TREATMENT OF CHILDREN WITH GERM CELL TUMORS
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This handbook extracts and organizes surgically relevant information from COG protocols for the management of extracranial Germ Cell (GCT) tumors, designed to streamline delivery of pertinent information you need to treat your patient.

There is one open COG clinical protocol, addressing low and standard risk groups, AGCT1531, *A Phase 3 Study of Active Surveillance for Low Risk and a Randomized Trial of Carboplatin vs. Cisplatin for Standard Risk Pediatric and Adult Patients with Germ Cell Tumors, an Intergroup NCTN Phase 3 Study*. It will enroll children and adults from pediatric oncology, gynecologic oncology, and genito-urinary oncology organizations. It aims to minimize toxicity by reducing or eliminating chemotherapy, while maintaining current survival rates.

Low risk patients are COG Stage 1 ovarian pure immature teratoma and COG Stage 1 germ cell tumors at any extracranial site. For these patients, chemotherapy will be eliminated.

Standard risk patients are broken into two age based strata: Standard risk 1 includes children to age 11 years with COG Stage II-IV ovarian, testicular, and extragonadal GCT; Standard Risk 2 includes patients age 11-25 years with COG Stage II-III ovarian, COG Stage II extragonadal, and COG Stage II-IV testicular good risk disease. The study will randomize these patients to receive either cisplatin (standard of care) or carboplatin, looking at survival as well as the long-term side effects of ototoxicity, nephrotoxicity, neurotoxicity, and quality of life. There is no open protocol for poor risk patients, COG Stage IV Ovarian and Stage III-IV extragonadal patients.

There is a One Minute Review for each type of tumor, which includes surgery guidelines, important comments, tissue handling, staging, and risk stratification with treatment. There follows: abstract with scientific aims/overview, general surgical guidelines for all tumors, staging and surgery guidelines for testicular, ovarian, and extragonal tumors, treatment details, change in size criteria, pathology definitions, adult staging systems, and normal ranges of half-lives of alpha feto-protein.

Updates and future protocols will occur as appropriate. Any suggestions for improvement are welcome.

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ONE MINUTE REVIEW-TESTICULAR GERM CELL TUMORS

SURGICAL PRINCIPLES

Preop: serum levels alpha-fetoprotein, beta hCG, and LDH; abdominal CT to stage lymph nodes. (Preop or immediately postop)

Surgery: Inguinal incision. Control of vas deferens and vessels, delivery of testicle out of scrotum, high ligation of cord structures at the internal ring.

Retroperitoneal Lymph nodes: Smaller than 1 cm, presumed clean. If larger than 2 cm, assumed disease. If between 1-2 cm, reassess at 4-6 wks and if still there assume disease. OK to biopsy but not mandated.

Standard risk- Completion of surgery and chemo: reimage. If residual retroperitoneal disease, (>1cm) biopsy/excise abnormal tissue for boys <11yrs; RPLND for boys≥ 11yrs.

Additional notes:

-AVOID TRANSCROTAL BIOPSY/CAPSULE VIOLATION; will upstage.
-If scrotal biopsy, stage II, but radical orchiectomy, no hemiscrotectomy.
-Both Pedi and Adult staging criteria, so extent of disease and size of lesion 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, none for low risk, discretion of practitioner.
-Metal clips should not be used.

TISSUE REQUIREMENTS

Obtain blood preoperative or intraoperative 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 transcrotal orchiectomy, 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 (< 5 cm from proximal end). Lymph nodes negative.
III	Retroperitoneal lymph node involvement- either > 2 cm on CT, or between 1-2 cm which fails to resolve after 4-6wks of therapy. Biopsy permitted, not mandated.
IV	Distant metastases, including liver, lung, bone, brain.

TREATMENT

Stage	Strata	Treatment
Stage 1	Low Risk	Surgery alone. Follow Serum markers.
Stage 2-4	Standard Risk	Surgery, randomize chemo to cisplatin or carboplatin

ONE MINUTE REVIEW-OVARIAN GERM CELL TUMORS

SURGICAL PRINCIPLES

Preoperative (or Intraoperative): alpha fetoprotein, beta hCG.

Surgical Staging: Laparotomy with peritoneal fluid/washings for cytology, oophorectomy without capsule violation. Uninvolved fallopian tube and uterus left alone. Staging must include comment on peritoneal implants, omentum, lymph nodes, and contralateral ovary. Biopsy any suspicious.

*****Laparoscopic resection permitted **up to 10 cm** size by imaging. **Must have staging components.** Remove in retrieval bag, without capsule violation, decompress cystic component only with neck of bag exteriorized. **CAPSULE VIOLATION, >10 CM size, OR INCOMPLETE STAGING WILL UPSTAGE, INCL 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, plan on post chemo 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, none for low risk, discretion of practitioner.
-Metal clips should not be used.

TISSUE REQUIREMENTS

Obtain blood preoperative or intraoperative for serum markers.
Fresh tumor delivered to pathologist.

Stage	Extent of Disease
I	Limited to ovary. Peritoneal cytology negative.
II	Ruptured, laparoscopic >10cm, morcellated; peritoneal cytology (-)
III	Gross residual, biopsy only, or lymph node(+); contiguous visceral involvement-omentum, intestine, bladder. peritoneal cytology (+).
III-X	Incomplete staging: no cytology, no staging description, no biopsy of abnl (Should 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 ,<11 yrs)	Standard risk	surgery, randomize chemo to cisplatin or carboplatin
4 ,≥ 11 yrs)	High Risk	No open protocol

ONE MINUTE REVIEW-EXTRAGONADAL GERM CELL TUMORS

SURGICAL PRINCIPLES

Sacrococcygeal tumors- Complete resection. If invades adjacent structures (rectum, sacrum, extensive abdominal involvement) or metastatic disease, initial biopsy only. Resect after chemotherapy, remove coccyx en bloc. 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 examination with limited biopsy. Complete excision following chemotherapy.

Other sites- Excised if possible without damage to adjacent structures. Sample enlarged nodes.

Additional Notes:

-Port not mandated. Chemo for standard risk, none for low risk, discretion of practitioner.
-Metal clips should not be used.

TISSUE REQUIREMENTS

Obtain blood preoperative or intraoperative for serum markers.
Fresh tumor delivered to pathologist.

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

TREATMENT

Stage	Strata	Treatment
1	Low	Surgery alone, observation
2	Standard	Surgery, randomize chemo with cisplatin, carboplatin.
3+4	Standard, <11yrs	Surgery, randomize chemo with cisplatin, carboplatin
3+4	High risk, ≥11 yrs,	No open protocol

INTRODUCTION AND ABSTRACT OF THE STUDY AGCT1531 (page 9)

INTRODUCTION

Although malignant germ cell tumors (MGCTs) account for only 3% of all tumors in children < 15 years of age, MGCT account for 15% of tumors between the ages of 15 - 29 and are the most common solid malignancy in AYA patients.[1] Currently, 5 year overall survival (OS) for children with non-localized MGCT is 85%.[2] Despite these excellent outcomes, challenges remain. Among the 85% who are cured, the current cisplatin-based regimens are known to have significant short- and long-term toxicities, including ototoxicity and nephrotoxicity, which, in recent studies, have been shown to continue to worsen after treatment has been completed.[3,4] Equally concerning are the reports among men treated for testicular cancer of a two-fold risk in second malignant neoplasms (SMNs) and cardiovascular disease. The risk of SMN does not abate with time but steadily accrues at the rate of ~1% per year. A 20 year old treated for testicular cancer has a 47% chance of a SMN by age 70.[3]

AGCT1531 addresses the need for rational reductions in therapy to ameliorate these late effects. The protocol builds upon the goals of past COG germ cell tumor trials to eliminate chemotherapy in low risk patients who are likely cured with surgery alone. For standard risk patients who must undergo chemotherapy, AGCT1531 will test whether carboplatin can be substituted for cisplatin, thereby reducing toxicity.

A new goal for this COG protocol is to expand care across the age spectrum of germ cell tumors. This trial has been developed from its inception with input from the rare tumor committee of the Gynecologic Oncology Group (GOG), now part of NRG. The trial will enroll adolescents and young adults using the CTSU mechanism for NCTN sites.

ABSTRACT

The aim of this study for low and standard risk germ cell tumor (GCT) patients is to minimize toxicity by reducing therapy while maintaining current survival rates. The trial will eliminate chemotherapy for low risk patients who are likely cured with surgery and will observe the salvage rates among those who recur. Low risk patients are defined as Stage I patients, ages 0 – 50 years old. Since the trial is enrolling patients from pediatric oncology, gynecologic oncology and genito-urinary oncology (testicular cancer) the relevant staging criteria can be found in Appendices II (COG), III (FIGO), IV (AJCC) and V (IGCCC [International Germ Cell Consensus Classification]). The low risk arm will have two strata. One strata will include patients with an *ovarian* pure immature teratoma: COG Stage I (FIGO Stage IA and IB), Grade 2 or 3 with a maximum alpha fetoprotein (α-FP) of 1,000 ng/mL. The other low risk strata will be comprised of patients with COG Stage I (FIGO Stage IA and B; AJCC Stage IA and B) germ cell tumors at any extracranial site (testes, ovary, extragonadal) that have at least one malignant histology, defined as embryonal carcinoma, choriocarcinoma or yolk sac tumor. Patients

with pure seminoma or dysgerminoma are excluded from this trial. Low risk patients who recur may receive treatment, if eligible, on the appropriate standard risk arm.

Among standard risk patients the trial will evaluate whether cisplatin, which is the standard-of-care in COG, can be replaced with a less toxic alternative platin analogue, carboplatin. The standard risk arm will be divided into 2 age-based strata: (1) Standard Risk 1 (SR1) arm, which includes patients up to 11 years of age with COG Stage II - IV ovarian, testicular or extragonadal GCT and (2) Standard Risk 2 (SR2) arm, which includes patients between 11 and 25 years of age with COG Stage II – III (FIGO Stage IC, II and III) ovarian, COG Stage II extragonadal and testicular, COG Stage II – IV with IGCCC good risk disease.

SR1 patients will be randomized to receive either 4 cycles of PEb (cisplatin, etoposide and bleomycin) or 4 cycles of CEb (carboplatin, etoposide and bleomycin). SR2 patients will be randomized to receive either 3 cycles of BEP (cisplatin, etoposide and bleomycin) or 3 cycles of BEC (carboplatin, etoposide and bleomycin). Bleomycin will be administered *once per cycle* for a total of 4 doses in SR1 patients versus *weekly* for a total of 9 doses in SR2 patients.

Several corollary studies, including evaluation of toxicities (patient-reported outcomes), pharmacogenetic analysis of adverse events, evaluation of a new miRNA diagnostic and prognostic test and molecular pathway analysis of pediatric, adolescent, and young adult GCT are important components of this clinical trial.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS) (pages 16-17)

1.1 Primary Aims

1.1.1 To evaluate whether a strategy of complete surgical resection followed by surveillance can maintain an overall survival rate of at least 95.7% at two years for pediatric, adolescent and adult patients (ages 0- 50 years) with Stage I (low risk) malignant germ cell tumors, and at least 98% for patients with ovarian pure immature teratoma.

1.1.2 To compare the event-free survival of a carboplatin vs. cisplatin-based regimen in the treatment of pediatric, adolescent and young adult patients with standard risk germ cell tumors.

1.1.2.1 To compare the EFS of a carboplatin-based regimen (CEb) vs. a cisplatin-based regimen (PEb) in children (less than 11 years in age) with standard risk GCT.

1.1.2.2 To compare the EFS of a carboplatin-based regimen (BEC) vs. a cisplatin-based regimen (BEP) in adolescents and young adults (ages 11 - 25 years) with standard risk GCT.

1.2 Secondary Aims

1.2.1 To compare the incidence of ototoxicity in children, adolescents and young adults with standard risk germ cell tumors treated with carboplatin-based chemotherapy as compared to cisplatin-based chemotherapy.

1.2.2 To refine and validate a novel patient-reported measure of hearing outcomes for children, adolescents and young adults with standard risk germ cell tumors.

1.2.3 To assess the utility of using an established panel of four circulating microRNAs as a universal marker of diagnosis, recurrence and response to therapy.

1.2.4 To identify novel genetic variants associated with an increased risk of platinum-associated ototoxicity as determined by standard audiology at the end of therapy using both a candidate gene and genome wide approach.

1.3 Exploratory Aims

1.3.1 To prospectively determine the correlation of tumor marker decline (α-FP and β-HCG) with clinical outcome in low and standard risk germ cell tumor patients.

1.3.2 To prospectively determine the clinical significance of activation of the BMP, Ras/MAPK and PI3K/mTOR signaling pathways in GCTs.

1.3.3 To investigate the prognostic significance of an established panel of four circulating microRNAs at diagnosis, during follow-up and at relapse in malignant GCTs.

1.3.4 To identify integrated messenger RNA/microRNA profiles in primary malignant GCTs that correlate with poor clinical outcome.

1.3.5 To evaluate the significance of tumor DNA methylation class.

1.3.6 To characterize the incidence of nephrotoxicity in children, adolescents and young adults with standard risk germ cell tumors treated with carboplatin-based chemotherapy and treated with cisplatin-based chemotherapy.

1.3.7 To compare self-reported peripheral neuropathy and other patient-reported outcomes between children, adolescents and young adults with standard risk germ cell tumors treated with carboplatin-based chemotherapy as compared to cisplatin based chemotherapy.

1.3.8 To determine the utility of novel biomarkers of kidney tubular injury to provide earlier diagnosis of nephrotoxicity and to compare the nephrotoxicity of cisplatin versus carboplatin.

1.3.9 Identify novel genetic variants of platinum neurotoxicity, nephrotoxicity and hematologic toxicity using both a candidate gene and whole gene approach.

1.3.10 Assess the relationship between hearing loss as measured by audiometry with the effects of tinnitus as assessed on the AYA-HEARS instrument.

OVERVIEW OF STUDY: (p 38)

Diagnosis	Site	Stage	Grade	Histology	Tumor Markers	Age (years)
Low Risk Stage I Immature Teratoma (IT)	Ovarian	COG Stage I FIGO Stage IA and IB	2 or 3	Pure immature teratoma, Mixed immature and mature teratoma (no pathological evidence of MGCT)	α-FP ≤ 1,000 ng/mL β-HCG institutional normal	< 50
Low Risk Stage I MCGT	Ovarian, Testicular, or Extragonadal	COG Stage I FIGO Stage IA and IB AJCC Testicular Stage IA and IB		Must contain at least one of the following: • yolk sac tumor, • embryonal carcinoma, or • choriocarcinoma (pure or mixed)		< 50
Standard Risk 1 (SR1)	Ovarian, Testicular, or Extragonadal	COG Stage II – IV FIGO Stage IC, FIGO Stages II – IV		Must contain at least one of the following: • yolk sac tumor, • embryonal carcinoma, or • choriocarcinoma (pure or mixed)		< 11
Standard Risk 2 (SR2)	Ovarian	COG Stage II and III FIGO Stage IC, II and III		Must contain at least one of the following: • yolk sac tumor, • embryonal carcinoma, or • choriocarcinoma (pure or mixed)		≥ 11 and < 25
	Testicular	COG Stage II - IV AJCC Stage II, III IGCCC Good Risk (See Appendix V)		Must contain at least one of the following: • yolk sac tumor, • embryonal carcinoma, or • choriocarcinoma (pure or mixed)	For IGCCC Good Risk: α-FP < 1,000 ng/mL β-HCG < 5,000 IU/mL and LDH < 1.5x normal	
	Extragonadal	COG Stage II		Must contain at least one of the following: • yolk sac tumor, • embryonal carcinoma, or • choriocarcinoma (pure or mixed)		

13.0 SURGICAL GUIDELINES FOR ALL TUMORS (PP139-140)

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

FOR ALL PROCEDURES OPERATIVE NOTE, PATHOLOGY REPORT AND PATHOLOGY CHECKLIST, IF APPROPRIATE, SHOULD BE SUBMITTED.

13.1 Surgical Guidelines Overview

Surgical guidelines for malignant germ cell tumors are complex due to the variety of primary sites, and multiple surgical procedures may be required. Surgery at diagnosis may consist of biopsy, partial resection or complete resection depending on anatomic factors. Recommendations for secondary procedures ("second-look") at completion of chemotherapy will depend on initial procedure, response to therapy, age and primary site. A second surgery for the express purpose of completing staging is not recommended on this protocol. Only patients who have undergone complete staging at the time of the initial surgery will be eligible for the Stage I/low risk strata. Please refer to guidelines for each primary site for guidance regarding initial and potential need for second procedures at completion of chemotherapy. All Stage I patients will undergo central rapid review within 72 hours of enrollment to confirm eligibility. See Section 3.1.6 for details.

13.2 Surgical Staging: Using Four Staging Systems (COG, FIGO, AJCC, and IGCCC)

Since this trial will be enrolling pediatric and adult patients, patients may be staged according to the relevant staging system in common practice, i.e., COG (pediatric), FIGO (gynecologic), AJCC (testicular) and IGCC (testicular). See Appendices II - V for these staging systems. However, in addition to recording "stage", surgeons should record the actual extent and location of disease and the size of lesions on the relevant surgical checklist. The reason this is important is because, for instance, a COG Stage II tumor is different than a FIGO Stage II tumor. The data on the surgical checklist will allow the data to be comparable across staging systems at the end of the trial.

TESTICULAR TUMORS
COG STAGING (P 165)

Testicular Germ Cell Tumors	
Stage	Extent of Disease
I	• Tumor limited to testis (testes) with negative microscopic margins, completely resected by high inguinal orchiectomy; • Tumor capsule cannot have been violated by needle biopsy, incisional biopsy or tumor rupture. Patients who have undergone scrotal orchiectomy without violation of the tumor capsule and with removal of the spermatic cord to the level of the internal ring are Stage I. Patients who have undergone excisional biopsy for frozen section analysis with completion orchiectomy and cord excision at the same operation can be designated Stage I. • no clinical, radiographic, or histologic evidence of disease beyond the testes. • Lymph nodes all < 1 cm maximum short axis diameter on multi-planar imaging. Note: Nodes 1 - 2 cm, require short interval follow-up in 4 - 6 weeks. If nodes are unchanged at 4-6 weeks (1 - 2 cm), consider biopsy or transfer to chemotherapy arm. If growing, transfer to chemotherapy arm.
II	• Completed orchiectomy but had violation of tumor capsule in situ (includes preoperative needle biopsy as well as incisional biopsy or intra-operative tumor capsule rupture) • microscopic disease in scrotum or high in spermatic cord (< 5 cm from proximal end). Failure of tumor markers to normalize or decrease with an appropriate half-life. • Lymph nodes negative.
III	• Retroperitoneal lymph node involvement, but no visceral or extra-abdominal involvement. • Lymph nodes ≥ 2 cm or lymph nodes > 1 - < 2 cm on short axis by multi-planar imaging CT that fail to resolve on reimaging at 4 - 6 weeks.
IV	Distant metastases including liver, lung, bone, brain

Surgical Guidelines for Testis Tumors (PP155-157)

13.4.1Surgical Staging

Surgery Guidelines – see Appendices II-V for staging systems. Both the pediatric COG staging and the adult AJCC staging are included. Surgeons should record extent of disease and size of lesions on the Surgical checklist for primary testicular tumor procedure. Retroperitoneal procedures should be recorded on the retroperitoneal checklist. A primary RPLND makes the patient ineligible for this study.

Note: Metal clips should not be used. The artifact produced by these clips makes interpretation of CT scans for residual disease unreliable.

13.4.2 Surgical Approach to Testis Tumors

Prior to surgical exploration for a possible testicular tumor, appropriate preoperative studies should include serum markers, including α-fetoprotein, β-HCG and LDH. As most testicular metastases are to the retroperitoneum, it is advisable to obtain an abdominal CT scan preoperatively. If the CT is obtained after surgical exploration of the inguinal region, reactive lymphadenopathy may be noted on CT scans and may be difficult to differentiate from metastatic disease. The surgical approach for a testicular tumor should be through an inguinal incision. Control of the testicular vessels is gained at the level of the internal inguinal ring. The testis is then mobilized from the scrotum. Occasionally, a large testicular mass cannot be manipulated from the scrotum to the inguinal region, and in this situation the inguinal incision should be enlarged to the superior aspect of the scrotum in order to avoid tumor rupture during mobilization. A radical orchiectomy is performed with high ligation of all cord structures at the level of the internal inguinal ring. If a benign tumor is suspected, complete excision of the mass without violation of the tumor capsule and frozen section analysis is a reasonable approach (following control of the vessels at the internal ring and draping off of the testis from the surgical field). If the frozen section is consistent with a benign tumor, the testis may be closed and replaced in the scrotum. If the frozen section is consistent with a malignant tumor or is indeterminate, then the orchiectomy is completed. In cases in which a scrotal orchiectomy has been performed without violation of the tumor capsule the patient may still be designated COG Stage I, assuming negative margins; however, the proximal cord structures should be resected to the level of the internal ring. If these should be positive for tumor, the patient would upstage to COG Stage II. If a trans-scrotal biopsy was performed at an initial separate procedure, the scrotum is considered to be contaminated and the patient should be designated COG Stage II however hemiscrotectomy is not required. In addition, a completion orchiectomy with removal of all cord structures to the level of the internal ring should be performed.

Retroperitoneal lymph node size should be determined by maximal short axis diameter on multi-planar CT scan imaging. Lymph nodes < 1 cm are considered negative. Lymph nodes 1 to < 2 cm are considered indeterminate, and lymph nodes ≥ 2 cm are considered to represent metastatic disease. Indeterminate lymph nodes (those 1 to < 2 cm in size) require follow-up imaging in 4 to 6 weeks. If they have decreased to < 1 cm in size, then the patient may remain Stage I. If they are unchanged or enlarging then they should be biopsied or patient should designated a COG Stage III and enrollment on the standard risk arm should be considered. When performed, biopsy should be by excision of suspicious nodes only with no more extensive retroperitoneal dissection. Those with negative node biopsies will remain Stage I. Patients with positive retroperitoneal lymph node biopsies (and no distant or visceral metastases) will be designated as COG Stage III.

13.4.3 Post Chemotherapy Assessment of Residual Disease

See the Post-Chemotherapy Evaluations Flowchart for decision making after chemotherapy. Evaluation of the tumor marker response and radiologic evaluation of any known disease at diagnosis must be undertaken and the results considered jointly. If the tumor markers have normalized, but there is a residual mass > 1 cm, even an enlarging mass, then surgery is indicated because it is possible that the residual mass is either a teratoma or in the case of an enlarging mass, growing teratoma syndrome (see Section 13.7). It is also possible, even in the setting of normalized markers to find viable GCT in the resected mass. If the tumor markers are still elevated (but not rising), and there is a residual mass, again surgery is also indicated if a complete resection is deemed possible. If the tumor markers normalize post-operatively and the resected mass has negative margins, this will constitute a surgical CR (see Section 10.2.1 for definition of response). Consultations with study members/ surgeons are advised.

13.4.4 Post Chemotherapy Surgery in Boys vs. Adolescents with Residual Mass

Patients less than 11 years of age with negative markers who have a residual mass at end of chemotherapy are rarely encountered. Only 2 of 57 boys under 11 years in the prior intergroup study had negative markers and residual mass (unpublished data, J Ross). Both had pure yolk sac histology at diagnosis and biopsy/excision of the residual mass showed only necrosis and fibrosis. In this age group, boys with negative markers and a residual mass greater than 2 cm at 6 - 8 weeks after completion of therapy should undergo excision if feasible (or biopsy if sacrifice of structures would be at risk), but formal retroperitoneal lymph node dissection is not indicated.

For patients < 11 years of age with a new or growing residual mass and normal tumor markers, the mass should be excised (or biopsied if excision is not feasible) with no more extensive retroperitoneal surgery. Patients under age 11 should not have a post-chemotherapy RPLND; in the experience of COG, the residual Disease found after chemotherapy in these young patients is limited to the enlarged node and occult disease throughout the lymph node chain has not been observed.

Patients ≥ 11 years of age with a residual retroperitoneal mass (and either normalized or falling markers) should undergo a retroperitoneal lymph node dissection (RPLND) by a surgeon with a large experience in this operation. A bilateral nerve-sparing RPLND or unilateral modified template RPLND should be performed (see Section 13.7).

OVARIAN TUMORS
COG STAGING, APPENDIX II, P 164

Ovarian Malignant Germ Cell Tumors	
Stage	Extent of Disease
I	• Ovarian tumor removed intact without violation of the tumor capsule. • No evidence of partial or complete capsular penetration. • Peritoneal cytology negative for malignant cells, • Peritoneal surfaces and omentum documented to be free of disease in operative note or biopsied with negative histology if abnormal in appearance. • Lymph nodes all < 1.0 cm by short axis on multiplanar imaging or biopsy proven negative (Note: Nodes 1 - 2 cm, require short interval follow-up in 4 - 6 weeks. If nodes are unchanged at 4-6 weeks (1 - 2 cm), consider biopsy or transfer to chemotherapy arm. If growing, transfer to chemotherapy arm.)
II	• Ovarian tumor completely removed but with preoperative biopsy, violation of tumor capsule in situ, or presence of partial or complete capsule penetration at histology. • Tumor greater than 10 cm removed laparoscopically. • Tumor morcellated for removal so that capsule cannot be assessed for penetration. • Peritoneal cytology must be negative for malignant cells. • Lymph nodes, peritoneal surfaces and omentum documented to be free of disease in operative note or biopsied with negative histology if abnormal in appearance.
III	• Lymph nodes $\geq$ 2 cm or lymph nodes > 1 -< 2 cm on short axis by multi-planar imaging CT that fail to resolve on reimaging at 4 - 6 weeks. • Ovarian tumor biopsied or removal with gross residual. • Positive peritoneal fluid cytology for malignant cells, including immature teratoma. • Lymph nodes positive for malignant cells, including immature teratoma. • Peritoneal implants positive for malignant cells, including immature teratoma.
III-X	Patients otherwise Stage I or II by COG criteria but with the following: • Failure to collect peritoneal cytology. • Failure to biopsy lymph nodes > 1.0 cm by short axis on multiplanar imaging. • Failure to sample abnormal peritoneal surfaces or omentum. • Delayed completion of surgical staging at a second procedure for those patients who had only oophorectomy at first procedure.
IV	Metastatic disease to the parenchyma of the liver (surface implants are Stage III) or metastases outside the peritoneal cavity to any other viscera (bone, lung, brain) and pleural fluid with positive cytology
Bilateral ovarian tumors may be any stage as long as other stage criteria are met. Tumor staged according to ovary with most advanced features.	

13.1 Surgical Guidelines for Ovarian Germ Cell Tumors (PP140-143)

It is not uncommon for a surgeon to fail to consider the possibility of malignancy when operating for an ovarian mass. The finding of a cystic component on imaging is falsely reassuring as nearly all of the patients enrolled on AGCT0132 had a cystic component on preoperative imaging. It should be stressed that ovarian masses in children have at least a 10 to 20% incidence of malignancy, and risk of malignancy should be kept in mind when operating for any ovarian mass in the pediatric and adolescent age group. In addition, the surgical procedures are done by many types of surgeons including pediatric surgeons, general surgeons, gyn- oncologic surgeons and general gynecologists. For all patients with ovarian tumors, the goals of initial exploration are to completely evaluate the extent of disease, maximize safe and complete tumor resection, and spare uninvolved reproductive organs.

Although a significant number of these patients present as an acute abdomen, α-fetoprotein and β-HCG should be determined preoperatively if possible. If not done preoperatively, these markers should be drawn in the operating room. The completed POG/CCSG intergroup trial (POG 9048/9049) demonstrated a yield of close to 25% positivity from peritoneal cytology and a low yield from biopsy of normal appearing lymph nodes, omentum and contralateral ovary. These findings formed the basis for the current pediatric guidelines that were used in the next COG GCT study, AGCT0132[116]. The required staging procedures are detailed in Section 13.3.1. The standard of care for ovarian malignancy remains a laparotomy with collection of peritoneal fluid soon after entry into the abdomen. As we expect that many patients will present to the oncologist having undergone a laparoscopic approach and/or with incomplete staging, the staging guideline information has been expanded to allow consistent assignment of patients to appropriate group with addition of a new group that signifies that staging was incomplete (e.g. Stage III-X). A second surgery for the express purpose of completing staging is not recommended on this protocol. Only patients who have undergone complete staging at the time of the initial surgery will be eligible for the Stage I/low risk strata.

It is anticipated that the majority of adult patients with ovarian MGCT will have undergone a more extensive operative procedure following the guidelines for epithelial ovarian cancer in adult women. Those patients who would be classified as FIGO 1A would be eligible for the low risk arm in this study. FIGO 1B patients may be considered low risk as long as all other Stage I criteria are met. It is important to reiterate that patients (regardless of age) must meet all minimum requirements as described below in the surgical guidelines to be eligible for low risk. Although the pediatric based guidelines do not require as much tissue sampling, peritoneal fluid for cytology must be collected and inspection and documentation of lymph nodes, peritoneal surfaces, omentum and opposite ovary must be confirmed. The tumor must be removed in a manner as

described in detail below with precautions to eliminate risk of intraoperative spill and delivery of an intact specimen to the pathologist. Failure to complete the required minimum evaluation at any age will make the patient intermediate risk.

13.1.1 COG Malignant Ovarian Germ Cell Tumor Surgical Guidelines at Diagnosis

The surgical approach for ovarian tumors with known malignancy preoperatively (elevated tumor markers or distant metastases) has historically been by open technique. Ovarian GCT are usually large tumors and are always friable. Even benign germ cell tumors are known to be at increased risk of recurrence in the setting of intraoperative spill.[117]

In the POG/CCSG intergroup study, the surgeon's intraoperative assessment of capsular integrity was in error 20% of the time. In AGCT0132, 3 patients that were deemed Stage I had partial capsular penetration of the tumors, and 2 of those patients had a recurrence on observation. For these reasons, it is important to avoid capsular disruption intraoperatively and the tumor must be provided to the pathologist intact to allow thorough assessment of the tumor capsule. The current study will expand the guidelines to allow tumors less than 10 cm in diameter by imaging to be approached laparoscopically if desired. This will require the tumor to be placed into a retrieval bag *without capsule violation*; and if a cystic component is decompressed it must be done with the neck of the bag exteriorized through the incision to avoid any possibility of spill (the glue technique done with the bag secured to the intraperitoneal tumor is not acceptable for Stage I). All other staging criteria must still be completed to be considered Stage I. Tumors larger than 10 cm removed by laparoscopic approach will not be eligible for the low risk arm in this study.

The recent AGCT0132 study revealed nearly double the rate of success with surgery and active surveillance for patients in whom guidelines were completely followed, compared to those where staging was incomplete or not followed (Nine out of 21 patients recurred who had complete staging versus 3 out of 4 among those with incomplete staging).

The required components of surgical staging include: 1) cytologic assessment of peritoneal fluid, 2) inspection of and biopsy of any ABNORMAL appearing peritoneal surfaces, lymph nodes, omentum, contralateral ovary and 3) removal of the primary tumor without violation of the tumor capsule in situ. Patients may have undergone additional staging components in accordance with adult guidelines for epithelial ovarian cancer with omentectomy and sampling of normal appearing tissues but the components listed in the previous sentence constitute the *minimum requirements at all ages*. Failure to document inspection and confirmation of normal appearance for

omentum, peritoneal surfaces, lymph nodes and opposite ovary precludes eligibility for the low risk arm.

Upon entering the peritoneal cavity, any peritoneal fluid should be collected for cytology. In the absence of fluid, peritoneal washings are collected for cytologic examination. The pelvic viscera are examined and pelvic and retroperitoneal lymph nodes are palpated on both sides. The omentum and peritoneal surfaces are palpated and visualized. Specific findings about lymph nodes, omentum and peritoneal surfaces must be individually recorded in the operative note as normal or abnormal. Suspicious or enlarged lymph nodes should be biopsied. If the omentum is adherent or has nodules or implants, partial or complete omentectomy to include the lesions should be done. Studding of the peritoneal surfaces with nodules will require that multiple nodules be biopsied without sacrifice of adjacent organs.

13.1.1.1 Unilateral Ovarian disease

If resection would require en bloc removal of structures in addition to the ovary and tube, only a biopsy of the tumor should be done with the expectation of post-chemotherapy resection. Complete oophorectomy should be done for unilateral tumors when feasible. Uninvolved fallopian tubes should be preserved. Hysterectomy is not indicated at primary operation. Lesions adherent to the uterus may be managed by separation of the adherence if easily separated. A normal appearing contralateral ovary should be left alone.

13.1.1.2 Bilateral Ovarian Disease

The completed intergroup trials revealed bilateral lesions in 6% of patients (n = 10). Of these, 4 were benign teratomas and 6 were malignancies. Recommendations for management of bilateral disease begin with careful inspection of both ovaries. Preservation of normal ovarian parenchyma is encouraged if possible. If either side has a discreet lesion with a clearly demarcated capsule from normal ovarian tissue, the lesion may be removed without violating the tumor capsule. If there is no evidence of normal residual tissue on either side, bilateral tumor biopsies without resection should be done with plan for post chemotherapy exploration and ovary sparing resection of residual masses.

13.1.2 Post Chemotherapy Surgery

After completion of chemotherapy, all patients will be assessed with tumor markers and imaging at 4 - 6 weeks.

For patients with biopsy only at diagnosis, oophorectomy of the primary site should be undertaken with sparing of the ipsilateral fallopian tube if possible. For patients with

bilateral disease with biopsy only at diagnosis, enucleation of the tumor is preferred if possible.

For patients with negative tumor markers and no evidence of disease on cross-sectional imaging who had primary resection of the involved ovary, no surgery is indicated.

See the Post-Chemotherapy Evaluations Flowchart for decision making after chemotherapy. Both the tumor marker response and radiologic evaluation of the mass must be undertaken simultaneously. If the tumor markers have normalized, but there is a residual or even an enlarging mass, or residual nodes ≥ 1 cm, then surgery is indicated because it is possible that the residual mass is not viable tumor but rather necrosis or teratomas or in the case of an enlarging mass, growing teratoma syndrome (see Section 13.7). If the tumor markers are still elevated (but not rising), and there is a residual mass, again surgery is indicated if a complete resection is deemed possible. If the tumor markers normalize post-operatively and the resected mass has negative margins, this will constitute a CR (see Section 10 for definition of response). Consultations with study surgeons are advised.

In all secondary procedures, some degree of adherence to surrounding pelvic viscera may be seen but can usually be separated with dissection and removal of adjacent structures should not be done. Hysterectomy is not indicated. Any residual evidence of adenopathy or implants should be resected or biopsied.

13.3.2.1Recurrence during Surveillance

If there is recurrence during surveillance, refer to Section 4.2.2 for information regarding patients with Stage I Grade 2, 3 Ovarian IT, and refer to Section 4.3.2 for information regarding patients with Stage I MGCT.

If markers are normal and a mass is present on imaging, resection or biopsy is indicated. Consideration should be given to the possibility of growing teratoma syndrome (see Section 2.9 and Section 13.7).

EXTRAGONADAL GERM CELL TUMORS

COG STAGING, APPENDIX II: GUIDELINES FOR STAGING, P165

Extragonadal Germ Cell Tumors	
Stage	Extent of Disease
I	• Complete resection at any site, including coccygectomy for sacrococcygeal site. • Must have negative tumor margins and intact capsule. • For any tumors involving abdominal cavity or retroperitoneum, peritoneal fluid or washings must be done for cytology and be negative for malignant cells • Lymph nodes 1 cm or less by imaging of abdomen, pelvis and chest. Note: Nodes 1 - 2 cm, require short interval follow-up in 4 - 6 weeks. If nodes are unchanged (1 - 2 cm), consider biopsy or transfer to chemotherapy arm. If growing, transfer to chemotherapy arm. For any tumors involving abdominal cavity or retroperitoneum, peritoneal fluid or washings must be done for cytology and be negative for malignant cells.
II	• Microscopic residual; • Gross total resection with preoperative biopsy, intraoperative biopsy, microscopic residual or pathologic evidence of capsular disruption. • Lymph nodes negative by abdomen, pelvic and chest imaging. Peritoneal fluid cytology negative.
III	• Gross residual or biopsy only; • lymph nodes positive with tumor resection. Lymph nodes $\geq$ 2 cm or lymph nodes >1 - < 2 cm on short axis by multi-planar imaging CT that fail to resolve on reimaging at 4 - 6 weeks.
IV	Distant metastases including liver, lung, bone, brain

13.5 Surgical Guidelines for Malignant Extragonadal Germ Cell Tumors (PP145-147)

13.5.1 Presacral (Sacrococcygeal) Primary Site

Sacrococcygeal tumors generally present in two clinical patterns: those presenting with large, primarily external and predominantly benign lesions noted in the neonatal period, and those presenting between birth and four years, with lesions primarily in the pelvis and predominantly malignant. Nearly all neonatal tumors should be completely excised

in the neonatal period. Older children should be evaluated for feasibility of complete resection. If a complete excision cannot be accomplished without significant risk to adjacent structures, a biopsy should be performed of an easily reachable portion of tumor. Prior studies have demonstrated no difference in survival in patients treated with initial biopsy and neoadjuvant chemotherapy compared with upfront resection and chemotherapy.[118]

Most presacral lesions will be initially approached through a posterior, transsacral incision. In all cases, the coccyx must be completely removed with the primary tumor. Extent of disease should be carefully determined preoperatively for this tumor, including the possibility of extension through the sacral foramina. With lesions involving the rectum, sacral bone or extensive abdominal involvement, complete resection is not appropriate at diagnosis and an initial biopsy should be performed with subsequent neoadjuvant chemotherapy. Superior extension into the pelvis usually requires a laparotomy and if performed, retroperitoneal lymph nodes should be examined and biopsied if enlarged. If the peritoneal cavity is entered, a sample of fluid or washings should be obtained for cytology. Most of these tumors will shrink significantly with chemotherapy and most require only a sacral incision after neoadjuvant chemotherapy.

13.5.2 Mediastinal Primary Site

Malignant lesions of the chest may be approached through a lateral thoracotomy or median sternotomy, as determined by the location of the lesion. The lesion should be completely excised if possible, and the margin of resection should include adherent non-vital structures such as the thymus. Regional lymph nodes should be evaluated and biopsied when possible in all patients. For lesions deemed unresectable, percutaneous or open biopsy may be performed and followed by neoadjuvant chemotherapy.

13.5.3 Retroperitoneal Primary Site

Large retroperitoneal tumors with α-FP elevation are most likely malignant yolk sac tumors. Unless the lesion is small and resectable, initial biopsy with neoadjuvant chemotherapy should be initiated. If the peritoneal cavity is entered for open or laparoscopic biopsy, a sample of peritoneal fluid or washings should be obtained for cytology. For primary tumor resections, any enlarged lymph nodes should be sampled at the time of resection.

13.5.4 Vaginal Primary Site

Yolk sac tumor of the vagina is a rare tumor occurring exclusively in children less than three years of age. The mass can be confused with sarcoma botryoides. Although initial results were poor with radical surgery, results with platinum-based chemotherapy and limited surgery have been encouraging.[119] Vaginal preservation should be part of the

initial approach. A pelvic and abdominal CT scan should be performed to allow full evaluation of extension. Only small lesions which can be resected with vaginal preservation should be excised at initial presentation. In others, a careful vaginal examination and limited biopsy should be performed.

13.5.5 Other Primary Sites

Malignant germ cell tumors found at other locations should be completely excised if possible without sacrifice of adjacent organs. For large or infiltrative lesions, biopsy only may be appropriate at the initial operation, with planned secondary procedures for delayed excision after chemotherapy. Any enlarged regional lymph nodes in the area must be sampled at the time of resection. Similarly, if laparotomy is performed, retroperitoneal lymph nodes should be examined and biopsied if enlarged and a sample of peritoneal fluid or washings should be obtained for cytology.

13.5.6 Post-Chemotherapy Surgery

Malignant germ cell tumors at all sites may have either new or persisting elements of benign immature or mature teratoma that may result in a new or persistent mass after chemotherapy with normal tumor markers. Residual masses after chemotherapy may also contain a non -GCT somatic malignancy. See Section 13.7 for guidance on growing teratoma syndrome.

For patients with biopsy at diagnosis or partial resection:

1. **Sacrococcygeal/Pre-Sacral Primary site**: If laparotomy is performed, enlarged lymph nodes should be sampled and peritoneal fluid should be obtained for cytology. Resection of residual sacrococcygeal/presacral tumor with complete coccygectomy should be performed. If no tumor is visualized on imaging, the coccyx should still be excised.
2. **Mediastinum**: Any residual post chemotherapy mass > 1 cm in short diameter should be excised.
3. **Retroperitoneum**: Since a large number of these tumors have immature teratoma post chemotherapy, residual masses are common and any residual mass should be resected. These are often more resectable than they appear on imaging since they typically push normal structures away rather than invading these structures.
4. **Vaginal**: After completion of chemotherapy, repeat evaluation and complete excision of residual disease should be performed. Again, vaginal preservation should be the goal of therapy and if a large residual lesion precludes vaginal preservation, a biopsy only should be performed to see if there is residual viable tumor.
5. **Other extragonadal primary sites**: Post-chemotherapy surgery with resection of residual mass is indicated for patients with surgically accessible disease sites, especially if a surgical CR can be anticipated. Post-chemotherapy surgery should include local lymph node sampling when applicable.

13.5.7 Recurrence from Surveillance of Stage I

13.5.7.1 If tumor markers are elevated, no surgery is indicated and if the patient meets eligibility criteria for standard risk arm of this protocol, the patient can be transferred to that arm of the protocol after full staging workup. If the patient fails to meet eligibility for the standard risk arm, then the patient should be enrolled on a poor risk protocol or as per the physician's discretion. If tumor markers are normal and a mass is present on imaging, resection or biopsy is indicated. Consideration should be given to the possibility of Growing Teratoma Syndrome (see Section 13.7).

13.6 Surgery at Relapse

General principles that apply to all sites if there is evidence of recurrence after completion of planned therapy should be followed as noted in the table below. The finding of mature or immature teratoma (see Section 13.7) would be treated with surgery only, the finding of second somatic malignancy would be chemotherapy based on histology, and the finding of malignant germ cell tumor may require salvage chemotherapy.

4.0 TREATMENT PLAN (paraphrased from pp 43-115)

LOW RISK: 2 STRATA:

– Low Risk Stage I Grade 2, 3 Ovarian Immature Teratoma (IT) (p 45-47)
Low risk IT patients, after complete resection of pure immature teratoma, will be followed closely with radiologic and serologic monitoring for evidence of residual disease.

– Low Risk Stage I MGCT (p 48-50)
Low risk Stage I ovarian, testicular, or extragonadal malignant germ cell patients, after complete resection of the tumor, will be followed closely with radiologic and serologic monitoring for evidence of residual disease.

If tumor markers do not decline appropriately based on half life and fail to normalize, then the patient should undergo restaging. If a new mass is observed, second look surgery is recommended, with complete surgical resection if possible. If pathology shows malignant GCT, then the patient may be treated on the appropriate standard risk stratum.

-STANDARD RISK: 2 STRATA, AGE BASED

Standard Risk 1 (SR1 arm) for children less than 11 years of age, with COG Stage II-IV ovarian, testicular, or extragonadal germ cell tumors. (p51-81) Patients are randomized to receive either **4** cycles of cisplatin, etoposide, and bleomycin (PEb) or 4 cycles of carboplatin, etoposide, and bleomycin (CEb). Each cycle lasts 21 days, and Bleomycin will be administered *once per cycle* for a total of **4** doses on this arm.

After completing chemotherapy, all patients will undergo both tumor marker measurements and tumor radiologic imaging. (With determination of biologic response and radiologic response) All patients with post-chemotherapy residual tumor (defined as any lesion(s) greater than 1 cm in short diameter on cross-sectional imaging) should undergo a rigorous attempt at complete surgical resection within 2-6 weeks of completing chemotherapy. (With determination of surgical response and pathologic response; detailed information on responses in the following section, Change in Tumor Size) The presence of teratoma or necrotic tissue in the resected specimen is considered a pathologic complete response. The presence of viable cancer in residual tumor complete resected is considered a pathologic partial response but a surgical complete response. Residual viable cancer that was not completely resected is considered surgical and pathologic partial response. Such a patient has experienced an event, and additional therapy based on viable cancer is up to the physician's discretion.

Standard Risk 2 (SR2 arm) for patients between 11 and 25 years of age, with COG Stage II-IV IGCCC good risk testicular, COG Stage II-III ovarian, and Stage II extragonadal patients. (p 82-115) Randomized to receive either 3 cycles of cisplatin, etoposide, and bleomycin (BEP) or 3 cycles of carboplatin, etoposide, and bleomycin. Each cycle lasts 21 days, and Bleomycin will be administered *weekly* for a total of **9** doses in this patient.

After completing chemotherapy, all patients will undergo both tumor marker measurements and tumor radiologic imaging. (With determination of biochemical and radiologic response; detailed information on responses in the following section, Change in Tumor size) For tumor imaging evaluation, all patients with post-chemotherapy residual tumor (defined as any lesion(s) greater than 1 cm in short diameter on cross-sectional imaging) should undergo a rigorous attempt at complete surgical resection without 2-6 weeks of completing chemotherapy. The presence of teratoma or necrotic tissue in the resected specimen is considered a pathologic complete response. The presence of viable cancer in residual tumor completely resected is considered a pathologic partial response but a surgical complete response. Such a patient has experienced an event, and additional therapy based on viable cancer is up to the physician's discretion

Corollary studies will include evaluations of toxicities, including nephrotoxicity, ototoxicity, neurotoxicity, second malignancies, miRNA diagnostic and prognostic tests, and patient reported outcomes.

Additional aspects of evaluation and recurrence are addressed in the following section, Changing size Criteria and Growing Teratoma Syndrome.

10.2 Change in Tumor Size Criteria for Patients with Solid Tumors (p 134-136) including Growing Teratoma Syndrome

For the purposes of this study, patients who will be evaluated for change in tumor size

are defined as those enrolled on the SR1, SR2 or started on the SR1 or SR2 treatment after recurrence on the LR stratum. Response will not be assessed in IT or LR patients prior to detection of disease recurrence.

Change in tumor size will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1),[115] with the modification that confirmatory scans will not be required once a patient is assessed to by in complete or partial response. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.2.1 Definitions

Biochemical PD – Alphafetoprotein or beta-HCG that is five times the upper limit of normal and rising on at least 2 measurements at least 1 week apart.

Biochemical CR - Alphafetoprotein or beta-HCG that is less than five times the upper limit of normal and either stable or decreasing.

Radiological CR – No radiographic (CT or MRI) evidence consistent with tumor.

For the assessment of radiological partial response (radiological PR; rPR) or radiological stable disease (radiological SD; rSD) tumor burden will be calculated as the sum of the longest dimension of each of the lesions considered malignant germ cell tumor. The baseline tumor burden for the calculation of rPR or rPR will be the tumor burden as calculated from the last CT scan or MRI prior to the start of chemotherapy. Other imaging modalities, such as ultrasound, are not considered to provide valid measurements for the calculation of rPR or rSD.

Radiological PR – A patient who has a reduction of at least 30% when compared with the baseline tumor burden will be considered to have experienced radiological PR on the date of the first imaging that confirms the status of rPR.

Radiological SD – A patient who has change in tumor burden less than 30% of the baseline tumor burden but which does not demonstrate and increased of more than 20% when compared with baseline tumor burden will be considered to have experienced radiological SD on the date of the first imaging that confirms the status of rSD.

Pathological CR – A patient will assessed for surgical CR when a surgery on sites considered to represent malignant germ cell tumors is done as part of protocol therapy. A patient is considered to have experienced a pathological CR if all tissue samples removed at the time of a surgical intervention are free of evidence of germ cell tumor.

Surgical CR – A patient will assessed for surgical CR when a surgery on sites considered to represent malignant germ cell tumors is done as part of protocol therapy.

If all sites considered to represent tumor are removed and malignant germ cell tumor is identified in the surgical specimen but there is no tumor at the margin of the surgical resection, the patient will be considered a surgical CR.

Surgical PR – A patient will considered a surgical PR when a surgery on sites considered to represent malignant germ cell tumors is done as part of protocol therapy. If malignant germ cell tumor is identified in the surgical specimen but the patient does not have complete resection of all sites of disease the patient will be considered a surgical PR.

10.2.3 Growing Teratoma Syndrome

The growing teratoma syndrome **(declining markers in the setting of radiographic increase in disease)** does not represent disease progression and therefore is NOT a criterion for removal from the trial. In severe cases of growing teratoma syndrome where surgical intervention is necessary, resection is permitted. Following resection, patients will be allowed to reenter the treatment program at the discretion of the treating investigator, assuming that pathologic findings confirm teratoma (the majority of the resected specimen), the time lapse between cycles is less than 8 weeks, and they have not developed disease progression in the form of new metastases during the time lapse between treatment cycles. A rise in serum tumor markers due to delay in treatment to allow for surgery, should not in itself disqualify the patient from re-entering the protocol.

10.2.4 Progressive Disease

The patient will be considered to have experienced progressive disease if any of the following occur:

i. Rise in serum tumor markers to greater than 5 times the upper limit of normal[1] (at least one of alphafetoprotein or beta-HCG) on two measurements at least one week apart.

ii. Increasing size of non-teratomatous tumor masses or development of new tumor masses. Specifically excludes growing mature teratoma.

[1] Serum tumor marker levels may be mildly elevated in some cases as a normal variant. Measurement by an alternative pathology laboratory is recommended. Cases in which borderline elevations are persistently present without any indication of progressive elevation and in the absence of any other clinical evidence of residual/progressive malignancy, may be considered as having “normal” tumor marker levels.

For the purposes of Section 9, any patient enrolled with a malignant germ cell tumor will be considered to have an event only if progressive disease is detected.

APPENDIX XI: PATHOLOGY CENTRAL REVIEW REQUIREMENTS (pp181-183)

Tumors to be included:

- Immature teratoma (LR only)
- Yolk sac (endodermal sinus) tumors
- Embryonal carcinoma
- Choriocarcinoma
- Mixed tumors of germ cell histology that include at least one of the following histologies (yolk sac, choriocarcinoma, or embryonal carcinoma)

Tumors to be excluded:

- Pure germinoma/seminoma/dysgerminoma
- Mature teratoma
- Malignant germ cell tumors with secondary malignancies (i.e. tumors with neuroblastoma, PNET, squamous or adenocarcinoma).

Requirements for Pathological Diagnosis of Tumors Eligible for Protocol

I. Criteria to diagnose **yolk sac tumor**

Gross tumor composed of pale, slightly mucoid, moderately firm tissue

Microscopic appearance:

- Small pale cells with scanty cytoplasm and round to oval nuclei with small, inapparent nucleoli.

These cells are arranged many different patterns: reticular (microcystic), macrocystic, endodermal sinus, papillary, solid, glandular, myxomatous, sarcomatoid, polyvesicular vitelline, hepatoid and parietal.

- Intracytoplasmic and extracellular hyaline globules and strands which stain positively with PAS and are resistant to diastase digestion.

The criteria listed above are the essential features necessary for a diagnosis of yolk sac tumor. Immunohistochemical demonstration of alpha-fetoprotein is not necessary for the diagnosis, but should be present in at least some of the cells. Glypican 3 and cytokeratin are also positive.

II. Criteria to diagnose **embryonal carcinoma**

Gross tumor composed of pale, grayish white, bulging, moderately firm soft tissue with varying amounts of hemorrhage and necrosis.

Microscopic appearance:

- Sheets of large epithelial-like cells with round to irregularly oval nuclei containing one or more large nucleoli and having a coarse nuclear

membrane. The cells may vary considerably in size and shape and contain abundant cytoplasm.

- Cells may assume a tubulopapillary arrangement in foci, but must not be associated with intracytoplasmic and extracellular hyaline globules and strands which are PAS positive, diastase resistant. (These latter findings are characteristic of yolk sac tumors.)
- Tumor will usually have large foci of necrosis, frequently occupying a central location within sheets of cells. Some necrotic cells may resemble the hyaline globules seen in yolk sac tumors, but can generally be differentiated by their location in association with dying cells.
- A few embryoid bodies may be present. (NOTE: If the tumor is composed solely or predominantly of embryoid bodies, it should be classified as a polyembryoma. This tumor is also eligible for the protocol.)
- The stroma may vary from loose and edematous, to fibrous, occasionally to quite cellular.
- Immunohistochemically positive for cytokeratin, OCT4 and CD30

III. Criteria to diagnose **choriocarcinoma**

Gross tumor composed primarily of hemorrhagic, friable tissue, with or without a few patches of grayish-white tissue.

Microscopic appearance:

- Tumor composed of two cell types: the syncytiotrophoblast and the cytotrophoblast. The syncytiotrophoblast is a large, somewhat bizarre cell, with one to many hyperchromatic nuclei and generally abundant eosinophilic cytoplasm, which may or may not be vacuolated. The cytotrophoblast is present in closely packed nests and is a medium-sized, relatively uniform cell with clear cytoplasm, distinct cell margins and a vesicular nucleus. These two cell types must both be present, as individual syncytiotrophoblasts (positive for human chorionic gonadotropin) may be seen in any of the malignant germ cell tumors.

IV. Criteria to diagnose **germinoma (dysgerminoma or seminoma)**

Gross tumor composed of an encapsulated, solid mass of grayish-pink rubbery tissue with foci of necrosis and hemorrhage.

Microscopic appearance:

- Tumor composed of large round, oval or polygonal cells with abundant clear cytoplasm and large round nuclei with prominent nucleoli. These cells are arranged in nests separated by bands of fibrous tissue in which numerous lymphocytes are identified. Foci of necrosis are present and syncytial giant

cells may be seen. These tumor cells are positive for placental alkaline phosphatase.

V. Criteria to diagnose **teratomas with malignant elements:**

Only teratomas in which the malignant element is one of the malignant germ cell tumors (i.e., yolk sac tumor, embryonal carcinoma, choriocarcinoma) should be included in the protocol. Teratomas in which non-germ cell tumor malignancies (i.e., neuroblastoma, PNET, squamous or adenocarcinoma) are the malignant elements should be classified as teratomas with malignant elements and excluded in the protocol.

Any focus of germ cell malignancy meeting the criteria outlined above is sufficient to characterize the teratoma as part of a mixed germ cell tumor

VI. Criteria to diagnose **immature teratoma:**

Immature teratomas will be graded according to the system of Norris et al applied to ovarian teratomas:

- Grade 1: Neoplasms with some immaturity (of any cell type), but with immature neuroepithelium absent or limited to collectively occupying no more than one 4x objective, low power field (LPF) on a single slide, ≤1 LPF.
- Grade 2: Neoplasms with more immaturity and primitive neuroepithelium greater than 1 and not exceeding 3 low-power (4x objective) fields per slide, between 1-3 LPF's.
- Grade 3: Neoplasms in which immaturity and primitive neuroepithelium are prominent, primitive neuroepithelium present in ***>3*** low-power (***4x objective***) fields per slide, ***>3 LPFs.***

Immature teratomas with any foci (even microscopic) of yolk sac tumor, embryonal carcinoma, choriocarcinoma are included in the protocol. Immature teratomas with only non-germ cell tumor malignancies (i.e., neuroblastoma, PNET, squamous carcinoma, or adenocarcinoma) are classified as immature teratoma with malignant elements and are excluded in the protocol.

Immature and mature teratomas of the ovary may occasionally be associated with peritoneal nodules. If these nodules are composed entirely of mature glial tissue (demonstrated on microscopic sections), they are classified as gliomatosis peritonei, and their presence does not alter the stage of the primary tumor.* Thus, a Stage I mature ovarian teratoma with widespread peritoneal seeding by

nodules of mature glial tissue remains a Stage I tumor (it does not become a Stage III or IV tumor) and should be treated on this protocol.

*Note: These nodules must be sampled extensively to rule out the presence of malignant elements before the diagnosis of gliomatosis peritonei is made.

VII. Criteria to exclude other germ cell components or to exclude a malignant focus in a teratoma:

- Entire tumor plus any metastatic lesion must be available for gross and microscopic examination.
- A minimum of one microscopic section per centimeter of widest tumor diameter must be examined.
- A microscopic section from every area which appears grossly different must be examined.
- A minimum of one microscopic section per centimeter of widest diameter of each metastatic lesion must also be examined.

Serial sections of the entire tumor and all metastatic lesions would be necessary to prove a tumor to be completely pure or to prove a teratoma to be completely benign, but such a procedure would be impractical both financially and temporally. The protocol outlined above is the conventional pathologic approach to tumors and has proven to be reasonably reliable.

ADULT STAGING SYSTEMS: TESTICULAR

AJCC STAGING CRITERIA[132] Appendix IV (P 168)

ANATOMIC STAGE/PROGNOSTIC GROUPS				
GROUP	T	N	M	S (Serum Tumor Markers)
Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	PT3	N0	M0	S0
	PT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1

Stage III	Any pT/TX	Any M	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

Stage	**Primary Tumor (T)***
PTX	Primary tumor cannot be assessed
PT0	No evidence of primary tumor (e.g. histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
PT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion
Stage	**Pathologic (pN)**
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to five nodes positive, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than five nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor

pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Stage	**Regional Lymph Nodes (N): Clinical**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Stage	**Distant Metastasis (M)**
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Distant metastasis other than to nonregional lymph nodes and lung
Stage	**Serum Tumor Markers (S)**
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH < 1.5 x N* and β-hCG (mlu/mL) < 5,000 and α-FP (ng/mL) < 1,000
S2	LDH 1.5 - 10 x N or β-hCG (mlu/mL) 5,000 - 50,000 or α-FP (ng/mL) 1,000 - 10,000
S3	LDH > 10 x N or β-hCG (mlu/mL) > 50,000 or α-FP (ng/mL) > 10,000
	* N indicates the upper limit of normal for the LDH assay.

INTERNATIONAL GERM CELL CANCER CONSENSUS CLASSIFICATION

Justification for New Risk Stratification in Pediatric Germ Cell Tumors (p18-19)

A watershed in the care of testicular cancer patients was the creation in 1997 of the International Germ Cell Consensus Classification (IGCCC) that risk-stratified testicular cancer patients into good, intermediate and poor risk based on the histology, site of primary disease, location of metastases and elevation of tumor markers prior to initiation of chemotherapy[5]. The IGCCC, based upon a joint analysis of over 5,000 patients from the major clinical trials conducted in North America and Europe, became the accepted basis of clinical trial design and comparisons of results. After an analysis that applied the adult IGCCC to pediatric germ cell tumor patients showed low correlation between either COG stage or risk group,[1] COG initiated a collaboration with the National Cancer Research Institute/Children's Cancer and Leukemia Group (CCLG) of the United Kingdom to generate a pediatric-specific GCT risk stratification. Combining their 25 years of pediatric GCT clinical trial data, the resultant **Ma**lignant **G**erm Cell **I**nternational **C**onsortium (MaGIC) performed a multivariate analysis on a dataset of more than 1,000 patients. They demonstrated that the likelihood of cure is significantly associated with younger age (≤ 10 vs. 11+), lower stage (Stage II - III vs. IV), and site (testes vs. ovarian or extragonadal (EG)). Histology [yolk sac tumor (YST) vs. other] was of borderline significance whereas pre-operative tumor marker levels (α-FP and β-HCG) were not prognostic. Patients in the MaGIC analysis with an expected EFS of > 80% were assigned to the standard risk group and are eligible for AGCT1531 (see Table 1). The standard risk group was divided into two strata based on age (see Section 2.5 below for further information on rationale). Patients with an EFS < 70% are designated poor risk and will be treated on a separate protocol.

Table 1: Predicted Fraction of Pediatric Germ Cell Tumors Cured by Site, Age, and Stage and Risk Group Assignment[6]

Site, Age, Stage	Predicted Long-Term Disease Free, Using Cure Model (95% Confidence	Risk Group

	Interval)	
Testicular <11 years of age, Stage II-III	99% (96%-100%)	SR1
Ovarian <11 years of age, Stage II-III	97% (93%-99%)	SR1
Testicular <11 years of age, Stage IV	96% (91%-99%)	SR1
Testicular ≥11 years of age, Stage II-III	93% (84%-97%)	SR2 or PR*
Ovarian < 11years of age, Stage IV	92% (83%-96%)	SR1
Extragonadal < 11 years of age, Stage II-III	91% (86%-94%)	SR1
Ovarian ≥11 years of age, Stage II-III	85% (77%-91%)	SR2
Testicular ≥11 years of age, Stage IV	83% (67%-91%)	SR2 or PR*
Extragonadal < 11 years of age, Stage IV	79% (71%-84%)	SR1
Ovarian ≥11 years of age, Stage IV	67% (49%-80%)	PR
Extragonadal ≥11 years of age, Stage II	100% (48%-78%)	SR2
Extragonadal ≥11 years of age, Stage III	61% (95% CI 34%-79%)	PR
Extragonadal ≥11 years of age, Stage IV	40% (24%-56%)	PR

SR1= Standard Risk 1; SR2= Standard Risk 2; PR=Poor Risk

* IGCCC Good Risk Testicular over age 11 will be SR2; IGCCC Intermediate or Poor Risk Testicular over age 11 will be PR and treated on separate protocol

APPENDIX V: INTERNATIONAL GERM CELL CANCER CONSENSUS CLASSIFICATION (P169)

Histology	Good (Eligible for AGCT1531)	Intermediate (Ineligible for AGCT1531)	Poor (Ineligible for AGCT1531)
Non-seminoma (Pure Seminoma is ineligible for AGCT1531)	Meets all criteria below: • Gonadal or RP primary site • Absence of non-pulmonary visceral metastasis • (S0) or S1 STM • β-HCG <5,000IU/mL • α-FP <1,000ng/mL • LDH <1.5xULN	Meets all criteria below: • Gonadal or RP primary site • Absence of non-pulmonary visceral metastasis • S2 STM • β-HCG ≥5,000IU/mL and ≤50,000IU/mL • α-FP ≥1,000ng/mL and ≤10,000ng/mL • LDH ≥1.5xULN and ≤10xULN	Meets any of criteria below: • Mediastinal primary site • Presence of non-pulmonary visceral metastasis • S3 STM • β-HCG > 50,000IU/mL • α-FP >10,000ng/mL • LDH >10xULN

Abbreviations: RP, retroperitoneal; STM, serum tumor markers; SO, normal markers; S1,S2,S3, range listed above, ULN, upper limit of normal; α-FP, alpha fetoprotein: HCG, human chorionic gonadotropin; LDH, lactic dehydrogenase

* Non-pulmonary visceral metastasis refers to metastasis involving organs other than lung (lymph nodes do not count)

International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers.

ADULT STAGING SYSTEM: OVARY
APPENDIX III: FIGO OVARIAN STAGING (P 166)

FIGO Ovarian Staging

Stage	FIGO Criteria**
I	**Tumor confined to ovary**
IA	Limited to 1 ovary, capsule intact, no tumor on surface, negative washings
IB	Both ovaries, otherwise like IA
IC1	Surgical spill
IC2	Capsule rupture before surgery, or tumor on ovarian surface
IC3	Malignant cell in ascites or peritoneal washings
II	**Both ovaries or extension below pelvic rim or peritoneal primary**
IIA	Extension and/or implant on uterus and/or fallopian tubes
IIB	Extension to other pelvic intraperitoneal structures
III	**Positive RP LN and/or microscopic metastasis beyond pelvis**
IIIA1	Positive RP LN only (IIIA1i $\leq$ 10mm) (IIIA1ii >10mm)
IIIA2	Microscopic , extrapelvic (above pelvic brim), peritoneal involvement +/- positive RP LN
IIIB	Macroscopic, extrapelvic peritoneal metastasis $\leq$ 2cm +/- RP LN, includes extension to capsule of liver/spleen

IIIC	Macroscopic, extrapelvic peritoneal metastasis > 2cm +/- RP LN, includes extension to capsule of liver/spleen
IV	
IVA	Pleural effusion with positive cytology
IVB	Metastasis to: liver/spleen parenchyma, extra-abdominal organs (including inguinal LN and outside abdominal cavity)

Abbreviations: STM, serum tumor markers; LN, lymph nodes ; RP, retroperitoneal

* The presence of gliomatosis peritonei does not result in change in stage

** Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 124(1): pp1-5, 2014 [8]

ional GERM Cell Cancer Collaborative Group. J Clin Oncol 15:594-603, 1997

APPENDIX VIII: NORMAL RANGES OF α-FP IN INFANTS AND TUMOR MARKER DECLINE (P173)

A favorable tumor marker decline is defined as one in which the measured tumor marker level is equal to or less than the expected tumor marker level, based on the marker half-life.

To determine whether the decline is appropriate, note the tumor marker level on Day 1 (pre-chemotherapy) and at a later point in time. Calculate the number of half-life intervals between the two points. One half-life interval is 7 days for α-FP and 3.5 days for β-HCG. Based on the number of half-life intervals, calculate the expected tumor marker level at the later time point.

If the actual tumor marker level is equal to or less than the expected tumor marker level (or if it is less than 5 times the upper limit of institutional normal) the decline rate is favorable.

If the actual tumor marker level is greater than the expected tumor marker level (and it is more than 5 times the upper limit of institutional normal), the decline rate is unfavorable.

Note: This tumor marker decline calculation should not be used for infants less than 6 months of age, as they may have physiologic elevation of α-FP and altered decline rates.

Example 1.
Patient has an α-FP on Day 1 of 10,000 and an α-FP on Day 22 of 1,000.
Half-life interval of α-FP is 7 days.
Day 1 to Day 22 is 21 days, which is 3 half-life intervals.
Expected α-FP on Day 22 would be 10,000 ÷2 ÷2 ÷2 = 1,250.

Since the actual α-FP is lower than the expected α-FP, the decline is favorable.

Example 2.
Patient has a β-HCG on Day 1 of 80,000 and on Day 43 of 100.
Half-life interval of α-FP is 3.5 days.
Day 1 to Day 43 is 42 days, which is 12 half-life intervals.
Expected β-HCG on Day 43 would be $80,000/2^{12} = 20$.
Since the actual β-HCG is higher than the expected β-HCG and is more than five times the upper limit of normal, the decline is unfavorable.

Normal Ranges of Serum **α**–Fetoprotein (ng/mL) in Infants

Wu et al.		Blohm et al.	
Age	Mean ± standard deviation	Age	Mean (95% confidence interval)
Premature	134,734 ± 41,444	Premature	158,125 (31,261–799,834)
Newborn	48,406 ± 34,718	Newborn	41,687 (9,120–190,546)
0–2 weeks	33,113 ± 32,503	Day 8–14	9,333 (1,480–58,887)
2 weeks–1 month	9,452 ± 12,610	Day 22–28	1,396 (316–6,310)
2 months	323 ± 278	Day 46–60	178 (16–1,995)
3 months	88 ± 87	Day 61–90	80 (6–1,045)
4 months	74 ± 56	Day 91–120	36 (3–417)
5 months	47 ± 19	Day 121–150	20 (2–216)
6 months	13 ± 10	Day 151–180	13 (1–129)
7 months	10 ± 7	Day 181–720	8 (1–87)