely benign lesions (negative tumor markers).

LYMPH NODES: Retroperitoneal lymph nodes smaller than 1cm, are presumed to be clean. If larger than 2 cm, assumed to be disease. If between 1-2 cm, reassess at 4-6 wks and if still present, assumed disease. OK to biopsy but not mandated.

For standard risk, with resection and completion of therapy, reimage. If residual retroperitoneal disease, (>1cm) biopsy/excise abnormal tissue on boys <11 years, but RPLND for boys ≥ 11 years.

ADDITIONAL CONSIDERATIONS

-AVOID TRANSCROTAL BIOPSY/CAPSULE VIOLATION; WILL UPSTAGE
-If scrotal biopsy done, then stage II; will require radical orchiectomy, but not hemiscrotectomy
-Study both pedi and adult staging, so extent of disease and size of lesion **must be in dictation**
-In prepubescent boys, if lesion involves portion of testicle and believed teratoma, enucleation with frozen section to confirm mature teratoma; orchiectomy not necessary.
-Port not mandated. Chemo for standard risk, no chemo for low risk, so discretion of physician
-Metal clips should not be used.

TISSUE REQUIREMENTS

Obtain blood preoperatively (or intraop) for serum markers
Fresh tumor collected under sterile conditions, delivered to pathologist

Stage	Extent of disease
I	Limited to testis, completely resected by high inguinal orchiectomy, (or scrotal incision) capsule intact, lymph nodes negative (<1cm) normal tumor markers.
II	Violation of tumor capsule preop/intraop; microscopic disease in scrotum or high in spermatic cord (<5cm from proximal end) Lymph nodes negative.
III	Retroperitoneal lymph node involvement- either >2cm on CT, or between 1-2cm which fails to resolve after 4-6 weeks of therapy. Biopsy permitted, not mandated.
IV	Distant metastases, including liver, lung, bone, and brain.

Treatment

Stage	Strata	Treatment
I	Low Risk	Surgery alone. Follow serum markers
II-IV	Standard Risk	Surgery; randomize chemo to cisplatin or carboplatin

ONE MINUTE REVIEW- OVARIAN TUMORS

PREOP: Obtain serum markers- AFP, β-hCG, CA-125, Inhibin A, Inhibin B. Abdominal ultrasound, CT, and/or MRI to evaluate the primary tumor. Chest imaging obtained with elevated tumor markers. Elevated tumor markers and tumors with large solid components signify increased risk for malignancy.

SURGERY: Performed via laparotomy. (laparoscopy can be considered for tumors ≤ 10 cm) Staging includes: 1) Inspection of peritoneal surfaces, omentum, and retroperitoneal nodes and remove/biopsy only suspicious findings; 2) collect peritoneal fluid or washings for cytology; 3) assess contralateral ovary and biopsy suspicious lesions; 4) perform oophorectomy, preserving uninvolved fallopian tubes and uterus. Avoid capsule disruption (will upstage). An ovarian sparing approach should be employed for likely benign lesions and for bilateral disease.

*Laparoscopic resection permitted up to 10 cm size by imaging. Must have all staging components listed above. Removal in retrieval bag, without capsule violation, decompress cystic components only with neck of bag exteriorized. **Capsule violation, >10CM SIZE, or incomplete staging WILL upstage to include chemotherapy.**

Bilateral: Preservation of normal ovarian parenchyma encouraged. For discrete lesion with demarcated capsule, may be excised. If no evidence of normal ovarian tissue, bilateral biopsy, with plan on post chemotherapy exploration.

Additional Notes:
-Upstage will occur with: incomplete staging, rupture of capsule before pathologic exam, morcellated tumor, or laparoscopic removal of tumor larger than 10 cm.
-Port not mandated. Chemo for standard risk, no chemo for low risk, left to physician discretion.
-Metal clips should not be used.

TISSUE REQUIREMENTS

Obtain blood preoperatively (or intraop) for serum markers
Fresh tumor collected under sterile conditions, delivered to pathologist

Stage	Extent of Disease
I	Limited to overy. Peritoneal cytology negative
II	Ruptured, laparoscopic >10cm, morcellated, peritoneal cytology negative
III	Gross residual, biopsy only, lymph node (+); contiguous visceral involvement- omentum, intestine, bladder. Peritoneal cytology (+)
III-X	Incomplete staging: no cytology, no staging description, no biopsy of abnormality. (Does not receive second operation to stage)
IV	Distant metastases, including liver

Treatment

COG Stage	Strata	Treatment
1	Low Risk	Surgery alone, follow serum markers.
2, 3	Standard Risk	Surgery; randomize chemo to cisplatin or carboplatin
4, <11yr	Standard Risk	Surgery; randomize chemo to cisplatin or carboplatin
4, >11yrs	High Risk	no open protocol

ONE MINUTE REVIEW- EXTRAGONADAL TUMORS

PREOP: Serum AFP. CT or MRI to evaluate primary lesion.

SURGICAL PRINCIPLES

Sacrococcygeal tumors: Complete resection. Altman type I and II tumors best approached posteriorly; Altman types III and IV tumors may require abdominal or combined abdominal /perineal approach. Removal of coccyx en bloc with specimen essential. If ruptured, invades surrounding structures, or unresectable, initial biopsy and neoadjuvant chemotherapy should be given. Biopsy abnormal lymph nodes.

Mediastinal tumors- Median sternotomy/lateral thoracotomy, complete resection if possible, including thymus. Regional lymph nodes evaluated, biopsied if abnormal. Bulky mediastinal and neck lesions, open or percutaneous biopsy, resect after chemotherapy.

Retroperitoneal Tumors- Usually large, yolk sac, adherent. Resect small lesions, otherwise biopsy. Obtain peritoneal cytology, biopsy abnormal lymph nodes.

Vaginal tumors- Vaginal preservation. Small lesions resected, otherwise careful vaginal exam with limited biopsy. Complete resection following chemotherapy.

Other extra-gonadal tumors: Complete resection preferable, without damage to adjacent structures. Sample enlarged nodes. Neoadjuvant chemotherapy used to improve resectability.

Additional notes:

Port not mandated. Chemo for standard risk, no chemo for low risk, left to physician discretion. Metal clips should not be used.

TISSUE REQUIREMENTS

Obtain blood preoperatively (or intraop) for serum markers
Fresh tumor collected under sterile conditions, delivered to pathologist

Stage	Extent of Disease
I	Complete resection, coccygectomy for sacrococcygeal site, negative tumor margins.
II	Microscopic residual; lymph nodes (-)
III	Lymph node involvement, gross residual, or biopsy onlyt
IV	Distant metastases, including liver

Treatment

Stage	Strata	Treatment
1	Low Risk	Surgery alone. Observation, follow serum markers
2	Standard Risk	Surgery; randomize chemo to cisplatin or carboplatin
3, 4 <11yrs	Standard Risk	Surgery; randomize chemo to cisplatin or carboplatin
3,4 >11yrs	High Risk	No open protocol

Classification and Differential Diagnosis

The term "germ cell tumor" (GCT) may refer to a broad array of tumors from different sites, with different histologies, and with wide variability in clinical behavior. GCTs can be thought of as malignant vs. benign, and gonadal vs. extragonadal. Within each of these groups, GCTs can be further sub-categorized histologically based upon the World Health Organization classification. GCTs exhibiting the following histologies occur in both gonadal and extra-gonadal locations:

Benign	Malignant / Malignant Potential
Mature teratoma	Immature teratoma
	Yolk sac tumor
	Embryonal carcinoma
	Dysgerminoma / seminoma
	Choriocarcinoma
	Polyembryoma
	Mixed germ cell tumors

Preoperative serum tumor markers may suggest a diagnosis. Additionally, AFP should be serially followed with initiation of treatment to monitor for response and assess for GCT recurrence:

AFP	Most commonly elevated with yolk sac tumors. May be elevated with immature teratomas, embryonal carcinoma, mixed GCTs, and Sertoli-Leydig tumors.
β-hCG	Most commonly elevated with choriocarcinoma. May be elevated with dysgerminoma, embryonal carcinoma, and mixed GCTs.
CA-125	Most commonly elevated with epithelial tumors. May also be slightly elevated with most other types of ovarian tumors.
Inhibins	Most commonly elevated with granulosa cell tumors and Sertoli-Leydig cell tumors.

Teratomas are tumors composed of cells from more than one germ layer. An immature teratoma is distinguished from a mature teratoma by the presence of immature neuroepithelium, and is graded as either I, II, or II based on the percentage of immature elements. Mature teratomas do not exhibit malignant transformation, while immature teratomas possess potential for malignant degeneration and a greater propensity for recurrence following resection. When localized and completely resected, both are initially managed with surgery alone, however a more aggressive surveillance and follow-up regimen is generally undertaken for immature teratomas.

Dysgerminomas and seminomas are of identical histology and occur in the ovary and testicle, respectively (and can also occur in extra-gonadal locations). These tumors are rare in young children, but occur with increasing frequency among adolescents and young adults. Both are exquisitely sensitive to chemo- and radiotherapy. Of note, traditional adult classification systems distinguish testicular germ cell tumors as "seminomatous" vs. "non-seminomatous," as this classification provides a practical basis for determining treatment and prognosis.

Yolk sac tumors are derived from the embryonal yolk sac and represent the most common malignant GCT in young children. They are often highly responsive to chemotherapy and carry a relatively good prognosis compared with other histologies. Embryonal carcinomas are rare and may present in pure form or as part of mixed tumors, particularly in adolescents. Choriocarcinomas are extremely rare in children and are often resistant to treatment, carrying a poorer prognosis. Polyembryomas, likewise, are extremely rare, carry a poor prognosis, and may

occur in association with Kleinfelter syndrome. Finally, it is not uncommon for different histologic subtypes of GCT to be present in a single tumor, and these tumors are conventionally referred to as mixed GCTs. As an example, it is possible for a malignant GCT to contain significant elements of mature teratoma. Thus, a tumor that appears benign on imaging, may still harbor malignancy. Additionally, it is possible for secondary somatic malignancies such as sarcomas or PNETs to arise from GCTs (particularly immature teratomas) either initially or upon recurrence. The presence of a secondary somatic malignancy should influence therapy accordingly.

For purposes of developing a complete differential diagnosis, pediatric surgeons must also recall that GCTs represent only one subset of gonadal neoplasms. Although GCTs are most common in children, additional gonadal neoplasms include sex-cord stromal tumors (granulosa cell tumors, Sertoli-Leydig tumors), epithelial tumors (various subtypes of ovarian carcinoma, the most common type of ovarian cancer in adults), and paratesticular tumors such as rhabdomyosarcoma. Non-neoplastic diagnoses such as functional cysts, hydrosalpinx, ectopic pregnancy, endometriosis, hydrocele, varicocele, and torsion may need to be considered alongside neoplastic lesions in the initial differential diagnosis.

Staging

Pediatric GCTs are staged according to the Children's Oncology Group (COG) system. Distinct adult staging systems also exist. Examples of adult staging systems include the FIGO system for ovarian tumors and the AJCC staging system for adult testicular tumors. Because of important differences between the epidemiology and clinical behavior of pediatric versus adult tumors, the respective staging systems are considerably different from one another. Current pediatric COG-based guidelines, protocols, and ongoing studies are based upon the COG system delineated below:

Children's Oncology Group Staging for Pediatric Germ Cell Tumors			
Stage	**Testis**	**Ovary**	**Extragonadal**
I	Complete resection via orchiectomy. Lymph nodes negative.	Limited to ovary (with negative evaluation of peritoneum), no evidence of extra-ovarian 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

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, peritoneal evaluation positive	Lymph node involvement, gross residual disease, biopsy only
IV	Distant metastases	Distant metastases	Distant metastases
*Gliomatosis peritonei refers to mature peritoneal implants and does not result in stage change. Immature implants are not considered gliomatosis peritonei.			

Risk Groups

Risk groups for pediatric GCTs have been developed based on clinical and staging factors that are known to influence outcomes. The current system was developed with international collaboration between COG and the UK Children's Cancer and Leukemia Group (CCLG) as part of the Malignant Germ Cell International Collaborative (MaGIC). Risk status is clinically relevant for determining adjuvant treatment strategies and surveillance, providing a prognosis for patients and their families, and for the design of future trials.

Risk	Age (yrs)	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
High	≥ 11	Testis	IV	83
	≥ 11	Extragonadal	III	61
	≥ 11	Ovary	IV	60
	≥ 11	Extragonadal	IV	40

*Although classified as "low risk" by this revised system, extragonadal tumors managed outside the context of the current open COG protocol are still treated with chemotherapy and surgical resection

Adapted from Frazier *et al*, *J Clin Oncol*. 2015, 10;33: 195-201

Surgical Resection Guidelines

Surgical resection guidelines vary based on the location and biology of the tumor. In general, a complete surgical resection is the goal. In cases where the tumor is near or invades critical structures, as is often the case with mediastinal germ cell tumors, it is appropriate to biopsy first and then administer neoadjuvant chemotherapy followed by reassessment for surgical resection. Specific guidelines based on location are as follows:

Ovarian Germ Cell Tumors

At presentation, tumor markers should be obtained as previously delineated. Pre-operative imaging (CT or MRI of the abdomen and pelvis) will aid with assessing the primary tumor and disease extent. If a malignant GCT is ultimately diagnosed, chest CT is indicated to assess for metastatic disease. Neoadjuvant chemotherapy should be considered if there is spread to adjacent organs. In this scenario, the tumor should be assessed and biopsied initially, and a durable central line should be placed at the time of biopsy, followed by neoadjuvant chemotherapy then surgical resection. Current operative guidelines for presumed **malignant** GCTs of the ovaries include the following:

1. Complete surgical resection of intact tumor
2. When preoperative tumor markers are negative, ovarian-sparing resection should always be considered and attempted if it can be performed without compromising a complete resection (if pathology demonstrates malignancy a return to the OR for ipsilateral oophorectomy is indicated)
3. Salpingectomy indicated if directly involved by tumor, otherwise sparing is recommended
4. Peritoneal washing: send fluid fresh for cytology, if quantity insufficient can use washings
5. Contralateral ovarian biopsy if abnormal on preoperative imaging or during exploration
6. Omental biopsy if abnormal-appearing or involved with the tumor
7. Complete assessment of the peritoneal cavity for disease spread or peritoneal implants, followed by biopsy or resection of abnormal tissue
8. Any abnormal-appearing lymph nodes noted on imaging, by visual inspection or by palpation (greater than 2cm or suspicious in appearance) should be removed. Sampling of normal-appearing lymph nodes is not indicated.

Role of laparoscopy

- Small tumors can be removed in a bag through the umbilicus so long as the capsule is not violated. The tumor must be left intact and not morcellated.
- Assessment of peritoneum, peritoneal washings, biopsies, followed by Pfannenstiel incision if primary tumor removable through that incision
- Drainage of cystic component in a mature teratoma followed by removal though a small incision is done but not recommended unless there is clear indication that tumor is a mature teratoma (imaging, negative tumor markers), there is insufficient data regarding recurrence with spillage of fluid

Testicular Germ Cell Tumors

At presentation, tumor markers should be obtained as previously delineated. Pre-operative imaging (CT or MRI of the abdomen and pelvis) will aid with assessing disease extent. If a malignant GCT is ultimately diagnosed, chest CT is indicated to assess for metastatic disease. Current operative guidelines for presumed **malignant** GCTs of the testes include the following:

1. Complete resection of the tumor, usually with an orchiectomy. A testicular-sparing approach can be considered for prepubertal boys with likely benign lesions (negative tumor markers).
2. An inguinal approach with extension of the incision over the superior aspect of the scrotum for large tumors is used. In rare cases it may be necessary to divide the inguinal ligament to remove the tumor. **Never use a scrotal incision for resection or biopsy.**
3. The cord structures should be ligated and divided at the level of the internal ring
4. RPLND or sampling is not indicated for pre-pubertal (< 11yo) testicular lesions even with suspicious nodes on imaging. The approach instead involves resection of the primary tumor, assessment of the pathology, administration of chemotherapy, then re-imaging.
5. Post-pubertal boys with residual nodal disease after chemotherapy may rarely require RPLDN. RPLND, when needed, should be performed by a surgeon with significant volume and experience with this procedure as data suggests superior outcomes.
6. When possible, lung metastases should be resected if they persist following chemotherapy

Mediastinal Germ Cell Tumors

Mediastinal GCTs are commonly associated with vital structures of the chest and mediastinum, a feature that often precludes upfront resection. For these cases, biopsy followed by neoadjuvant chemotherapy prior to definitive surgical resection is indicated. Complete resection is the goal whether done upfront or following neoadjuvant chemotherapy. Tumors are almost always large at presentation, limiting the feasibility of a minimally invasive approach to definitive tumor resection unless the lesion significantly shrinks with chemotherapy. Because tumors with malignant GCT components may also contain mature teratoma not responsive to chemotherapy, it is common for these tumors to remain large following chemotherapy, even if tumor markers normalize.

1. Anesthesia Considerations
    - Any patient with CT or MRI revealing >35-50% compression of the trachea, peak expiratory flow rates of < 50% predicted, or who is unable to lie flat due to orthopnea is considered at elevated risk for cardiovascular or airway collapse with general anesthesia
    - In these situations, percutaneous image-guided biopsy under local anesthesia or light sedation is a reasonable option. Due to the heterogeneity of the tumor multiple core biopsies should be taken.
2. Biopsy techniques- Imaged-guided percutaneous biopsies, mediastinoscopy, Chamberlin approach, thoracoscopy, thoracotomy and sternotomy are all acceptable approaches for biopsy. The technique should be chosen based on anesthetic risk and surgeon experience. Sampling error can occur with core and open biopsies due to the tumor heterogeneity.
3. Surgical approach- median sternotomy, clam shell, trapdoor, and posterolateral thoracotomies have all been described.

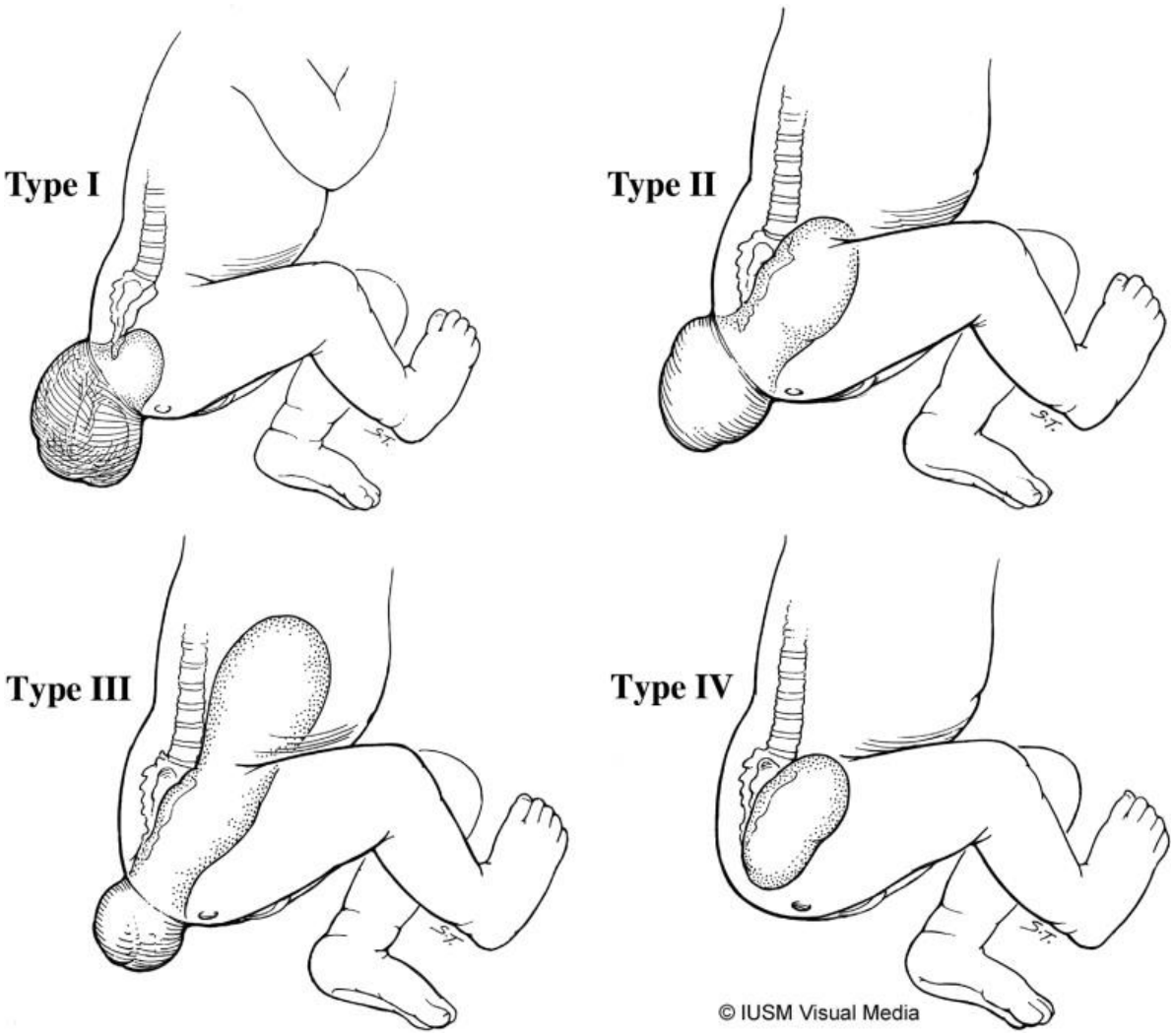
- Tumors most often arise from the thymus and are frequently adherent to pericardium, pleura, lung(s), vascular structures and phrenic nerve(s)
- Incision should be chosen to optimize exposure for a safe and complete excision
- It is not uncommon for the tumor to entrap a phrenic nerve. Some recommend diaphragmatic plication if the phrenic nerve is resected or heavily involved due to the pulmonary toxicity of bleomycin and long term decreased pulmonary function
- Complete surgical resection is the goal

Retroperitoneal Germ Cell Tumors

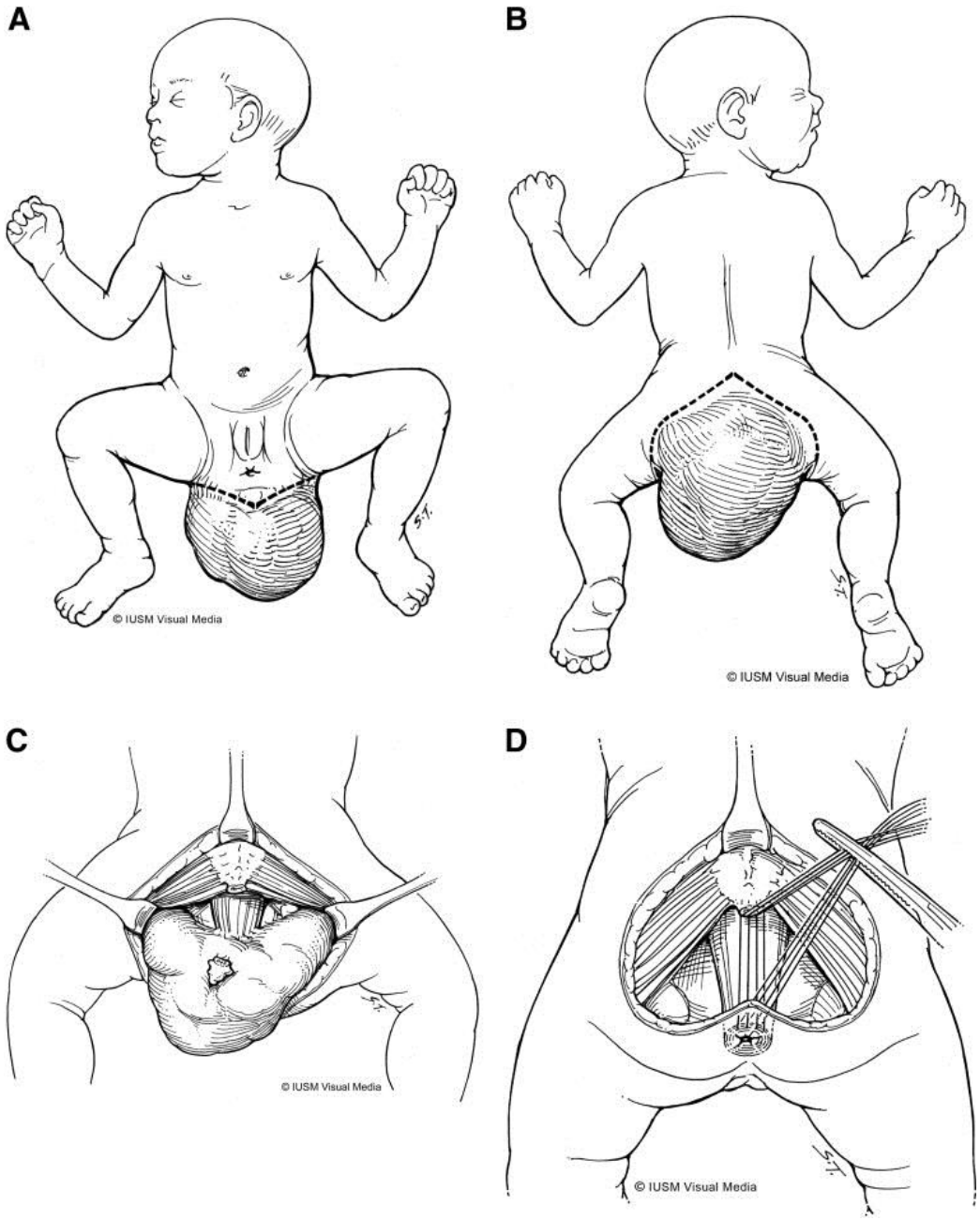
1. Complete surgical resection is the goal especially for mature teratomas, however, there are many case reports in the literature highlighting the significant morbidity and mortality of these resections when vital structures are encased or adherent to the tumor. If the tumor is adherent to vital structures it can be biopsied and if there are immature elements, a trial of chemotherapy can be initiated. If the tumor is responsive it can be resected after chemotherapy with less morbidity. As with mediastinal GCTs, tumors with malignant GCT components often also contain mature teratoma not responsive to chemotherapy and may remain large following chemotherapy, even if tumor markers normalize.
2. Any grossly abnormal lymph nodes should be resected and peritoneal fluid should be sampled or washings performed, with the fluid sent for cytology.
3. Special situations: adjacent organ resection has been described where complete excision was not possible without leaving tumor behind. Descriptions of partial gastrectomies, splenectomies, partial pancreatectomies, and partial IVC resections have been described.

Sacrococcygeal Germ Cell Tumors

1. Fetal intervention (resection, cyst drainage, laser ablation)
    - Indications: hydrops, high output cardiac failure at < 28 wks gestation
    - Should be performed at a fetal center
2. EXIT procedures- between 28-36 weeks gestation
    - Indications: fetal hemorrhage, high output cardiac failure, impending labor due to polyhydramnios
3. Surgical approach based on type (see below)
    - Types 1,2 can usually be approached posteriorly with infant in the prone position
    - Type 3 usually necessitates a combined posterior and abdominal approach
    - Type 4 are primarily approached from the abdomen

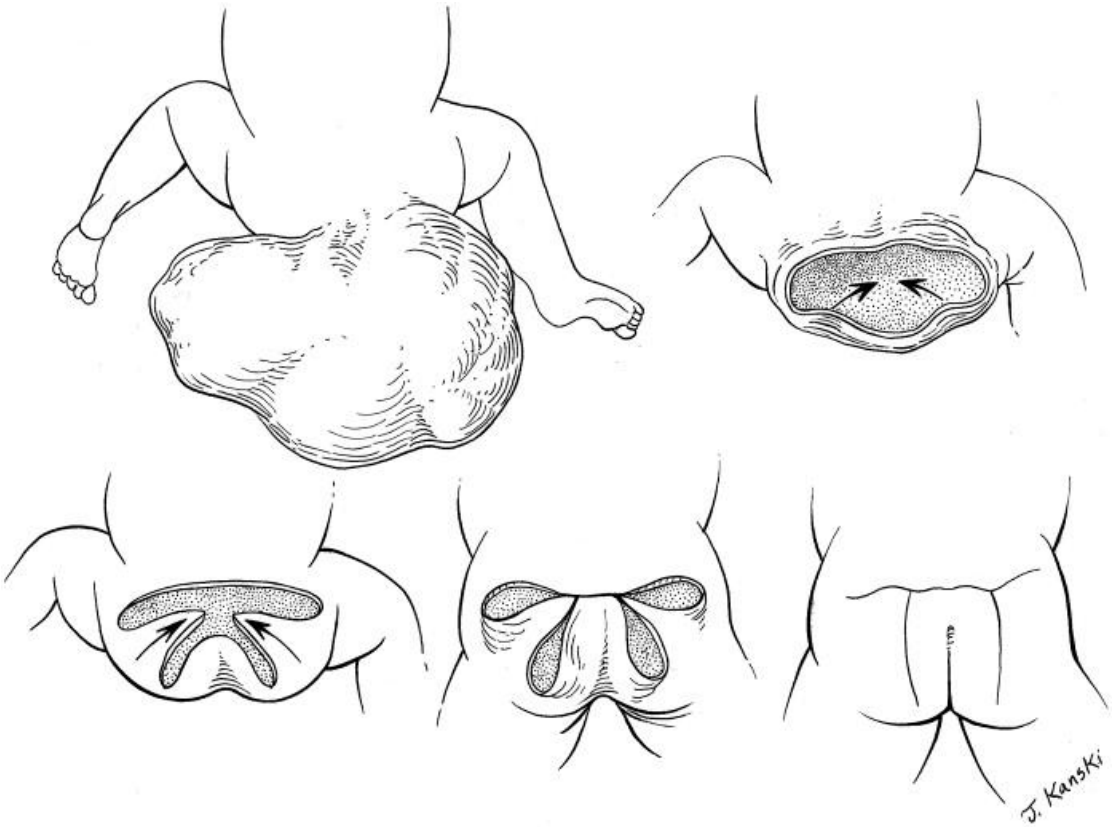


Courtesy of Indiana University School of Medicine Visual Media



Courtesy of Indiana University School of Medicine Visual Media

4. The blood supply to the tumor can be characterized pre-operatively with CT or MRI. In very vascular lesions, ligation of the middle sacral artery should be considered immediately prior to resection (via laparoscopy or open technique) to lessen the risk for major operative hemorrhage.
5. The coccyx must always be resected with the specimen.
6. Pelvic floor reconstruction is important for future continence. The levator ani muscles must be re-approximated to the presacral fascia in order to return the anus to a near normal position without positioning the anus too posteriorly.
7. Gluteal reconstruction
    - Several options, with a technique described by Fishman et al illustrated below.
    - Of note, gluteal muscles are splayed out thinly over the tumor and every attempt to save as much muscle as possible should be made. A nerve stimulator is useful during the construction.



Fishman SJ, *et al*. Contouring buttock reconstruction after sacrococcygeal tumor resection. J Pediatr Surg 2004;39:439-441.

8. Metastatic disease
    - Most common in older infants and children with type 4 lesions
    - Biopsy first, then neoadjuvant chemotherapy followed by resection of primary tumor
    - For type 4 lesions that present outside the neonatal period, consider CT/MRI of chest to rule out metastatic disease
9. Local invasion of vital structures
    - Biopsy with neoadjuvant chemotherapy (PEB) prior to surgical resection, vital structures should not be resected or sacrificed with resection

Cervical Germ Cell Tumors

1. Fetal Surgery
    - Indicated for less than 28 weeks gestation with hydrops
2. EXIT procedure
    - Intubation, tracheostomy, or resection can be performed on placental support in babies with compromised airway
    - Decision for EXIT procedure is based on tumor size, presence of polyhydramnios, and appearance of tumor
3. Airway management
    - Tumor can be densely adherent to the trachea, injury to the trachea may necessitate a tracheostomy at the time of resection. In addition, the tumor may

weaken the tracheal wall leading to tracheomalacia, in this case, prolonged intubation or tracheostomy may be necessary.

4. Complete resection of the tumor is the goal of surgery. Care is taken to preserve vital neck structures and during resection these structures (vagus, phrenic, RL nerves, carotid arteries and internal jugular veins) should be identified and spared if possible. In theory, unilateral carotid artery ligation can be performed with an intact circle of Willis.
5. Thyroidectomy
    - Cervical teratomas may arise from the thyroid gland and in some cases the thyroid, usually one lobe, is resected with the tumor. In cases where total thyroidectomy is required, lifelong thyroid hormone replacement will be necessary.

Growing Teratoma Syndrome

This phenomenon can occur with any germ cell tumor. Benign elements continue to grow often at rapid rate after initiation of chemotherapy. This highlights the importance of using chemotherapy only to treat malignant disease. Surgical resection is the only effective treatment for mature, growing teratomas.

Secondary Somatic Malignancies

As previously discussed, it is possible for secondary somatic malignancies such as sarcomas or PNETs to arise from GCTs (particularly immature teratomas) either initially or upon recurrence. As such, when a tumor persists despite appropriate therapy and negative tumor markers, or when a tumor recurs with negative tumor markers, a biopsy should be pursued to establish a diagnosis. The tumor should then be managed accordingly and will often require surgical resection.