Journal of Pediatric Surgery 54 (2019) 1921–1925

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Multicenter pre-operative assessment of pediatric ovarian malignancy☆,☆☆

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ARTICLE INFO

Article history:
Received 20 July 2018
Received in revised form 13 February 2019
Accepted 17 February 2019

Key words:
Oophorectomy
Ovarian neoplasms
Ovarian cysts
Ovarian diseases
Fertility

ABSTRACT

Purpose: The purpose of this study was to develop a pre-operative risk assessment tool for childhood and adolescent ovarian malignancy, in order to guide operative management of pediatric ovarian masses.
Methods: We conducted a retrospective analysis of patients <18 years old who underwent ovarian surgery at two quaternary care pediatric centers over 4 years (1/1/13–12/31/16). Probability of malignancy was estimated based on imaging characteristics (simple cyst, heterogeneous, or solid), maximal diameter, and tumor markers (α-fetoprotein, β-human chorionic gonadotropin).
Results: Among 188 children with ovarian masses, 11% had malignancies. For simple cysts, there were no malignancies (0/24, 95% CI = 0–17%). Among solid lesions, 44% (15/34, 95% CI = 28–62%) were malignant. Among marker-elevated heterogeneous masses, 40% (2/5, 95% CI = 12–77%) were malignant. Conversely, small (≤10 cm) and large (>10 cm) marker-negative heterogeneous lesions had malignancy proportions of 0% (0/39, 95% CI = 0–11%) and 5% (2/40, 95% CI = 1–18%), respectively.
Conclusions: Given the malignancy estimates identified from these multi-institutional data, we recommend an attempt at ovarian-sparing resection for simple cysts or tumor marker-negative heterogeneous lesions ≤10 cm. Oophorectomy is recommended for solid masses or heterogeneous lesions with elevated markers. Finally, large (>10 cm) heterogeneous masses with non-elevated markers warrant a careful discussion of ovarian-sparing techniques. Complete surgical staging is mandatory regardless of operative procedure.
Type of Study: Study of Diagnostic Test.
Level of Evidence: Level I.

Over the past decade, greater than 50% of children in the United States who underwent surgery for benign ovarian neoplasms were treated with oophorectomy, rather than ovarian-sparing techniques [1]. A policy of oophorectomy for benign disease unnecessarily increases risk of premature ovarian failure and impaired fertility, due to substantial rates of metachronous ovarian tumors and/or asynchronous ovarian torsion [2,3]. While providers have become increasingly aware of the potential long-term morbidity associated with oophorectomy for benign disease [4], the practice continues, possibly due in part to lack of familiarity with ovarian-sparing techniques and apprehensions about missed malignancy.

The ability to accurately, pre-operatively predict the probability of ovarian malignancy may assuage this concern and reduce the number of oophorectomies performed for benign disease. In recent years, several retrospective, single-institution studies have begun to risk stratify pediatric ovarian lesions with respect to malignancy [5–7]. Accurate prognostication could identify patients in whom ovarian lesions are likely to be benign and for whom ovarian-sparing approaches could be utilized. Furthermore, a clearer understanding of pre-operative risk

☆ Sources of funding: None.
☆☆ Disclosures: None of the authors disclosed any relevant financial relationships.
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https://doi.org/10.1016/j.jpedsurg.2019.02.019
0022-3468/

would allow for better informed discussions to take place between the surgeon and family.

The purpose of this study was to develop a pre-operative risk assessment tool for pediatric ovarian malignancy in a multicenter cohort, in order to help guide operative management and ultimately reduce unnecessary oophorectomies while ensuring that appropriate oncologic operations are performed in the setting of malignancy.

1. Methods

We conducted a retrospective study of consecutive patients <18 years old who underwent surgery for ovarian lesions at two quaternary care pediatric centers (Boston Children's Hospital and Riley Hospital for Children) over a 4-year period (1/1/13–12/31/16). Patients were identified by querying surgical pathology specimens that included any ovarian tissue. Each operation was performed by one of 38 board-certified pediatric surgeons, 3 adult gynecologists, or 2 pediatric gynecologists. Patients with gonadal dysgenesis or previously diagnosed metastatic disease were excluded.

The primary outcome was final pathologic diagnosis of malignancy, defined by the World Health Organization [8]. Some tumors (e.g., immature teratomas, granulosa cell tumors, and borderline tumors) may demonstrate a spectrum of potentially malignant behavior; however, these tumors were classified as "malignant" for the purposes of this study. Data points were collected based on prior work estimating risk of malignancy from imaging characteristics, tumor diameter, and laboratory markers [7]. Lesional size, measured using Response Evaluation Criteria in Solid Tumors (RECIST) criteria as the maximal diameter in centimeters documented on the imaging report, was collected as a continuous variable [9]. Additionally, diameter was dichotomized separately for each imaging category based on the value which maximized the Youden index (J), calculated by the equation: sensitivity + specificity − 1 [10]. Based on preoperative imaging, each lesion was categorized as simple cyst, heterogeneous, or solid.

Simple cysts were anechoic cystic lesions lacking internal Doppler flow, septations, solid elements, or mural nodules. A cystic lesion otherwise meeting these criteria with a lone peripheral calcification was considered a simple cyst. Heterogeneous lesions were defined as <50% solid and included non-simple cysts, such as those with wall thickening, septations, multiple calcifications, and/or mural nodules. Solid lesions were defined as lesions that were predominately (≥50%) solid.

Tumor markers included alpha-fetoprotein (α-FP) and beta-human chorionic gonadotropin (β-hCG), which were collected as continuous variables and then dichotomized. Owing to subtle differences in laboratory assays, thresholds for normal α-FP and β-hCG differed slightly between the two institutions. For Boston Children's Hospital, α-FP and β-hCG were considered elevated if ≥15 ng/mL and ≥ 1.0 mIU/mL, respectively; for Riley Hospital for Children, α-FP and β-hCG were each considered elevated if ≥25 ng/mL and ≥ 3.0 mIU/mL, respectively (institutional α-FP nomograms were used for children <2 years of age). Inhibin B levels were collected when available [11], however not included in the algorithm, because this test was not routinely obtained over the study period. Wilson's method with continuity correction was used to calculate 95% confidence intervals of proportions [12]. Missing data were handled with a complete case approach. Analysis was performed with SAS version 9.3.

2. Results

Among 188 children with ovarian lesions, the median (interquartile range [IQR]) age was 13.9 (9.1–15.7) years. There were 24 (13%) simple cysts, 127 (69%) heterogeneous lesions, and 34 (18%) solid lesions (three patients had missing imaging characteristics and were excluded from further analysis). Median (IQR) age at diagnosis was 12.6 years (11.9–15.3) for patients with cystic lesions, 12.3 years (10.9–15.9) for patients with heterogeneous lesions, and 9.9 (5.4–14.6) for patients with solid lesions. Patients underwent one or more ultrasound (n = 151, 82%), computed tomography (n = 50, 27%), and magnetic resonance (n = 10, 5%) examinations (including prior to transfer). The majority of simple cysts (14/24, 58%) were cystadenomas or cystadenofibromas. The overall median lesional diameter was 8.0 cm (IQR, 5.0–12.6 cm). Among 126 patients with α-FP values, 6 (5%) were elevated, and among 151 patients with β-hCG values, 5 (3%) were elevated. Among 69 patients with inhibin B values, 5 (7%) were elevated. Of those lesions, 4 were granulosa cell tumors and one was a serous cystadenoma.

The overall malignancy proportion was 11% (n = 20). The majority of malignant tumors (Table 1) were granulosa cell tumors (36%, n = 8) or immature teratomas (27%, n = 6). Malignant lesions were more likely to be larger (median [IQR] 11.9 [10.3–15.1] vs. 7.6 [4.9–11.8] cm) and solid (75%, n = 15 vs. 12%, n = 19), compared with benign lesions. Using the Youden index, a diameter of 10 cm was determined to be the optimal threshold in order to discriminate between malignant and benign lesions (the same threshold was found for the subgroup of heterogeneous lesions). Based on this size threshold, 75% (n = 15) of malignant and 31% (n = 51) of benign lesions were large (i.e., >10 cm). For malignant, compared with benign ovarian lesions, α-FP and β-hCG were more frequently elevated (α-FP, 28%, n = 5 vs. 1%, n = 1; β-hCG, 11%, n = 2 vs. 2%, n = 3). Characteristics of patients with elevated α-FP or β-hCG are reported in Supplemental Table 1. Further comparisons of traits between malignant and benign ovarian lesions are displayed in Table 2.

Using the pre-specified algorithm of imaging characteristics, lesional size, and tumor markers, Table 3 displays the associated proportion of malignancy. Based on imaging characteristics, 0% (0/24, 95% CI = 0–17%) of simple cysts were malignant. Among predominately solid lesions, 44% (15/34, 95% CI = 28–62%) were malignant. The malignancy proportion remained elevated for solid lesions that were ≤ 10 cm (22%, 5/22), including those ≤10 cm with non-elevated tumor markers (13%, 2/15).

Heterogeneous lesions had an overall malignancy proportion of 4% (5/127, 95% CI = 1–9%). Among heterogeneous lesions with elevated tumor markers, 40% (2/5, 95% CI = 12–77%) were malignant. Conversely, among heterogeneous lesions with non-elevated tumor markers, those that were small (≤10 cm) had malignancy proportions of 0% (0/39, 95% CI = 0–11%), while large (>10 cm) heterogeneous lesions had malignancy proportions of 5% (2/40, 95% CI = 1–18%). Of the latter two patients with heterogeneous, large lesions without elevated tumor markers that were "malignancies," both were immature teratomas with calcifications on imaging studies and non-elevated inhibin B levels. Fig. 1 displays a summary of the proposed decision strategy.

3. Discussion

In this multicenter study, we propose a pre-operative risk stratification algorithm for potential ovarian malignancy based on imaging characteristics, lesional diameter, and tumor markers. The goal of this algorithm was to provide estimates of malignancy probability and, ultimately, to minimize performance of oophorectomy for benign disease while

Table 1
Distribution of 20 malignant ovarian tumors.

Category	*Number (%)*
Malignant germ cell tumor	
Immature teratoma	6 (30)
Dysgerminoma	2 (10)
Yolk sac	2 (10)
Sex cord stromal tumors	
Granulosa cell	8 (40)
Sertoli-Leydig	1 (5)
Carcinoma/borderline tumors	1 (5)

Table 2
Comparison of factors associated with malignant and benign ovarian lesions.

Variable	*Malignant*	*Benign*
Number (%)	20 (11)	168 (89)
Center		
BCH	9 (45)	115 (68)
RHC	11 (55)	53 (31)
Age, years	9.9 (4.6–14.5)	14.1 (10.1–15.9)
Weight, kg	31 (17–53)	56 (37–70)
Diameter, cm	11.9 (10.3–15.1)	7.6 (4.9–11.8)
Large >10 cm	15 (75)	51 (31)
Imaging characteristic		
Simple cyst	0 (0)	24 (15)
Heterogeneous	5 (25)	122 (74)
Solid	15 (75)	19 (12)
Laboratory values		
Elevated α-FP[a]	5 (28)	1 (1)
Elevated β-hCG[b]	2 (11)	3 (2)
Elevated Inhibin B[c]	4 (50)	1 (2)

α-FP, alpha-fetoprotein; *β-hCG*, beta-human chorionic gonadotropin; *BCH*, Boston Children's Hospital, *RHC*, Riley Hospital for Children.
Number (%) or median (interquartile range).
[a] n = 126.
[b] n = 151.
[c] n = 69.

ensuring that appropriate oncologic operations are performed when the probability of malignancy is high. Existing studies have shown improved rates of ovarian-sparing surgery for benign disease using multidisciplinary institutional algorithms [4,13], which the results of this study might help inform. Especially given the possibility of metachronous ovarian tumors or asynchronous ovarian torsion over the reproductive lifespan, preventing oophorectomy for benign lesions will reduce the risk of premature menopause and its short-term and long-term sequelae (e.g., infertility, osteoporosis, cardiovascular disease, and neurocognitive effects) [14–16]. Complete surgical staging with collection of peritoneal washings, examination of peritoneal surfaces, examination and palpation of retroperitoneal lymph nodes, examination and palpation of omentum, examination and palpation of contralateral ovary (with biopsy of any abnormalities) should be considered mandatory regardless of operative procedure undertaken [17].

Compared with prior work [5,7], the present study incorporated patients from ≥1 institution, which may improve generalizability. Furthermore, this study utilized pre-specified and clearly defined imaging characteristics, such that the resulting algorithm may be transportable to a variety of contexts. Additionally, rather than providing relative measures of association (e.g., adjusted odds ratios), which can be challenging to interpret for combinations of risk factors, we estimated stratum-specific probabilities of malignancy with confidence intervals.

Based on these results, the proposed operative management is relatively straightforward for simple cysts (ovarian-sparing techniques), solid masses (oophorectomy), and ovarian lesions associated with elevated α-FP or β-hCG (oophorectomy). In contradistinction, heterogeneous lesions >10 cm with non-elevated tumor markers carry an intermediate (5%) probability of malignancy and warrant multidisciplinary discussion among providers and patients to weigh the risks and benefits of ovarian-sparing techniques. In this context, it is important to note that there is mounting anecdotal evidence that patients undergoing an ovarian sparing procedure for lesions ultimately diagnosed as immature teratomas might be safely observed, as opposed to undertaking the traditional recommendation of completion oophorectomy. The strategy of "watchful waiting" for patients with immature teratomas who have undergone ovarian-sparing resection merits further study. This approach may avoid oophorectomy without compromising outcome, especially for children with low-grade immature teratomas. Given that our series classifies immature teratomas within this 5% risk for malignancy, we suggest that ovarian-sparing techniques be strongly considered for heterogeneous, tumor marker-negative lesions.

Table 3
Malignancy rate (based on imaging characteristics, maximum lesional diameter, and tumor markers) and operative recommendations.

Lesion characteristics	*Malignancy proportion*[a]	*Recommendation*[b]
Simple cyst	0% (0/24, 0–17%)	Ovarian sparing
Solid-predominant mass	44% (15/34, 28–62%)	Consider oophorectomy
Heterogeneous mass		
Tumor marker elevated	40% (2/5, 12–77%)	Consider oophorectomy
Tumor marker non-elevated ≤10 cm	0% (0/39, 0–11%)	Ovarian sparing
Tumor marker non-elevated >10 cm	5% (2/40, 1–18%)	Ovarian sparing[c]

[a] Percent malignancies (number of malignancies / all tumors, 95% confidence interval).
[b] Staging maneuvers should be considered part of optimal treatment regardless of operative procedure undertaken.
[c] With discussion, given a 5% malignancy proportion.

Given the inclusion criteria, we were unable to estimate the number of nonoperatively managed simple cysts. However, in this series of operatively-managed ovarian lesions, most simple cysts were cystadenomas or cystadenofibromas (14/24, 58%) for which ovarian-sparing operative management is appropriate. It is worth noting that borderline tumors, which are rare in the pediatric and adolescent population, may appear cystic and require special consideration for management and follow-up. Lesions in this series meeting image criteria for "simple cyst" included one mature teratoma, and nine non-neoplastic lesions (including follicular cysts, cystic corpus luteum, simple cysts, paratubal cysts, hemorrhagic cysts, and endometriomas). In the setting of non-neoplastic simple cystic lesions, non-operative or operative management could be undertaken, depending on the clinical scenario. Ovarian-sparing approaches are preferable if an operative strategy is undertaken.

It should be noted that alternatives to immediate oophorectomy have been proposed even when risk of malignancy is high. These include intra-operative biopsy (frozen section) to guide intraoperative decision making and ovarian-sparing techniques with planned re-operation and completion oophorectomy if a malignancy is confirmed on final pathology. The clinical utility of intra-operative biopsy and frozen section for pediatric ovarian neoplasms remains controversial. Although data for adults with ovarian lesions suggest that intraoperative frozen section can provide an accurate diagnosis and guide intraoperative decision-making, no such data exists for children and adolescents where tumor histology can vary considerably from that of adults [18]. Given the considerable heterogeneity that can be present within neoplasms of germ cell origin, for example, it is not clear that frozen section can reliably provide information with immediate clinical utility. In addition, intra-operative biopsy risks upstaging from tumor spillage. Nevertheless, clinicians may legitimately choose to discuss pros and cons of various options with patients and their families, and the proposed algorithm may be useful in facilitating these discussions.

Additionally, we acknowledge that the recommendation for children with solid or heterogeneous lesions with positive markers to undergo oophorectomy may be controversial, owing to the fact that >50% of these patients may ultimately be diagnosed with benign lesions. While it is true in these contexts that re-operation following initial attempt at ovarian-preservation can be pursued if a malignancy is diagnosed, we caution that the routine application of this approach risks upstaging if tumor capsule violation and/or spillage occurs. This would potentially expose the patient to toxic therapies and compromised outcomes that might have otherwise been avoided [19]. Regardless of the associated controversy, these results may be a useful tool to inform surgeons and patients about the risks associated with any decision. Ultimate management may differ based on clinical context and the values of the patient and clinician.

Several other risk factors were considered but not included in the final algorithm. Prior studies have estimated measures of association

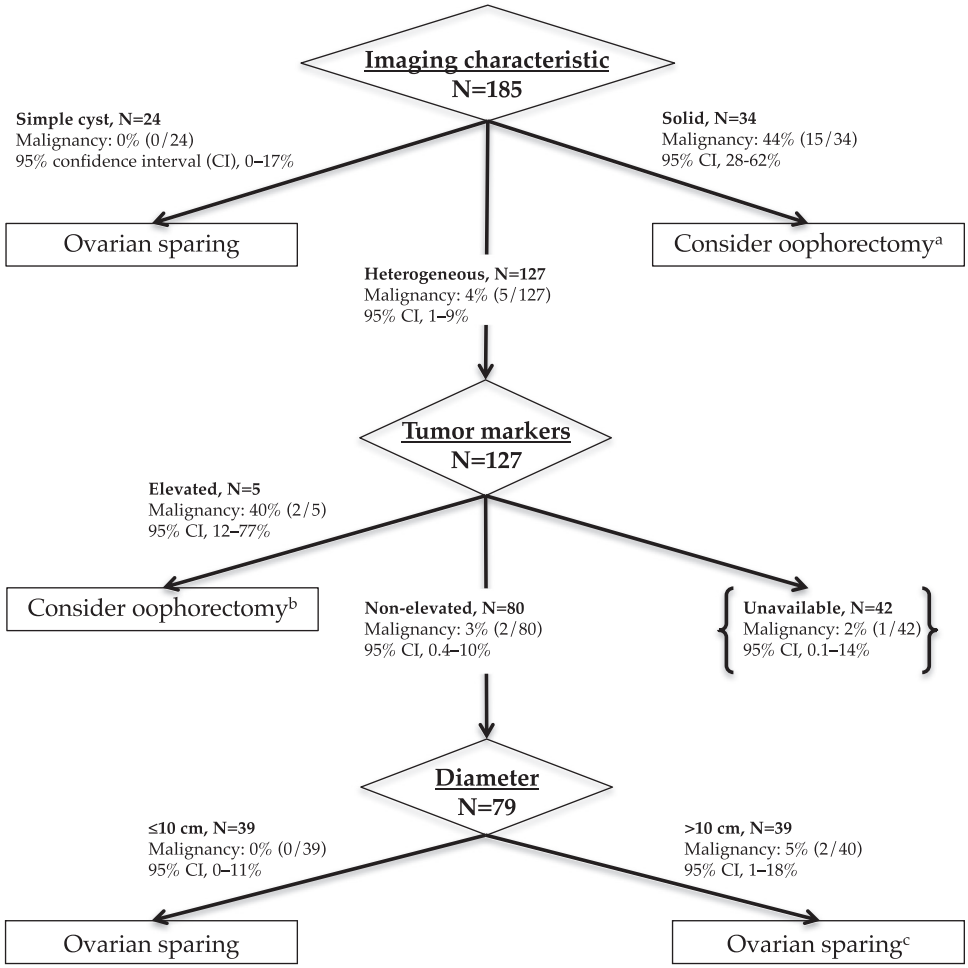

Fig. 1. Decision strategy for operative management of ovarian lesions [a] Given the elevated risk of malignancy associated with solid lesions, oophorectomy should be considered. At the clinician's discretion, risks and benefits of an ovarian-sparing approach, including completion oophorectomy at a separate operation if a malignancy is diagnosed, can be discussed with the patient and/or caregivers. [b] Given the elevated risk of malignancy associated with elevated tumor markers, oophorectomy should be considered. Evidence is mounting that immature teratomas, which may be associated with elevated tumor markers, may be successfully managed with ovarian-sparing techniques. At the clinician's discretion, risks and benefits of an ovarian-sparing approach, including completion oophorectomy at a separate operation if a malignancy is diagnosed, can be discussed with the patient and/or caregivers. [c] Recommend discussion of risks and benefits with the patient and/or caregivers, with strong consideration of ovarian sparing surgery.

for age and presenting symptoms [5–7]. In this study, age at presentation was found to be generally younger for patients with malignant (compared with benign) ovarian lesions. While several studies did not identify a relationship between age and malignancy [5–7], analysis of data from the Malignant Germ Cell International Collaborative reported decreased odds of cure among patients who presented with extracranial germ cell tumors at age ≥ 11 years [20]. We did not include age, because it did not provide a meaningful discrimination for malignancy, although it may be an important factor for consideration by clinicians and future studies.

Similarly, several radiographic findings, such as dermoid plug [21], ascites, thick septations, papillary projections, lymphadenopathy, and invasion of adjacent structures should be factored into decision making on a case-by-case basis, but were not included in the algorithm because of inconsistencies in the use of computed tomography, ultrasonography, and magnetic resonance imaging. These potentially subtle radiographic findings may help to further narrow the differential diagnosis for the broad range of ovarian lesions and should be reviewed by an experienced radiologist and discussed in a multidisciplinary setting in the face of diagnostic uncertainty [22]. It should be noted that the algorithm only considers radiographic features of the primary lesion. Clearly, imaging findings that are suggestive of local spread and/or metastatic disease must be considered as they will impact further diagnostic work-up and ultimate treatment.

In order to maximize generalizability, we incorporated the two most commonly used tumor markers, α-FP and β-hCG, as predictors of ovarian malignancy. Inhibin B may be a marker for stromal-based tumors, and should be checked whenever possible in the preoperative evaluation of the child with an ovarian lesion. In this series, however, this test was not consistently obtained, thus preventing our ability to comment on its utility. Especially given that stromal-based tumors comprised 40% of malignancies in this series, it is essential to send inhibin B levels during evaluation for an ovarian lesion. Lack of elevated tumor markers was not able to consistently rule out malignancy, especially given that some tumor types (e.g., dysgerminoma and immature teratoma) are unlikely to have elevated markers. Finally, thrombocytosis has been reported as a marker for malignancy [23], but is limited in specificity. While α-FP, β-hCG, and inhibin B should be universally sent for the evaluation of ovarian lesions, other tests (e.g., LDH, uric acid, inhibin A, CA19–9, CEA, and CA-125) may be incorporated based on institutional or clinician preference.

While patients who presented with ovarian torsion were included in this study, torsion was not included as a risk factor for malignancy in the algorithm. First, torsion may have been suspected pre-operatively and absent intra-operatively or vice versa, which would distort the preoperative algorithm. Exclusion of torsion discovered intraoperatively could introduce selection bias. While previous work has reported an association between ovarian torsion and benign disease [5,7], the presence of

torsion does not mechanistically reassure against malignancy. We did not exclude patients with torsion from the algorithm, arguing that its use may be particularly beneficial in such settings, when both information and time are restricted. We emphasize that tumor markers (including but not limited to α-FP, β-hCG, and inhibin B) should universally be sent, regardless of whether results will be available prior to surgery, and even intraoperatively as may be the case with ovarian torsion.

There were several limitations to our study. First, although two institutions were included, both are quaternary care centers and these findings should be tested in other clinical settings. Referral patterns and therefore ovarian lesion types may vary from other hospitals. Second, these data were retrospectively acquired and are at risk of inherent bias. However, the cohort was obtained based on consecutive pathology cases. Lesions were dichotomized into malignant or benign pathology; however, some classes of tumors may exhibit a range of potential malignant behavior, which is important to consider in decision-making and counseling patients. Third, while imaging characteristics were based on interpretation by a board-certified radiologist, the studies were not centrally reviewed for this analysis. Similarly, because lesional volume was not consistently reported, maximal diameter was incorporated into the algorithm, although volume may be a useful metric for distinguishing benign from malignant ovarian lesions [24]. Finally, like any algorithm, there are important aspects of this proposed strategy which were oversimplified for ease of use and interpretation. For example, diameter and tumor markers were dichotomized. Like any dichotomous threshold, diameter of 10 cm should not be applied inflexibly as a cut-off for malignancy; rather, concern for malignancy based on tumor diameter should be treated as a continuum. This may be particularly important to consider for pediatric patients given the wide continuum of ovarian size over the period from infancy into young adulthood. Institutional thresholds were used to determine if α-FP and β-hCG should be considered elevated. Using this strategy of tumor marker thresholds was likely conservative with respect to sensitivity of discriminating malignancy, producing some false positives as is generally true of screening tests and can be observed in our series. In this respect, we caution that interpretation of elevated tumor markers be done with consideration of the complete clinical context. Along the same lines, tumor marker data were incompletely collected. Similarly, symptomaticity and physical exam signs (e.g., excess acne, hirsutism) were subjective and incompletely recorded. These characteristics were not included in the decision algorithm, however should be incorporated into clinical decision-making as well as prospective research studies.

In conclusion, we propose an algorithm for the management of pediatric ovarian lesions based on the results of a multicenter study. This algorithm includes pre-specified, clearly delineated criteria and we suggest operative recommendations based on these estimates. When interpreting and acting on a given patient's risk based on this algorithm, there should be a low threshold to engage in multidisciplinary discussion and decision-making including providers from surgery, gynecology, radiology, and oncology specialties. Complete surgical staging should be considered mandatory regardless of operative procedure undertaken.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2019.02.019.

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