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

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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 which patients may or may not benefit from an ovarian-sparing approach. This proposed strategy 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.

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.

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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 specimens 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)

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Table 2
Baseline characteristics of 502 patients with ovarian tumors.

Variable	*Overall*	*Benign*	*Malignant*	*P*
n (%)	502 (100.0)	458 (91.2)	44 (8.8)	
Age at surgery, years	14.6 (11.2–16.9)	14.5 (11.3–16.9)	14.7 (8.1–16.5)	0.63
Age ≥ 9 years at surgery	411 (82.2)	379 (92.2)	32 (72.7)	0.08
Caucasian race	321 (63.9)	287 (62.7)	34 (77.3)	0.05
Presentation				
Pain	277 (57.9)	252 (58.1)	25 (56.8)	0.87
Nausea/vomiting[a]	112 (23.4)	107 (24.7)	5 (11.4)	0.05
Mass/distention[a]	55 (11.5)	36 (8.3)	19 (43.2)	<0.01
Incidental[a]	132 (27.7)	128 (29.6)	4 (9.1)	<0.01
Prenatal	10 (2.1)	10 (2.3)	0 (0.0)	0.61
Presentation site				0.16
Gynecology	121 (29.4)	113 (30.4)	8 (20.5)	
ER	168 (40.9)	153 (41.1)	15 (38.5)	
PCP	101 (24.6)	86 (23.1)	15 (38.5)	
Other	21 (5.1)	20 (5.4)	1 (2.6)	
Premenarchal	74 (37.2)	67 (36.8)	7 (41.2)	0.72
Age at menarche	12.0 (11.0–13.0)	12.0 (11.0–13.0)	12.0 (11.0–13.0)	0.66
Tumor size, cm[a]	7.8 (5.2–12.8)	7.4 (5.0–11.2)	14.0 (10.0–20.0)	<0.01
Large (≥9 cm)[a]	184 (43.0)	148 (38.3)	36 (85.7)	<0.01
Noncystic imaging profile	178 (41.5)	144 (37.2)	34 (80.9)	<0.01
Side[a]				0.05
Left	195 (39.2)	172 (38.0)	23 (52.3)	
Right	242 (48.7)	222 (49.0)	20 (45.5)	
Bilateral	60 (12.1)	59 (13.0)	1 (2.3)	
Positive laboratory test				
+ β-hCG or α-FP, n = 389[a]	21 (5.4)	8 (2.3)	13 (35.1)	<0.01
+ β-hCG, n = 385[a]	6 (1.6)	2 (0.6)	4 (10.8)	<0.01
+ α-FP, n = 246[a]	18 (7.3)	6 (2.8)	12 (35.3)	<0.01
+ CA-125, n = 134[a]	8 (6.0)	4 (3.3)	4 (28.6)	<0.01
+ Inhibin A, n = 58[a]	2 (3.5)	0 (0.0)	2 (40.0)	<0.01
+ Inhibin B, n = 40	3 (7.5)	2 (5.4)	1 (33.3)	0.21
+ LDH, n = 221[a]	3 (1.4)	0 (0.0)	3 (9.7)	<0.01
+ Platelets, n = 358[a,b]	105 (29.3)	88 (27.2)	17 (48.6)	<0.01
Torsion, n = 95	36 (37.9)	34 (37.0)	2 (66.7)	0.55
Nontorsion, n = 260[a,b]	69 (26.5)	54 (23.6)	15 (48.4)	<0.01
+ WBC, n = 358[a]	137 (38.3)	116 (35.9)	21 (60.0)	<0.01
Torsion, n = 63	63 (64.3)	60 (63.2)	3 (100.0)	0.55
Nontorsion, n = 257[a]	73 (28.4)	55 (24.3)	18 (58.1)	<0.01
Follow-up, months	4.5 (0.6–32.3)	3.7 (0.6–26.8)	37.0 (10.1–55.0)	<0.01

Data reported as number (%) or median (interquartile range). α-FP, alpha-fetoprotein; β-hCG, beta human chorionic gonadotropin; CA-125, cancer antigen 125; LDH, lactate dehydrogenase; WBC, white blood cells.

[a] $P < 0.05$.

[b] Stratified into torsion and nontorsion to account for WBC and platelet role as acute phase reactants.

31.2% (95% CI, 18.0–48.6%). These malignancies included four immature teratomas, three borderline carcinomas, two juvenile granulosa cell tumors, and one dysgerminoma.

Last, the malignancy rate among patients with solid tumors was 26.5% (95% CI, 16.2–40.3%). Large solid tumors were malignant in 69.2% (95% CI, 42.4–87.3%) of cases. The malignancy rate among solid, nonlarge tumors was 11.1% (95% CI, 4.4–25.3%). Among these nonlarge, solid tumors, tumor marker status was not significantly associated with malignancy ($P = 0.99$) and those nonlarge, solid tumors with negative tumor markers had a similar malignancy rate of 10.0% (95% CI, 3.5–25.6%).

3. Discussion

For children with ovarian tumors, the decision to pursue oncologic surgery, fertility-preserving surgery, or watchful waiting should be made after an individualized discussion involving the surgeon, patient, and family. We report a 24% occurrence of oophorectomy for benign disease; proportions as high as 75% are reported in the literature [6]. In these cases, the use of oophorectomy likely stems from the small, but real, risk of underlying malignancy (8.8% in the present study), which ranges from 6% [7] to 64% [8] depending on patient population and referral patterns [9].

As such, nationwide surgical management of ovarian lesions varies with demographic, hospital, and physician factors. In a 2012 study of more than 2000 adolescent patients with benign ovarian masses in a nationwide commercial database, Berger-Chen and colleagues report that African American patients, patients in the Northeast, and patients treated in low-volume hospitals were less likely to undergo laparoscopy (vs. open resection) [1]. Surgeon specialty substantially affects the operation as well. Retrospective analyses demonstrate that the presence of a gynecologic oncologist confers a significantly higher rate of complete surgical staging [10] and ovarian-sparing surgery [11], compared with a pediatric general surgeon. We likewise found that pediatric general surgeons were significantly more likely to perform oophorectomies than gynecologists.

These differences may partly be attributed to referral patterns. For example, in the present study we note a significantly higher proportion of ovarian malignancies treated by pediatric general surgeon specialty (vs. gynecology). Another possible explanation is that the technique of ovarian cystectomy for large ovarian masses [12] may be more familiar to gynecologists than to pediatric surgeons. Because the oocytes reside in the thinned out cortex, it has been shown that the ovary can be preserved with this technique. Furthermore, it is common gynecologic practice to treat patients who have negative tumor markers with a "controlled" ovarian cystectomy. This procedure avoids spillage of potential malignant cells and is performed via an open procedure with exteriorization of the mass and the use of laparotomy pads to adsorb any potential spillage [13]. Such variability underscores the need for treatment guidelines. The operation for an ovarian tumor should depend more

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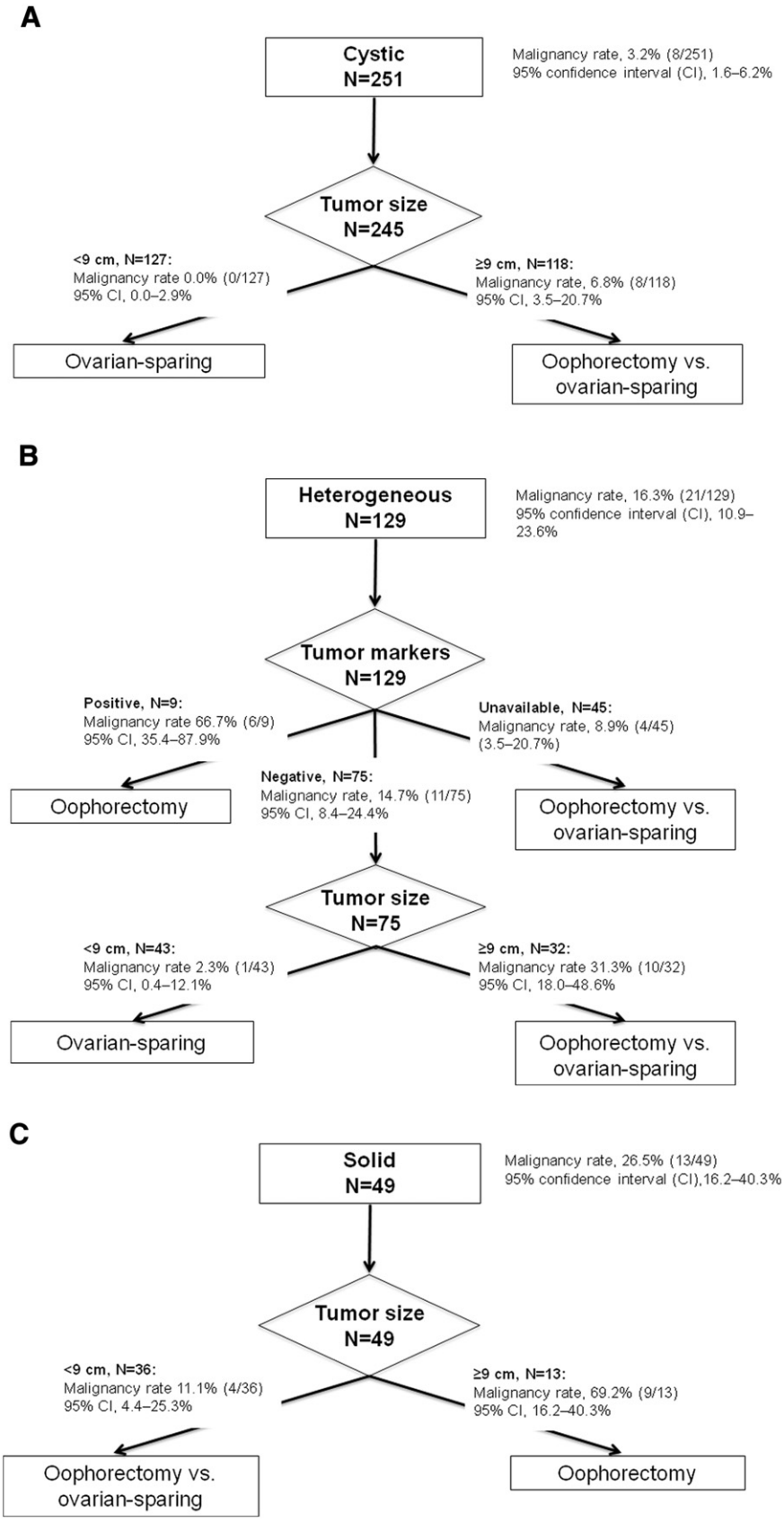

Fig. 1. A. Preoperative risk stratification of radiographically cystic ovarian lesions. B. Preoperative risk stratification of radiographically heterogeneous ovarian lesions. C. Preoperative risk stratification of radiographically solid ovarian lesions.

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on tumor characteristics and informed patient family preference, than on surgeon specialty, hospital location, and patient demographics.

The optimal balance between maximal oncologic surgery and fertility-preserving surgery is especially problematic because, in addition to a lack of preoperative guidelines based on tumor characteristics and laboratory values, the long-term consequences on fertility of unilateral oophorectomy are unknown. In a recent survey study by Zhai and colleagues, gonadal function estimated by menstrual regularity was suggested not to be impaired following oophorectomy compared with ovarian salvage [14]. This finding coincides with literature showing no reduction in pregnancy rates after achieving the stage of embryo transfer among women with a single ovary, compared to women with both ovaries [15]. Finally, a cohort study comparing women who underwent unilateral oophorectomy with those who underwent appendectomy or cholecystectomy documented no statistically significant difference in 10-year postoperative fertility between groups [16].

Initially, these findings might suggest liberal use of oophorectomy for ovarian tumors. However, such a policy of categorical oophorectomy for ovarian masses would leave an undesirably high proportion of patients agonadal because of metachronous lesions. In our study, 5% of patients experienced recurrence of benign tumors after a median follow-up duration of nine months, similar to rates reported in the literature of 14% [17] and 18% [3] at three and eight years after surgery, respectively. Furthermore, evidence at the hormonal level points to potential gonadal impairment after unilateral oophrectomy. van Dorp and colleagues report decreased serum levels of anti-Mullerian hormone (a marker of ovarian reserve) among childhood cancer survivors with unilateral oophorectomy compared to no prior oophorectomy [18]. Women who have undergone unilateral oophorectomy have been shown to have a decreased response to ovarian induction with human menopausal gonadotropins, compared to women without prior oophorectomy [11]. At the epidemiologic level as well, women with single ovaries attend infertility clinics more frequently compared with the general population [11]. Given the potential implication for childbearing later in life and the many years before which metachronous lesions may occur, ovarian tumors with low risk of malignancy warrant fertility-preserving surgery whenever possible.

Most surgeons aspire to preserve fertility to as great an extent as possible. The variability described above largely stems from an inability to preoperatively differentiate patients with benign lesions from those with malignancies. Based on our analysis of 502 patients with ovarian tumors, we proposed situations based on imaging characteristics and tumor marker status in which (1) malignancy risk is high and oophorectomy may be recommended, (2) malignancy risk is low and oophorectomy is unwarranted, and (3) malignancy risk is intermediate. For each recommendation, provider–patient discussion is imperative.

Cystic tumors (3.3% malignancy rate) were less likely to be malignant than those heterogeneous (16.3%) or solid (26.5%). The link between noncystic imaging characteristics and tumor size with malignancy is well-supported in the literature [8,19–21]. Although cystic appearance is reassuring, a 2004 multicenter study by the Pediatric Oncology Group and Children's Cancer Study Group report that 57% of ovarian malignancies likewise contain gross cystic components [2], implying the need for caution when employing any single preoperative risk factor.

Among patients with small (<9 cm) cystic lesions, the malignancy rate in our cohort was 0% and, as such, serial imaging or ovarian-sparing surgery with cystectomy may be pursued. The situation is more complex for large (≥9 cm) cystic tumors, which carry an intermediate rate of malignancy (6.8%). In our study, tumor marker status was not significantly associated with malignancy in large cystic tumors, as no patient with malignant large cystic tumors had positive tumor markers. Given their size, these larger tumors are unlikely to spontaneously resolve [22]. It may be possible to stratify this group further using more specific radiographic findings. For example, half of the large and predominantly cystic tumors that were found to be malignant had small solid foci on imaging. However, identifying the nuanced radiographic features associated with malignancy extended beyond the scope of this study. As a result, it is most prudent for the group of patients with large (≥9 cm) cystic tumors to undergo counseling. The decision to undergo an ovarian-sparing or oncologic procedure should be individual, until further information becomes available. Furthermore, it is important to consider the option of a second look procedure if surgical pathology were to unexpectedly return as positive for malignancy. Such a strategy may maximally preserve fertility for patients with moderate or indeterminate preoperative risk of malignancy. However, this benefit must be tempered by the potential missed opportunity for surveillance of stage I disease: among patients with positive margins after partial oophorectomy (who would otherwise have had stage I disease if an oncologic surgery had been performed), chemotherapy would be required after completion oophorectomy.

For patients with heterogeneous ovarian tumors, tumor marker status was a useful decision point. The malignancy rate of tumor marker-positive heterogeneous tumors was 66.7%. Given the well-substantiated relationship between alpha-fetoprotein and beta-hCG and malignancy, unilateral oophorectomy and surgical staging per COG guidelines is warranted [2].

Patients with negative tumor markers were subdivided into those with nonlarge (<9 cm) and large (≥9 cm) tumors. Among tumor marker negative patients with nonlarge tumors, the malignancy rate was 2% and oophorectomy is unnecessary. In contradistinction, 31.3% of tumor marker-negative large heterogeneous tumors were malignant (most commonly immature teratomas). These lesions warrant caution and a discussion of the risks and benefits of each surgical option. For individualized patients with negative tumor markers and large, heterogeneous tumors, ovarian-sparing surgery with a laparotomy and "controlled" cystectomy may be acceptable. For example, the presence of a "dermal plug" on ultrasound may potentially be reassuring for a benign process even in a large heterogeneous mass [23].

Solid lesions were the highest risk category, with an overall malignancy rate of 26.5%. This rate was slightly lower than the 43% (n = 6/14) [19] and 100% (n = 8/8) [20] reported in the literature for solid ovarian tumors. A policy of categorical oophorectomy with solid tumors, while not unreasonable, would miss the opportunity for fertility-preserving surgery among patients who have mature teratomas. Nonlarge solid tumors had an 11.1% malignancy rate. Negative tumor markers did not indicate a substantially lower malignancy rate (10.0%). Especially in such cases of nonlarge solid tumors, an informed discussion with the patient and her family is indispensable.

There were several limitations to our findings. There was elevated potential for bias by confounding because of the retrospective study design. Additionally, the sample size of patients with malignancy was relatively small and may have underpowered the statistical analysis. The preferences of individual providers may have led to more or less extent of surgery and other differences in clinical management. We expect that these differences in clinical decision making would be nondifferential and, thus, bias the results toward the null. Certain specific imaging characteristics have been developed to help distinguish between ovarian tumors [24–26]. It was not possible to retroactively apply such radiographic criteria to our retrospective cohort, especially because original images were not always available. In future investigation, we plan to continue to work with radiologists at our institution in order to determine and validate high- and low-risk tumor characteristic with the goal of sparing patients from oophorectomy when able. In our decision strategy, we included alpha-fetoprotein and beta-hCG as tumor markers, because these were the most pervasively used tests over the time period of the study. In the future, other tumor markers, such as inhibin A, inhibin B, and CA-125, may become more useful in discriminating malignant from benign lesions. In order to avoid bias that would occur by excluding patients without availability of tumor markers, we included a category of no tumor marker drawn in our decision analysis. Similarly, we did not exclude patients who presented with torsion, although their presentation and timing of management differs greatly

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from patients who did not present with torsion. We did not conduct a subset analysis of patients who presented with ovarian torsion because the small sample size was prohibitive. Finally, the above decision strategy was derived from a large cohort of children with ovarian tumors, but has not yet been validated. The prospective application of the preoperative risk stratification outlined above is an opportunity for future research.

In summary, we have defined a risk stratification system for children with ovarian masses, based on preoperative laboratory values and tumor characteristics. These findings may provide a framework for surgeons who encounter ovarian masses. Ultimately, the decision to pursue a fertility-preserving or an oncologic (oophorectomy with staging) surgery depends on individualized discussion involving the surgeon, patient, and family.

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