Outcome and Staging Evaluation in Malignant Germ Cell Tumors of the Ovary in Children and Adolescents: An Intergroup Study

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Purpose: The aim of this study was to perform an evaluation of outcome and the role of surgical staging components in malignant germ cell tumors (GCT) of the ovary in children and adolescents.

Methods: From 1990 to 1996, 2 intergroup trials for malignant GCT were undertaken by Pediatric Oncology Group (POG) and Children's Cancer Study Group (CCG). Stage I-II patients were treated with surgical resection and 4 cycles of standard dose cisplatin (100 mg/m^2/cycle), etoposide, and bleomycin (PEB) chemotherapy. Stage III-IV patients were treated with surgical resection and randomly assigned to chemotherapy with PEB or high-dose cisplatin (200 mg/m^2/cycle) with etoposide and bleomycin (HDPEB). Patients unresectable at diagnosis had second-look operation after 4 cycles of chemotherapy if residual tumor was seen on imaging studies. IRB approval of the protocols was obtained at each participating institution. An analysis of outcome data, operative notes, and pathology reports in girls with ovarian primary site was done for this report.

Results: There were 131 patients with ovarian primary tumors of 515 entered on these studies. Mean age was 11.9 years (range, 1.4 to 20 years). Six-year survival rate was stage, I 95.1%; stage II, 93.8%; stage III, 98.3%; stage IV, 93.3%. In only 3 of 131 patients were surgical guidelines followed completely. Surgical omissions resulting in protocol noncompliance resulted from failure to biopsy bilateral nodes (97%), no omentectomy (36%), no peritoneal cytology (21%), no contralateral ovary biopsy (59%). More aggressive procedure than recommended by guidelines included total hysterectomy and bilateral salpingo-oophorectomy in 6 patients and retroperitoneal node dissection in 10 patients. Correlation of gross operative findings with pathology results was carried out for ascites, lymph nodes, implants, omentum, and contralateral ovary.

Conclusions: Pediatric ovarian malignant GCT (stages I-IV) have excellent survival with conservative surgical resection and platinum-based chemotherapy. Survival appears to have been unaffected by deviations from surgical guidelines. New surgical guidelines are proposed based on correlation of gross findings, histology, and outcome in these intergroup trials.
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MALIGNANT GERM cell tumors account for approximately 20% of ovarian masses in children and adolescents. Historically, these children had a poor prognosis with surgery alone. Early regimens combining radiation therapy with VAC (vincristine, Actinomycin D, cyclophosphamide) and doxorubicin brought survival to 60%.[1] Further improvement in survival rate was accomplished with the introduction of platinum-based regimens.[2] Surgical staging guidelines were adopted from the adult experience with ovarian epithelial cancer. The efficacy of these guidelines in children and adolescents has not been evaluated. The recently completed intergroup POG/CCG (Pediatric Oncology Group, Children's Cancer Study Group) studies on malignant extracranial germ cell tumors provided an opportunity to examine the details of the ovarian surgical staging procedure as well as survival outcomes with current platinum-based chemotherapy.

MATERIALS AND METHODS

Two intergroup studies for extracranial malignant germ cell tumors in children and adolescents were undertaken by the Pediatric Oncology Group (POG) and Children's Cancer Study Group (CCG) from 1990 to 1996. Children with stage I and II ovarian tumors were entered onto POG 9048/CCG 8891 and were treated in a nonrandomized fashion with tumor resection followed by 4 cycles of chemotherapy. The regimen included cisplatin, 100 mg/m^2/d×5, etoposide 100 mg/m^2/d×5 and bleomycin 15 mg/m^2/d×1 (PEB) for each cycle. Children with stage III and IV ovarian tumors were entered onto POG 9049/CCG 8882. This high-risk group was treated with surgical resection at diagnosis if possible followed by 4 cycles of chemotherapy. Patients then were randomly selected to either standard PEB or high-dose cisplatin at 200 mg/m^2/d×5 with etoposide, 100 mg/m^2/d×5, and bleomycin, 15 mg/m^2/d×1 (HD PEB) per cycle. If the tumor was not

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Table 1. Staging System for Pediatric Ovarian Germ Cell Tumors

Stage I	Limited to ovary (ovaries); peritoneal washings negative; tumor markers normal after appropriate half-life decline (AFP 5 days, HCG 16 hours)
Stage II	Microscopic residual or positive lymph nodes (<2 cm) Peritoneal washing negative for malignant cells, tumor markers positive or negative
Stage III	Lymph node involvement (>2 cm) gross residual or biopsy only; contiguous visceral involvement (omentum, intestine, bladder); peritoneal washings positive for malignant cells; tumor markers positive or negative.
Stage IV	Distant metastases, including liver.

resected at diagnosis, second-look surgery with attempted resection was to be undertaken after 4 cycles of chemotherapy.

Surgical guidelines recommended complete evaluation of disease at diagnosis with safe resection and sparing of uninvolved organs. The main components of the staging procedure included (1) collection of ascites or washings on entering the peritoneal cavity, (2) examination of the peritoneal surfaces with biopsy or excision of any nodules, (3) examination and palpation of lymph nodes in the retroperitoneum with bilateral sampling at four defined sites, (4) complete omentectomy, (5) bivalve and biopsy of the contralateral ovary, and (6) complete resection of the tumor-containing ovary with sparing of the fallopian tube if not involved. The staging system is outlined in Table 1.

For this review, an analysis of girls with ovarian primary site was undertaken. A detailed review of operative notes and pathology reports was focused on compliance to the recommended components of the staging laparotomy. The yield and utility for each step was examined. Events and survival data were calculated using the Kaplan-Meier method.

RESULTS

There were 131 girls with malignant germ cell tumors of the ovary entered onto the combined intergroup studies including 41 stage I, 16 stage II, 58 stage III, and 16 stage IV tumors. Age ranged from 1.4 to 20 years with mean age of 11.9 yrs.

Information on clinical presentation was available from the operative notes in 82 patients. Of these 82 girls, 9 presented with an acute abdomen with a preoperative diagnosis of appendicitis in 7 and peritonitis in 2. Three of these girls had torsion of the tumor at laparotomy. Four girls presented with signs of precocious puberty, and the remainder presented with a variety of symptoms including subacute or chronic pain, abdominal distension, change in weight, or palpable mass.

Tumors ranged in size from 5 to 37 cm. At least 75 of 131 tumors had a grossly cystic component including 27 that had no teratoma elements. Histology of the tumors showed mixed tumors in most patients with teratoma elements coexisting in 60 girls (Table 2). Patients with pure germinoma histology were only eligible for enrollment in the high-risk study (stages III and IV). Interestingly, 2 girls later found to have XY genotype had additional malignant elements in underlying gonadoblastoma (germinoma, EST).

Table 2. Histology of Pediatric Ovarian Germ Cell Tumors

Histology	No. of Patients
Teratoma + EST	39
Teratoma + Other malignant elements	21
Pure EST	25
Pure germinoma	23
Pure choriocarcioma	2
Multiple malignant elements without teratoma	10
Gonadoblastoma + other	2

Abbreviation: EST, endodermal sinus tumor.

Management of the primary tumor for the stage I and II patients included unilateral salpingo-oophorectomy (USO) in 40 patients, unilateral oophorectomy in 14, total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) in 1, bilateral oophorectomy in 1, and enucleation of the mass with preservation of the ovary in 1. Estimated blood loss for this group exceeded 300 mL in only 1 patient. There was 1 operative complication of vaginal injury that was repaired primarily.

Management of the primary tumor for the stage III and IV patients included USO in 49 patients, unilateral oophorectomy in 6, TAH-BSO in 5, bilateral salpingo-oophorectomy in 3, bilateral oophorectomy in 1, enucleation of the mass with preservation of the ovary in 1, and biopsy only in 6. Estimated blood loss exceeded 300 mL (range, 350 to 1600 mL) in 13 patients. One patient had injury to the external iliac artery requiring vein graft repair and an injury to the sigmoid colon requiring repair.

The recommended surgical guidelines were seldom followed completely (Table 3). Analysis of the various aspects of the staging guidelines and correlation of histology with gross findings was carried out for each component. Complete data points were not available in all patients because of incomplete operative or pathology reports, but sample size is recorded for each variable.

Tumor Capsule

Preoperative rupture of the tumor capsule was recognized at laparotomy in 30 of 130 girls. Fourteen patients had accidental disruption of the tumor capsule during operative manipulation and 8 had deliberate violation of the tumor capsule either to achieve intraoperative biopsy or to facilitate removal through a smaller incision.

Of 63 patients felt to have an intact tumor capsule by the surgeon, pathologic results of capsular integrity were

Table 3. Compliance With Surgical Guidelines for Pediatric Ovarian Germ Cell Tumors

Staging Component	Stage I & II (%)	Stage III & IV (%)
Ascites/washings	82%	81%
Examine perit. surfaces	92%	88%
Omentectomy	53%	72%
Bilateral lymph node sampling	1%	2%
Biopsy contralateral ovary	41%	40%

Table 4. Ascitic Fluid Analysis in Pediatric Ovarian Germ Cell Tumors

Sample	No Result	Negative	Abnormal
Washings only, no ascites (n = 16)	7	8	1 Imm. teratoma
Clear ascites (n = 17)	5	12	0
Bloody ascites (n = 19)	5	7	7 Malignant cells
Ascites, not described (n = 46)	8	25	13 Malignant cells 1 Imm. teratoma
Fluid from ruptured cyst (n = 2)	0	0	1 Teratoma

available in 51. In these 51 patients, the capsule was microscopically intact in 30, infiltrated (partial invasion of the capsule) in 10, penetrated (complete invasion through the capsule) in 9, and ruptured in 2.

Adherence of the tumor to surrounding structures was fairly common. Higher-stage tumors were more likely to be adherent to surrounding pelvic viscera. Surgical management consisted of in continuity resection for most omental and tubal adherence. Adherence to pelvic viscera was most often treated with separation of the adherent plane.

Ascitic Fluid/Peritoneal Washings

Ascites was documented to be present in 84 patients. No comment on presence of ascites was made in 10 laparotomies. Samples of ascitic fluid or washings were obtained in 100 patients, and 23 of these had positive cytology (Table 4). There were 58 specimens in the stage III patients, and 16 of these were positive. Five of these girls were stage III based on the ascitic fluid findings alone and had intact tumor capsules and negative nodes.

Peritoneal Implants

Examination of the peritoneum was documented in 114 patients. Eight patients had random biopsies of normal areas. Pathology results were negative in 7 of 7 available reports. Twenty-nine biopsies were obtained from abnormal areas. Histologic findings in these samples were negative in 5, gliomatosis in 6, and malignancy in 18. There were no cases of isolated implants located on the diaphragmatic surfaces. In both patients with documented malignant diaphragm implants, malignant implantation was also documented from pelvic implants.

Omentum

Omentectomy was carried out per protocol in 77 patients. Histology was available in 74. Twenty-two of 23 grossly normal specimens had negative microscopic examination findings, and 1 had microscopic deposits of endodermal sinus tumor. Forty-five specimens were grossly abnormal because of adherence to the primary tumor or to nodules. Seven of this group had malignancy, 6 had teratoma, 2 had granulomatous inflammation, and 19 were negative. Of 9 omental specimens that were not grossly characterized, 5 were negative, 3 had no result, and one showed malignant tissue.

Fallopian Tube

The ipsilateral fallopian tube was preserved in 27 of 125 patients that underwent tumor resection at diagnosis. One tube was resected because of torsion and necrosis. Thirteen of 98 resected tubes contained malignant tumor.

Lymph Nodes

Only 3 patients had bilateral node sampling as recommended. Ten patients had formal retroperitoneal lymph node dissection. The appearance of the lymph nodes to inspection and palpation was documented in 64 patients. All 18 samples from grossly normal lymph nodes were negative at microscopic examination. In lymph nodes that were sampled because of firmness or enlargement, 19 of 46 contained metastatic malignant tumor.

Contralateral Ovary

Bilateral germ cell lesions were documented in 11 girls at diagnosis and included 4 teratomas, 2 gonadoblastomas, 3 germinomas, and 2 endodermal sinus tumors. Five of 7 with bilateral malignancies were treated with bilateral oophorectomy, and 2 had biopsy. Two of 4 girls with contralateral teratoma had enucleation only, and 2 had bilateral oophorectomy. Appearance of the contralateral ovary was documented in 42 patients. Complete removal of a normal contralateral ovary as part of a TAH/BSO was done in one stage I girl. Twenty-one biopsies of normal-appearing ovaries were all negative. Five biopsies performed with no comment on the gross appearance of the ovary were all negative. Twenty-one biopsies of grossly abnormal ovaries showed the 11 bilateral lesions described above, 1 metastatic implant, and 9 negative specimens.

Biopsy Only/Follow-Up Laparotomy

Six girls had biopsy at diagnosis followed by chemotherapy. One had biopsy of a vertebral metastasis without further surgery. The remaining 5 girls all had diagnostic laparotomy and were treated with chemotherapy followed by second-look laparotomy at 3 to 6 months. All

Table 5. Event-Free Survival (EFS) and Survival in Pediatric Ovarian Germ Cell Tumors

Stage	No.	6-yr EFS (%)	6-yr Survival (%)
I	41	95	95.1
II	16	87.5	93.8
III	58	96.6	97.3
IV	16	86.7	93.3

had decrease in size of the mass. Operative report is unavailable for 1. Two were treated with salpingo-oophorectomy and 2 with TAH/BSO. One specimen contained mature teratoma, and 3 had no evidence of tumor.

Outcome

Overall survival rate was excellent as shown in Table 5. There were 2 events in each stage as described in Table 6. Of particular interest was the patient with relapse of choriocarcinoma in the contralateral ovary. She had documented inspection, bivalve, and negative wedge biopsy of this ovary at her primary diagnostic laparotomy.

DISCUSSION

Survival rate of girls with malignant germ cell tumors of the ovary was excellent in this study with an incidence of only 3% (4 of 131) primary tumor–related mortality. Previous recommendations for extensive surgical resection of reproductive organs[1] have been successfully abandoned without compromise in outcome. The high survival rate with conservative surgery can be credited to the development of effective chemotherapeutic agents. There still is significant variability in surgical procedure, however, and poor compliance to surgical guidelines.

Discussion of the diagnosis and management of ovarian masses in children and adolescents has been clouded by the frequent application of adult principles and statistics. The inclusion of neonates in some pediatric series of ovarian masses also distorts the distribution of lesions encountered because neonatal ovarian masses are uniformly benign follicular cysts owing to maternal estrogen stimulation. If reviews are restricted to series of only pediatric ovarian lesions excluding neonates, the risk of malignancy is found to be 16% to 24% with an overall

Table 6. Events in Pediatric Ovarian Germ Cell Tumors

Stage	Event (Interval From Diagnosis)	Outcome
I	AML (5 mo)	Dead
I	Perit. implants (21/2 yr)	Dead
II	Myelodysplasia (9 mo)	Alive
II	Tumor relapse (9 mo)	Dead
III	Relapse contralat ovary (8 mo)	Alive
III	Local relapse in pelvis (6 mo)	Dead
IV	Lung mets (6 mo)	Dead
IV	Local relapse (5 mo)	Alive

Table 7. Risk of Malignancy in Pediatric Ovarian Masses Excluding Neonates

Study	No. of Patients	Malignant No.	% Malignant
Ein et al 1970[3]	75	12	16
Harris and Boles 1974[4]	25	6	24
Ehren et al 1984[5]	63	13	20
Brown et al 1993[6]	81	10	23
Combined data	244	50	20

incidence of 20% (Table 7). This includes both solid and cystic lesions. A frequently quoted risk of malignancy in cystic ovarian lesions is 2%.[7-9] This 2% risk figure is derived from a large review of mainly adult ovarian tumors that were felt to be benign cystic teratomas and indicated the risk of secondary malignant degeneration of epithelial elements.[10] Although a comparable study of cystic lesions in pediatric ovarian lesions has not been done, our study shows that gross cystic components are common in malignant ovarian tumors in childhood with an incidence of 57%. This included not only tumors with a component of teratoma but also many cases of pure germinoma or endodermal sinus tumor. It appeared from review of the operative notes that there were no gross findings to aid in distinguishing benign from malignant lesions in the lower stage tumors.

Presentation as an acute abdomen is a frequent occurrence and was found in 11% of girls in our study as well as in 11% of girls in Baranzelli's study of malignant ovarian germ cell tumors in children.[11] This clinical setting will produce a need for operative intervention without the advantage of preoperative tumor markers or complete imaging information. Because there are no gross tumor characteristics that define malignancy, and the risk of malignancy is significant, pediatric ovarian lesions should always be managed and completely staged with the assumption that malignancy is present.

In this study of malignant ovarian germ cell tumors, the incidence of capsular breech was significant. Gross preoperative rupture was recognized in 23% of patients, and, perhaps more importantly, an additional 22% of tumors were found to have microscopic penetration of an apparently intact capsule. This finding suggests that the surgeon's assessment of capsular integrity is frequently in error and that the pathologist must receive an intact specimen for complete examination to accurately stage the tumor. Adherence to surrounding structures was common at all stages and did not require sacrifice of significant structures for good outcome. Surgical complications and increased blood loss were seen more often in advanced-stage tumors with extensive adherence treated with primary resection. Although several patients underwent radical resections including complete hysterectomy, survival was excellent in girls treated with

separation of the adherent plane or initial biopsy only with delayed resection. These findings would support initial conservative surgery limited to tumor excision for straightforward cases and biopsy only for densely adherent or extensive tumors. At postchemotherapy laparotomy, none of the additional organs removed with the primary tumor by radical resection contained viable malignancy, which also supports a conservative approach.

The yield of ascitic fluid cytology was high in this study confirming its role in accurate surgical staging. Five girls whose malignancy would have been otherwise considered stage I had their tumor upstaged to stage III based on cytology findings. The yield of washings alone is difficult to analyze because the limited available cytologic results.

Visual inspection was reliable for assessment of peritoneal surfaces, omentum, and fallopian tube. The omentum was involved with malignant tumor in only 8 girls and the fallopian tube in 13. Extension of the incision to visually inspect the diaphragm is not required as long as the pelvis is fully examined.

Bilateral lymph node sampling at 4 sites was recommended by protocol with the impression that contralateral positive nodes occurred frequently. This was only done in 2% of patients, and, therefore, the yield of bilateral sampling cannot be documented. However, documentation of palpation for firmness or enlargement was done in 49% of patients. There were no positive specimens in grossly normal nodes. The yield of malignancy in grossly abnormal nodes was 41%.

The use of laparoscopy has become increasingly common for many intraabdominal procedures in childhood.[8,12,13] Nevertheless, caution must be emphasized in the setting of pediatric ovarian masses. The important components in accurate staging for pediatric ovarian germ cell tumors appear to be ascitic cytology, inspection of the pelvic peritoneum, inspection of the omentum, palpation of retroperitoneal lymph nodes, and delivery of an intact specimen to the pathologist. The first 3 components are accomplished easily by laparoscopic or open technique. Laparoscopy offers some advantage in inspection of the diaphragm, but isolated diaphragm implants were not seen in this series. Open laparotomy is required both for palpation of the retroperitoneal lymph nodes and for delivery of an intact specimen to the pathologist. Initial examination of the peritoneal cavity, biopsy of obviously invasive tumors, and removal of grossly ruptured tumors may be effectively accomplished by laparoscopy without loss of staging information. Potentially lower-stage tumors will be more accurately staged by open technique. An anticipated goal of the next group of malignant germ cell trials will be to determine if stage I ovarian tumors can be managed safely by surgical excision alone and close monitoring with tumor markers and imaging. This will depend on accurate surgical staging at initial exploration. The success of surgical resection as sole therapy for boys with stage I testis tumors has been encouraging. In the POG 9048/CCG 8891 study, 78.5% of boys were cured with surgery alone, and all relapsing patients were saved with chemotherapy.[14] The TGM 85 and 90 protocols in France[11] have evaluated a surgery-only regimen for localized, completely resected malignant ovarian germ cell tumors in the pediatric population. They noted 6 relapses in 12 patients. Five of these were salvaged with chemotherapy.

Current platinum-based regimens produce excellent survival for all stages of malignant ovarian germ cell tumors in the pediatric age group. Surgical management involves tumor removal with conservation of pelvic structures. The diagnostic yield of the various components of surgical staging for pediatric ovarian germ cell tumors has been objectively analyzed in this large series of patients. The revised surgical procedural guidelines include (1) collection of ascites or washings on entering the peritoneal cavity, (2) examination of the peritoneal surfaces with biopsy or excision of any nodules, (3) examination and palpation of lymph nodes in the retroperitoneum with sampling of any firm or enlarged nodes, (4) inspection and palpation of the omentum with removal if any adherent or abnormal areas noted, (5) inspection and palpation of the opposite ovary with biopsy of any abnormal areas, and (6) complete resection of the tumor-containing ovary with sparing of the fallopian tube if not involved. Future advances in treatment should focus on reducing the morbidity of therapy. This will include modifications in chemotherapy and improved stratification of higher-risk patients. The contribution of meticulous surgical staging to accurately describe the extent of disease should be encouraged as a complementary tool in the evaluation and care of these children.

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Discussion

Unidentified Speaker: In your abstract you mentioned that patients that were considered unresectable at diagnosis had a second-look operation after 4 cycles of chemotherapy only if the imaging studies were positive. If they were negative, did you not look at them? It says, if residual tumor was on the imaging studies.

D.F. Billmire (response): That is what the protocol formally recommended. In fact, all these girls did have some evidence of residual disease, but exploration would be recommended anyway I think.

T. Meyer (Austin, TX): What I am wondering is, if so many of the patients did not have their nodal status assessed, how can we know that the stage II patients are actually stage II and not stage III, and are we overtreating then a lot of the IIIs and IVs that could be treated like the stage IIs?

D.F. Billmire (response): I think that is a good question. I think it bears out the importance of our being meticulous in our staging procedures. In this particular study, all patients received chemotherapy. The only difference was the randomization for the high-dose arm, so whether you were stage I or stage IV everyone received platinum-based chemotherapy. As we go forward, I think that there is a potential to reduce treatment in selected patient groups, but it will be incumbent on us to obtain the proper staging information so that the subgroups can be accurately evaluated.