Original Report

Imaging Appearance of Nongerminoma Pediatric Ovarian Germ Cell Tumors Does Not Discriminate Benign from Malignant Histology

Deborah Billmire MD [1,*], Bryan Dicken MD [2], Frederick Rescorla MD [1], Jonathan Ross MD [3], Jin Piao PhD [4], Li Huang PhD [4], Mark Krailo PhD [5], Farzana Pashankar MD [6], Lindsay Frazier MD [7], on behalf of the Children's Oncology Group

[1] *Division of Pediatric Surgery, Indiana University, Indianapolis, Indiana*
[2] *Division of Pediatric Surgery, University of Alberta, Edmonton, Alberta, Canada*
[3] *Department of Urology, Rush University, Chicago, Illinois*
[4] *Children's Oncology Group, Monrovia, California*
[5] *Department of Research Preventive Medicine, University of Southern California, Monrovia, California*
[6] *Department of Pediatrics, Yale School of Medicine, New Haven, Connecticut*
[7] *Department of Pediatrics, Harvard University, Dana Farber Cancer Institute, Boston, Massachusetts*

A B S T R A C T

Study Objective: Pediatric ovarian neoplasms with imaging appearance suggestive of teratoma are often presumed to have low risk of malignancy. We assessed the pre-operative imaging appearance of pediatric malignant ovarian germ cell tumors (MOGCT) and the presence of associated teratoma in a series of MOGCT.
Design: Retrospective review of clinical and pathology data.
Setting: Multicenter trial for extracranial malignant germ cell tumors in young female individuals by the Children's Oncology Group (COG study AGCT0132) that included yolk sac tumor, embryonal carcinoma and choriocarcinoma.
Participants: Female individuals 0-20 years of age at enrollment with ovarian primary nonseminomatous malignant germ cell tumors.
Interventions: Review of data forms, including prospectively collected surgical checklist documenting imaging characteristics of the tumor, and review of pathology reports.
Main Outcome Measures: Description of imaging appearance and frequency of mixed histology with benign teratoma elements.
Results: A total of 138 female individuals (11 months to 20 years of age) had primary ovarian tumors. Imaging appearance and pathology information were available for 133 patients. Among the 133 patients, tumor appearance was solid (10.5%), solid with calcification (3.0%), mixed cystic and solid (58.7%), mixed cystic and solid with calcification (24.8%), and unknown (3.0%). In all, 54% had elements of teratoma in addition to malignant histology.
Conclusion: Mixed cystic and solid appearance with or without calcification was seen in 83.5% of pediatric ovarian malignant germ cell tumors. Associated benign teratoma was common. The presence of a mixed cystic and solid appearance on preoperative imaging should not dissuade the surgeon from obtaining preoperative serum markers and undertaking complete surgical staging.
Key Words: Ovarian germ cell tumors, Ovary yolk sac tumor, Teratoma

Ovarian masses are encountered at all ages in childhood and adolescence. In neonates, these masses are almost exclusively follicular cysts due to maternal hormone influence, and most can be managed nonoperatively.[1] Simple cysts beyond the neonatal period may present with pain due to hemorrhage or torsion, but are clearly recognized by their simple wall, unilocular appearance, and absence of any solid components. True neoplastic lesions account for approximately 73% of masses, and 16-22% of these are malignant.[2,3] Because the majority of neoplastic lesions are benign teratomas (also called dermoid cysts) that have a mixed cystic and solid appearance and that frequently have calcifications, surgeons may assume that this finding on imaging indicates a benign tumor. This leads to incomplete staging if a malignant tumor is present, and may affect the subsequent need for chemotherapy.

Recent attention has been focused on imaging characteristics that are predictive of malignancy, but non-neoplastic simple cysts are often included in these series and will have an impact on the risk predictor calculations. Diameter greater than 9 cm and solid appearance have been predictive of malignancy in recent pediatric series of ovarian masses, but they have included simple cysts in the calculations. In addition, these reports are based on case series of ovarian masses from single institutions, so the actual number of malignant cases is very small and the size cutoff is not absolute.[2,4,5] Once simple cysts are excluded, the important dilemma is whether or not a neoplastic lesion

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* *Address correspondence to:* Deborah F. Billmire, MD, Division of Pediatric Surgery, Riley Hospital for Children, Suite 2500, 705 Riley Hospital Drive, Indianapolis, IN 46202. Phone: (317) 274-4682; fax: (317) 274 4461
E-mail address: dbillmir@iupui.edu (D. Billmire).

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may be malignant. The size range and imaging appearance of pediatric malignant ovarian germ cell tumors is unknown. This review was undertaken to summarize the preoperative ovarian imaging findings in the Children's Oncology Group study AGCT0132 of all of the enrolled ovarian malignant germ cell tumors in female pediatric and adolescent patients.

Materials and Methods

The Children's Oncology Group study AGCT0132 for malignant extracranial germ cell tumors enrolled patients between November 2003 and July 2011. Details have been reported elsewhere.[6–8] Data for this analysis are current to June 30, 2018. Required histology included yolk sac, embryonal carcinoma, or choriocarcinoma. Pure germinoma and pure immature teratoma were not eligible. Low-risk (stage I gonadal) patients were treated with surgery, and surveillance with chemotherapy was reserved for relapse. Intermediate-risk (stage I-III extragonadal, stage II-IV testicular, stage II-III ovarian) patients were treated with chemotherapy in addition to surgery.

Primary ovarian malignant germ cell tumors were seen in 138 patients: 29 low risk (stage I) and 109 intermediate risk (stages II and III). A surgical checklist was required at enrollment for all patients. The ovarian surgical checklist included a request for the institution to provide an imaging description of the tumor as one of the following: purely cystic, cystic with calcifications, purely solid, solid with calcifications, mixture of solid and cystic components, mixture of solid and cystic components with calcifications, or unknown. Unknown appearance category was needed for those without preoperative imaging or with a procedure done at an outside institution without submission of preoperative imaging. The surgical checklists and institutional and central review pathology reports were reviewed to evaluate imaging characteristics and histology for patients with ovarian germ cell tumors.

Results

Completed surgical checklists, operative notes, and pathology reports were available for 133 of 138 patients with characteristics summarized in Table 1 and form the basis for this review. Four intermediate-risk patients and 1 low-risk patient did not have a surgical checklist submitted and could not be included. As the study design excluded pure germinoma and as there were no pure embryonal carcinomas, all patients had elevated tumor markers at diagnosis. Alpha-fetoprotein (AFP) was measured in all patients (median: 3394.5 ng/mL; range: 2–4,233,000 ng/mL) as well as beta human choriono-gonadotrophin (BHCG) (median: 2 mIU/mL, range: 0–999,140 mIU/mL). The imaging appearance according to the surgical checklists is described in Table 2. No patients had purely cystic tumors with or without calcification. Overall, 58.7%% of the patients had an imaging appearance that was a mixture of solid and cystic components, and 24.8% had a mixture of solid and cystic components with calcification. A total of 72 patients (54%) had mixed histology that included teratoma (mature or immature) along with malignant histology (Table 3). Maximal tumor dimension ranged from 5.5 to 33.5 cm, with a median of 16 cm.

Discussion

This study was undertaken to evaluate the imaging characteristics of malignant nongerminoma ovarian germ cell tumors in pediatric and adolescent patients to determine whether there were distinguishing features that could aid in preoperative discussion and planning of the operation. We found that over 80% had a mixed cystic and solid appearance, which could easily be seen in a mature teratoma. We also noted that associated elements of benign teratoma were common and were seen in more than half of the patients.

Ovarian masses in the pediatric age group are somewhat uncommon and have an overall risk of malignancy of 10-15%. A recent paper[5] reviewed the imaging and marker characteristics of ovarian masses from 2 free-standing pediatric institutions. They included all ovarian masses in patients less than 18 years of age who were undergoing surgical management of ovarian masses. That series included 185 patients, with malignancy found in 11%. Imaging findings in their series revealed simple cysts in 24 (12.9%), solid masses in 34 (18.3%), and heterogeneous masses in 127 (68.6%). They did not distinguish whether calcification was present. All of the simple cysts were benign. Our series of exclusively malignant germ cell tumors also found no simple cysts on imaging. If the simple cystic lesions are excluded from the above series, then the distribution of solid and heterogeneous appearance was 34 of 158 (21.5%) solid tumors and 127 of 158 (80.3%) heterogeneous masses. This distribution of imaging appearance is similar to that in our series of patients with malignant germ cell tumors, in whom we noted 13.5% solid and 84.9% heterogeneous (mixed) masses. In addition, although risk

Table 1
Characteristics of 138 Girls With Primary Ovarian Tumors COG Stage I-III

Patient Characteristic	N (%) or Median (Range)
Age at enrollment (Month)	153 (11-245)
AFP (ng/mL)	3394.5 (2-4233000)
BHCG (mIU/mL)	2 (0-999140)
Tumor Diameter (cm)	16 (5.5-33.5)
COG Stage	
I	29 (21.0%)
II	47 (34%)
III	62 (44.9%)

Table 2
Summary of Imaging Appearance of Ovarian Tumor for the 133 Patients With Surgical Review

Appearance	N (%)
Cystic	0 (0%)
Cystic with calcification	0 (0%)
Solid	14 (10.5%)
Solid with calcification	4 (3.0%)
Mixed cystic and solid	78 (58.7%)
Mixed cystic and solid with calcification	33 (24.8%)
Unknown	4 (3.0%)

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Table 3
Frequency of Teratoma Elements by Imaging Appearance of Ovarian Tumor for the 133 Patients With Surgical Review

GCT Component(s)	Appearance				
	Solid N = 4	Solid with Calcification N = 4	Mixed N = 78	Mixed with Calcification N = 33	Unknown N = 4
Malignant GCT alone	11	2	42	4	2
Malignant GCT with					
Mature teratoma	1	2	18	18	1
Immature teratoma	3	0	26	21	2
Malignant GCT with any teratoma*	3/14	2/4	36/78	29/33	2/4

* Any T includes those tumors with any element of mature or immature teratoma as some had both types present.

factors for malignancy included size greater than 9 cm in greatest dimension, the malignant tumors in this series ranged in size from 5.5 to 33.5 cm. These results indicate that imaging characteristics and size alone do not differentiate benign from malignant ovarian masses. It was disappointing to note on review of the operative notes in this series that there were several instances in which the surgeon commented that the mass appeared to be classic for teratoma and/or failed to do full tumor staging. Mention of preoperative tumor markers was seldom included in the operative notes. It should also be noted that not all malignant germ cell tumors will have elevated serum markers. In all instances, ovarian masses that are not simple cysts should be approached with caution, and preoperative investigation including tumor markers must be completed. Full pediatric surgical staging should always be undertaken for ovarian masses, regardless of tumor marker findings.

Ovarian masses in the pediatric and adolescent age group are managed by a variety of surgical specialists. These factors make the experience for any individual surgeon limited both by experience and by training, and contribute to the failure to undertake complete surgical staging at the primary procedure. The finding of cystic areas or calcifications on preoperative imaging may lead to the assumption that the mass is a benign teratoma, and a limited procedure may be done. Malignancy is not discovered until the pathology has been assessed and the opportunity for appropriate staging has been lost. The increasing and appropriate emphasis on ovarian-sparing procedures to protect fertility in this age group has led to attempts to risk stratify for malignancy based on preoperative assessment. Recent reviews of single-institution series of ovarian masses in children have evaluated preoperative tumor marker and imaging findings to aid in risk stratification of malignancy. As none of these classifications are 100% sensitive or specific, there is a possibility of under-staging by omitting required steps, or of up-staging by deliberately violating the tumor capsule of a malignant ovarian tumor during the surgical procedure. As an example, failure to collect peritoneal fluid or to do a complete assessment of the peritoneal cavity may lead to missed pathology. In the previous Pediatric Oncology Group/Children's Cancer Study Group (POG/CCSG) intergroup study that formed the basis for the revised COG guidelines, 5 patients with otherwise stage I tumors were accurately recognized to be stage III based on peritoneal cytology alone, confirming the importance of complete assessment.[9] Furthermore, surgical technique aimed at reducing mass size by planned puncture, or by an accidental capsule entry or rupture during manipulation for a presumed benign lesion, will upstage a patient who might otherwise be a candidate for surgery and surveillance. Laparoscopic enucleation of ovarian masses has been shown to result in a higher rupture rate of the lesion than open technique.[10]

The current pediatric surgical ovarian germ cell tumor guidelines used by the Children's Oncology Group (COG) were published in 2004.[9] Despite their simplicity, compliance with the guidelines remains a significant problem. A 15-year retrospective study by Oltmann et al in 2010[4] revealed only 24% compliance with COG guidelines, and a similar 22-year retrospective study by Madenci et al in 2016[11] showed only 27% compliance with guidelines, without any change in performance after the 2004 guidelines were published. The pediatric guidelines are less extensive than the adult FIGO guidelines in terms of tissue sampling, but remain critical in accurate assessment and treatment planning. Inspection and documentation of all defined parameters in the operative note are absolute requirements for confirmation of stage I status and the possibility that a surveillance strategy, rather than chemotherapy, can be recommended. “Not documented” has to be considered as not having been done. In the surgery and surveillance arm of the AGCT0132 study for stage I ovarian tumors, relapse occurred in 9 of 21 patients who were confirmed as stage I by central review; but relapse was seen in 3 of 4 patients who were assigned as stage I by the enrolling institution but had incomplete staging on central review.[6] Overall survival for the stage I tumors was 96% at 4 years.

A limitation of this study is the inclusion of only malignant nongerminoma ovarian tumors. A strength of this study is the large number of malignant tumors with prospectively documented imaging appearance that could not be obtained in a single-institution review.

It is recommended that all pediatric and adolescent ovarian neoplasms be approached with the concern that malignant histology may be present, regardless of tumor size or appearance, and that the COG guidelines for staging be completed. The guidelines include collection of peritoneal fluid for cytology, inspection and documentation of omentum, peritoneal surfaces, lymph nodes and opposite ovary. Biopsy of any abnormal findings is required. The tumor should be removed without violation of the tumor capsule in the peritoneal cavity. These tasks are easily accomplished in all patients with minimal expenditure of time and little to no morbidity. Preoperative computed

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tomographic imaging provides guidance to aid in identifying suspicious, enlarged nodes that should be biopsied. A low yield of positive peritoneal cytology should be expected,[12] but the information is of high importance. A laparoscopic approach does not preclude the steps of the staging procedure, and inspection of the peritoneal surfaces may even be more easily accomplished. The ovarian mass should be excised with care to avoid rupture of the tumor capsule. Tumors with elevated markers should be treated with oophorectomy. Tumors with negative markers may be considered for an ovary-sparing approach but complete performance and documentation of the staging procedure is imperative and should always be done. Care should be taken to minimize the risk of tumor spill when excising the mass from the ovarian parenchyma, as this not only upstages malignant tumors but also increases the risk of recurrence for benign teratomas.[10]

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