Preoperative risk stratification of children with ovarian tumors☆,☆☆

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ARTICLE INFO

ABSTRACT

Background: The appropriate operative approach to pediatric patients with ovarian tumors must balance real risk of malignancy with maximal preservation of reproductive potential. We evaluate preoperative risk of malignancy in order to more precisely guide treatment, so as to err on the side of ovarian preservation if at all possible.
Methods: We retrospectively reviewed the records of all patients undergoing surgical intervention for ovarian tumors at a single institution. The primary endpoint was ovarian malignancy.
Results: Of 502 patients who underwent surgery for ovarian tumors, 44 (8.8%) had malignancies. Malignancy rate (95% confidence interval) was low for cystic lesions <9 cm (0.0%, 0.0–2.9%) and for tumor marker-negative heterogeneous lesions <9 cm (2.3%, 0.4–12.1%). High-risk profiles for malignancy included tumor marker-positive heterogeneous lesions (66.7%, 35.4–87.9%) and solid tumors ≥9 cm (69.2%, 16.2–40.3%). Intermediate risk tumors included cystic tumors ≥9 cm (6.8%, 3.5–20.7%), tumor marker-negative heterogeneous lesions ≥9 cm (31.2%, 18.0–48.6%), and solid tumors <9 cm (11.1%, 4.4–25.3%).
Conclusions: We developed a decision strategy to help determine who may and may not require an ovarian-sparing approach, which warrants prospective application and validation. Ultimately, the decision to pursue an oncologic surgery with oophorectomy and staging (as opposed to fertility-preserving surgery) should be made after individualized discussion involving the surgeon, patient, and family.

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The management of pediatric and adolescent ovarian lesions must carefully balance maximal preservation of reproductive potential with adequate intervention to address the real risk of malignancy. However, because preoperative malignancy status is typically unknown, appropriate operative management often presents a conundrum. Rate of cystectomy (vs. oophorectomy) varies widely with physician specialty, among other factors [1]. Imagine an adolescent patient who presents to her pediatrician with abdominal pain. Ultrasonography reveals a 10 cm, complex unilateral ovarian mass. Tumor markers are found to be negative. In this setting, she is referred to one of three physicians for surgical evaluation: a pediatric surgeon, pediatric gynecologist, or adult gynecologist. With this identical vignette, she may be exposed to any of the following 'correct' interventions: (1) exploratory laparotomy with unilateral salpingo-oophorectomy and staging procedures per Children's Oncology Group (COG) guidelines [2]; (2) ipsilateral ovarian-sparing procedure with tumor enucleation/"cystectomy" (laparoscopic or open); or (3) a combination of the two procedures. Ultimately, the role of an ovarian-sparing procedure as compared with an oncologic surgery will depend on physician and patient comfort with projected oncologic risk, which is often not obvious at patient presentation. This variation in care behooves a collaborative effort between all specialties treating pediatric and adolescent ovarian lesions to improve patient quality of life and preservation of fertility while advancing evidence-based standards of care. As such, the preoperative determination of oncologic risk in this cohort must be precise to appropriately guide treatment. Determining this risk will inform operative management strategy (ovarian preservation versus oncologic procedures), so as to err on the side of ovarian preservation if at all possible in light of an historical metachronous ovarian tumor rate of nearly 20% in these patients [3]. In this study, we leverage preoperative risk factors to estimate a priori risk of malignancy.

1. Methods

1.1. Patient population

We retrospectively reviewed the records of all patients who underwent surgical intervention for ovarian tumors between January 1995 and December 2012 at Boston Children's Hospital. All patients with ovarian pathology specimen(s) were included. Patients diagnosed with Turner syndrome or androgen insensitivity syndrome were excluded from the analysis. Each surgery was performed by one of 32 board-certified pediatric general surgeons or gynecologists. Imaging characteristics were obtained by ultrasound, computed tomography, or magnetic resonance imaging. Ovarian lesions were defined, based on imaging characteristics, as predominantly cystic, predominantly solid, or heterogeneous.

1.2. Statistical analysis

The primary endpoint was ovarian malignancy, defined by final pathological interpretation. Patient demographics, presentation characteristics, preoperative laboratory values, perioperative data, and outcomes were collected. A lesion was considered to be "incidental" if the patient was asymptomatic and it was identified on imaging without prior suspicion. Univariable associations were assessed using the Chi square or Fisher's exact test for categorical variables and using the Mann–Whitney U test for continuous variables. Wilson's method without continuity correction was used to calculate 95% confidence intervals of proportions [4]. In order to determine the optimal threshold to discriminate malignancy (optimal operating point) for the continuous variables, age and tumor size, we identified the value for each that maximized the Youden index (J), a summary statistic based on receiver operating characteristic curves that equally weights sensitivity and specificity (sensitivity + specificity − 1) [5]. Patients with missing data were excluded from each respective analysis. A two-tailed P value <0.05 was considered statistically significant. All data were analyzed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

2. Results

Five hundred two patients underwent surgical interventions that included complete or partial oophorectomy during the study period. Forty-four (8.8%) tumors were malignant. The most common malignant diagnoses were immature teratomas (20.5%, n = 9) and granulosa cell tumors (18.2%, n = 8). Of the 458 benign tumors, 45.4% (n = 208) were mature teratomas. Among patients with benign ovarian lesions, 24% (n = 111) underwent complete unilateral oophorectomy. The remainder underwent partial oophorectomy, including cystectomy. Among patients postoperatively found to have functional cysts, 15.0% (16/107) underwent complete unilateral oophorectomy. Of patients treated by a pediatric surgeon, 62.1% (95/177) underwent oophorectomy, compared with 37.9% of patients treated by a pediatric gynecologist (58/321, P < 0.01). Patients treated by pediatric surgeons were more likely to have malignant lesions (56.8%, 25/177), compared to pediatric gynecologists (43.2%, 19/321, P < 0.01). Histopathological subtypes are displayed in Tables 1A and 1B, respectively.

The median age at intervention was 14.6 years (range, 0–24.9) and did not significantly differ by malignancy status ($P = 0.63$). Patients presenting with a mass or symptomatic abdominal distention were more likely to have malignant tumors ($P < 0.01$), while incidentally-discovered tumors were more likely to be benign ($P < 0.01$). Ovarian torsion afflicted 23.9% of patients (n = 120). Patients with benign tumors were more likely to have ovarian torsion identified intraoperatively (25.5%, n = 117), compared to patients with malignant tumors (6.8%, n = 3, P < 0.01).

Median tumor diameter was 7.8 cm (range, 1.0–42.0) and increasing tumor size was significantly associated with malignancy ($P < 0.01$). The

optimal tumor size threshold for discriminating malignancy was 9 cm, based on receiver operating characteristic curves. Forty-three percent (n = 184) of tumors were ≥9 cm in diameter ("large"). Of these large tumors, 19.6% (36/184) were malignant. Eighty-six percent (n = 36) of malignant tumors were large, compared with 38.3% (n = 148) of benign tumors ($P < 0.01$). Results were similar when using tumor diameter-to-age ratio. On preoperative imaging, noncystic lesions were associated with malignant pathology ($P < 0.01$).

Elevation of each of the following laboratory tests was associated with malignancy: beta-hCG, alpha-fetoprotein, CA-125, inhibin A, LDH, platelets, or WBC (Table 2). Owing to the limitations of this retrospective review, not all patients had each tumor marker test analyzed. An overview of preoperative characteristics and their associations with malignancy is displayed in Table 2.

In practice, imaging is typically obtained as the next evaluative step after history, physical examination, and routine laboratory tests. Therefore, we stratified patients into cystic, heterogeneous, and solid imaging profile cohorts. A decision strategy for each cohort, based on tumor size and tumor markers is displayed in Fig. 1A–C. Among patients with cystic lesions, the malignancy rate among tumors <9 cm was 0.0% (95% confidence interval [CI], 0.0–2.9%). Among patients with cystic tumors ≥9 cm, the malignancy rate was 6.8% (95% CI, 3.5–20.7%). These malignant tumors included three granulosa cell tumors, three borderline carcinomas, one immature teratoma, and one sex-cord stromal tumor. The presence or absence of tumor markers did not significantly change these proportions, as no patient with malignant large cystic tumors had positive tumor markers.

Patients with heterogeneous lesions and positive tumor markers (i.e. alpha-fetoprotein and beta-hCG) were found to have a 66.7% (95% CI, 35.4–87.9%) malignancy rate. For those patients with unavailable or not performed tumor markers, the malignancy rate was 8.9% (3.5–20.7%). Finally, patients with heterogeneous lesions and negative tumor markers were further stratified by tumor size. Patients with nonlarge (<9 cm) tumors had a malignancy rate of 2.3% (95% CI, 0.4–12.1%). Conversely, patients with heterogeneous lesions, negative tumor markers, and large (≥9 cm) tumors had a malignancy rate of

Table 1A
Distribution of 44 malignant ovarian tumors.

Category	Number (%)
Malignant germ cell tumor	
Immature teratoma	9 (20.5)
Dysgerminoma	8 (18.2)
Nondysgerminoma with malignant components	6 (13.6)
Sex cord stromal tumors	
Granulosa cell	8 (18.2)
Sertoli-Leydig	4 (9.1)
Mixed	2 (4.5)
Carcinoma/borderline tumors	7 (15.9)

Table 1B
Distribution of 458 benign ovarian lesions.

Category	Number (%)
Dermoid	208 (45.4)
Functional cyst	108 (23.6)
Cystadenoma	73 (15.9)
Gonadal dysgenesis	17 (3.7)
Endometrioma	14 (3.1)
Fibroma	13 (2.8)
Infarcted ovary	12 (2.6)
Histopathologically normal ovary	6 (1.3)
Tubo-ovarian abscess	2 (0.4)
Benign sclerosing stromal tumor	1 (0.2)
Microcalcifications	1 (0.2)
Nodular tissue	1 (0.2)
Papilloma	1 (0.2)
Sex cord tumor like structures	1 (0.2)