HHS Public Access

Author manuscript

J Pediatr Surg. Author manuscript; available in PMC 2020 April 24.

Published in final edited form as:

J Pediatr Surg. 2020 January ; 55(1): 122–125. doi:10.1016/j.jpedsurg.2019.09.062.

UNDERSTANDING THE VALUE OF TUMOR MARKERS IN PEDIATRIC OVARIAN NEOPLASMS

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AL, MF, GH, PH, AO, RB, PD, PE, JF, JG, RK, DL, ML, CL, GM, MR, TS, PM, KD, and JA contributed to study conception and design. AL, AA, CB, KC, BR, MR, MS, and JS contributed to acquisition of the data. AL, AO, and JA contributed to analysis and interpretation of data. AL, AO, and JA drafted the manuscript. All authors provided revision of the manuscript for important intellectual concepts.

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Abstract

Purpose: To determine the diagnostic accuracy of tumor markers for malignancy in girls with ovarian neoplasms.

Methods: A retrospective review of girls 2–21 years who presented for surgical management of an ovarian neoplasm across 10 children's hospitals between 2010–2016 was performed. Patients who had at least one concerning feature on imaging and had tumor marker testing were included in the study. Sensitivity, specificity, and negative and positive predictive values (PPV) of tumor markers were calculated.

Results: Our cohort included 401 patients; 22.4% had a malignancy. Testing for tumor markers was inconsistent. AFP had high specificity (98%) and low sensitivity (42%) with a PPV of 86%. The sensitivity, specificity, and PPV of beta-hCG was 44%, 76%, and 32% (respectively). LDH had high sensitivity (95%) and Inhibin A and Inhibin B had high specificity (97% and 92%, respectively).

Conclusions: Tumor marker testing is helpful in preoperative risk stratification of ovarian neoplasms for malignancy. Given the variety of potential tumor types, no single marker provides enough reliability, therefore a panel of tumor marker testing is recommended if there is concern for malignancy. Prospective studies may help further elucidate the predictive value of tumor markers in a pediatric ovarian neoplasm population.

Keywords

ovarian neoplasms; tumor markers; preoperative risk; oophorectomy; ovary-sparing surgery

Introduction

Ovarian masses in children are relatively rare. Ovarian masses can be classified as physiologic cysts or neoplasms. Previous studies have shown ovarian neoplasms to occur at an annual incidence of 2.2–2.6 cases per 100,000 pediatric patients (1). The rate of malignancy among these masses is reported at frequencies ranging from 4% to 27% (1–4). When patients present with an ovarian mass without signs or symptoms concerning for torsion or need for emergency surgery, adequate time exists for preoperative workup and planning. Recently, efforts are being made to promote ovary-sparing surgery in the appropriate setting (5–7). However, one of the challenges facing surgeons is how best to preoperatively risk stratify the patient who presents with an ovarian neoplasm (3, 4, 8–10). Elements of the patient's history, physical exam, imaging, and laboratory testing may be used to determine the best operative approach for patients with ovarian masses that are

concerning for malignancy. The goal of this study was to describe the reliability of tumor markers in the preoperative evaluation of pediatric ovarian neoplasms.

Methods

A retrospective cohort study was conducted at ten participating institutions of the Midwest Pediatric Surgery Consortium (www.mwpsc.org).This study was approved by the institutional review boards of each institution with a waiver of consent. All patients receiving care at the ten participating institutions meeting eligibility criteria were included in the study. Patients were identified using the International Classification of Disease, 9th Edition, Clinical Modification (ICD-9-CM) and Current Procedural Terminology (CPT) procedure codes for ovarian neoplasms. Data were recorded and managed using the Research Electronic Data Capture tool.

Eligibility criteria included female gender, surgical management for ovarian neoplasms between January 1, 2010 and December 31, 2016, and age 2–21 years at the time of surgery. Electronic medical records were reviewed for patient characteristics, admission characteristics, laboratory and imaging results, operative findings, pathology reports, and post-operative complications. Patients who had at least one concerning feature for malignancy on imaging (size > 8 cm, presence of free fluid, solid components, papillary projections, ill-defined borders, extension into surrounding structures, lymphadenopathy, or metastatic or complex components) and had tumor marker testing were included in the study (Table 1). Patients with simple cysts, congenital ovarian abnormalities, torsion without a neoplasm, or unavailable pathology results were excluded.

The primary objective of this study was to better understand diagnostic accuracy of tumor markers for pediatric ovarian neoplasms. Preoperative tumor markers assessed included beta human chorionic gonadotropin (beta-hCG), lactate dehydrogenase (LDH), alpha fetoprotein (AFP), cancer antigen 125 (CA-125), cancer antigen 19–9 (CA 19–9), carcinoembryonic antigen (CEA), Inhibin A, and Inhibin B. Thresholds for elevated tumor markers were identified a priori based on standardized laboratory values at our institutions (Table 2).

Demographic and clinical characteristics of patients in our at-risk cohort were described with frequencies and percentages for categorical variables and medians and interquartile ranges for continuous variables. Bivariate relationships between patient characteristics and malignancy were assessed using Chi-squared, Fisher’s exact, and Wilcoxon-Mann-Whitney U tests where appropriate. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated to better understand the association between tumor markers and malignant disease; point estimates with exact confidence intervals are reported. All statistical analyses were performed using SAS Enterprise Guide Version 7.1 (SAS Institute, Cary, NC).

Results

Eight hundred and nineteen patients who underwent surgery for an ovarian neoplasm across ten children’s hospitals were identified. Of those, 650 patients had a concerning feature on imaging, and 401 underwent serologic evaluation for tumor markers. Patients identified as

having both concerning features on imaging and tumor marker testing comprised our cohort of 401 patients. This cohort of high risk patients included 78 patients with a malignant neoplasm and 323 patients with benign pathologies (Table 3). Among the malignant neoplasms, the most common were germ cell tumors (n=39), sex cord stromal tumors (n=22), and epithelial ovarian tumors (n=12). There were no differences in age or race/ethnicity by malignancy status. Imaging characteristics including the presence of free fluid, solid components, papillary projections, ill-defined borders, extension, lymphadenopathy, and metastatic or complex components were significantly associated with malignant pathology (Table 3). Further, malignant neoplasms were on average 15.1 cm, compared to 10.0 cm in benign neoplasms in this high-risk cohort ($p<0.001$).

The rate of testing for tumor markers in this high-risk cohort varied considerably (Table 4). The most frequently tested tumor markers were AFP at 94%, beta-hCG at 78%, CA 125 at 54%, and LDH at 39%. Less than 30% of patients underwent CA 19–9, Inhibin A, Inhibin B, and CEA testing. Patients with malignant pathologies were more likely to have any elevated tumor markers, with the exception of CA 19–9.

Diagnostic accuracy of each tumor marker for any malignant pathology is presented in Table 5. The only tumor marker with high sensitivity was LDH. Of the patients tested for LDH, 98% of patients with malignant disease had elevated LDH. Sensitivity for all other tumors, or their ability to detect malignant disease was less than 60%. Several tumor markers had a specificity > 90% including CEA, AFP, Inhibin A, and Inhibin B. Of the patients tested for CEA, 100% of patients with benign pathology had normal levels of CEA. Similarly, of the patients tested for AFP, 98% of patients with benign disease had normal levels of AFP.

CEA, AFP, and Inhibin A had the highest overall positive predictive value (PPV) for any malignancy (100%, 86%, and 82% respectively) (Table 5). All tumor markers tested had high negative predictive value (NPV), with the lowest being CEA at 78% (95% CI: 70%, 86%), and the highest being LDH at 92% (95% CI: 81%, 100%) (Table 5).

Discussion

This study demonstrates the variability in tumor marker testing during the workup of pediatric ovarian neoplasms. Although the role of tumor markers may vary based on suspected or confirmed pathology, our study shows that AFP, LDH, CA 125, CA 19–9, beta-hCG, CEA, Inhibin A, and Inhibin B may all be used to risk stratify pediatric patients with an ovarian neoplasm and help guide appropriate surgical management. However, while malignancy ultimately requires histopathological analysis, the high sensitivity, specificity, PPV, and NPV of the various tumors markers suggest that they are both valuable and accurate for preoperative risk stratification when evaluated as a panel of tumor markers.

Previous studies have evaluated different groupings of tumor markers, often concluding that any elevated tumor marker alone is a significant risk factor for malignancy. Papic et al. reported 150 pediatric patients undergoing ovarian surgery for a mass or cyst, of whom 110 had any tumor marker testing done (4). Notably, 40 of those 150 patients had a final diagnosis of a benign cyst (n=38) or endometriosis (n=2), which may have correlated with

the reported rates of tumor marker testing. Of those patients who underwent testing, no patients with benign disease had an elevated AFP or beta-hCG. However, two patients with benign disease had elevated LDH and nine of thirteen patients with a malignancy (69%) had an elevated LDH. Overall, 83% of patients with a malignancy in this study had an elevated AFP, beta-hCG, or LDH. Within our cohort, we also found that LDH has a high sensitivity but low specificity for malignancy.

Oltmann et al. reviewed 424 pediatric patients who underwent ovarian surgery, of whom 157 had tumor markers drawn, including beta-hCG, AFP, CA 125, and CEA. The exclusion of LDH as a tumor marker in this study may explain their low rate of any elevated tumor markers (54%) among patients with malignancy. An elevated beta-hCG, AFP, or CA 125 were significantly associated with malignancy on univariate analysis, but nearly the same number of patients with a malignancy (46%) did not have any elevated tumor markers. Notably, of the 46 malignant cases they identified, only 35 of those patients had tumor markers drawn. It is unclear if this was due to urgent presentation of these patients or other clinical decisions. Tumor markers were elevated in 6.5% of patients with benign disease, indicating that one must also be aware of the possibility of false positives in tumor marker testing.

One of the challenges in tumor marker testing is the variable origins of cell lines that may lead to ovarian malignancy in children, thus leading to different elevations in tumor markers depending on tumor pathology (11). Common malignant pathologies include germ cell tumors, sex cord stromal tumors, and epithelial tumors. In a retrospective review by Taskinen et al., 45 patients who underwent surgery for an ovarian neoplasm at a single institution were evaluated. This report provided a descriptive look at tumor marker testing and results by pathology (1). Unfortunately, the small cohort made it difficult to identify any significant correlation, but the authors reported that AFP and CA 125 were most often associated with malignant pathology.

Our study demonstrated trends in ovarian tumor marker analysis similar to those previously reported. The aforementioned articles each focused on different tumor markers as indicators for malignancy, highlighting the variability in the workup of pediatric patients with ovarian neoplasms. We also observed significant variation in the types and frequencies of tumor markers drawn (Table 4); our data demonstrate that any individual tumor marker may be necessary but not sufficient to preoperatively identify a pediatric ovarian malignancy.

As ovarian malignancies in children arise from a variety of cell lines, broad laboratory testing becomes essential with preoperative concern for malignancy. Across our consortium, we recommend preoperative testing for potential ovarian neoplasms with AFP, beta-hCG, LDH, CA 125, Inhibin A and Inhibin B. As the goal of this testing is to inform operative decision making by preoperative risk stratification, one of the challenges we observed is obtaining timely laboratory results. At some institutions, Inhibin A and B are outsourced, so results are often not available for several days. We advocate for consistent use of a standard preoperative panel of tumor markers if results are obtainable in a timely fashion.

While not classically related to pediatric or adolescent ovarian pathology, CEA demonstrated 100% specificity and PPV in this study due to a single patient with malignant disease. However, its sensitivity was only 5% and NPV 78%, therefore adding CEA to a preoperative panel may not add significant value to operative decision making. Similarly, CA 19–9, secreted by mucinous tumors of the gastrointestinal track and ovary, demonstrated low sensitivity and PPV, and only 73% specificity and 84% NPV; therefore, the addition of CA 19–9 may not add significant value in the preoperative workup of pediatric patients with concern for an ovarian neoplasm. It has previously been demonstrated that preoperative CA 19–9 levels are not predictive that ovarian mucinous neoplasms will be benign, borderline, or malignant (12). Although we did not include estrogen or testosterone in our analysis, these tumor markers may be useful if a patient exhibits symptoms of hyperestrogenism or hyperandrogenism, such as may be seen with sex cord stromal tumors.

Based on our results, we recommend utilizing a panel of tumor markers in patients with concerning ovarian lesions (AFP, beta-hCG, LDH, CA 125, Inhibin A, and Inhibin B) in order to minimize the risk of missing a malignancy. Unfortunately, we cannot determine the accuracy of using the panel of biomarkers in this cohort because all biomarkers were not obtained in all of our patients. Of the cohort of 401 patients, only 44 patients underwent the entire recommended panel of six tumor markers, and only eight underwent all eight markers analyzed. Due to the variability in testing of markers, we are limited in our ability to report on the diagnostic accuracy of the recommended panel of tumor markers as a whole. However, we are currently evaluating the accuracy of this panel of biomarkers for identifying malignancy in an ongoing prospective multi-institutional study.

This study has several limitations. Our data were retrospective in nature and limited to patients with concerning features on imaging, so levels of testing were probably much higher in this cohort due to selection bias. It is unclear if diagnostic accuracy would be comparable in a cohort of all patients who present with any ovarian lesion regardless of imaging characteristics. Laboratory cutoffs for positive results may also vary slightly from institution to institution, so borderline results may have variable interpretations. The challenge is that tumor markers are often only performed in patients with suspected malignancy, potentially changing estimates of sensitivity and specificity. With respect to sensitivity and specificity, prospective research evaluating tumor markers uniformly across all patients with pediatric ovarian neoplasms is needed. However, tumor marker testing in the setting of simple cysts or other benign appearing ovarian lesions is not recommended.

Conclusions

Preoperative workup of pediatric patients with ovarian neoplasms remains challenging, particularly in situations in which imaging features may raise concern for malignancy. This study revealed that no single tumor marker provides an accurate enough prediction of malignancy to be used alone; rather, a panel of tumor markers may help guide surgeons in preoperative risk stratification and operative planning along with patient history, physical exam, and imaging findings. Prospective research further examining the accuracy of preoperative risk stratification of pediatric ovarian neoplasms is needed.

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Table 1.

Concerning features on imaging

Size > 8 cm
Presence of free fluid
Solid components
Papillary projections
Ill-defined borders
Complex components
Extension into surrounding structures
Lymphadenopathy
Metastatic disease

Table 2.

Thresholds for abnormal laboratory testing

CA 125 > 35 U/mL
CA 19–9 >37 U/mL
AFP > 10 ng/mL
Quantitative beta-hCG > 2.3 mIU/mL
LDH > 170 U/L
CEA > 3 ng/mL
Inhibin A > 80 pg/mL
Inhibin B > 44 pg/mL for age 2–5 years; > 27 pg/mL for age 5–8; > 67 pg/mL for age 8–11; > 120 pg/mL for age 11–14; and >136 pg/mL for age 14–21

Table 3:

Patient Characteristics by Malignancy Status (n=401)

Characteristic	Malignant N=78 (19%)	Benign N=323 (81%)	P value
	N(%) or Median (IQR)	N(%) or Median (IQR)	
Age	13.7 (10.5, 15.8)	13.5 (11.3, 16.4)	0.08
Race/Ethnicity			0.20
Non-Hispanic White	54 (69.2%)	194 (60.1%)	
Non-Hispanic Black	6 (7.7%)	55 (17.0%)	
Hispanic	6 (7.7%)	31 (9.6%)	
Other and Multiracial	7 (9.0%)	18 (5.6%)	
Unknown	5 (6.4%)	25 (7.7%)	
Imaging			
Septations	23 (29.5%)	109 (33.7%)	0.79
Free Fluid	44 (56.4%)	124 (38.4%)	0.002
Solid Components	62 (79.5%)	209 (64.7%)	0.003
Papillary Projections	2 (2.6%)	1 (0.3%)	0.03
Ill-Defined Borders	6 (7.7%)	9 (2.8%)	0.02
Extension	6 (7.7%)	6 (1.9%)	0.005
Lymphadenopathy	10 (12.8%)	9 (2.8%)	<0.001
Metastatic	18 (23.1%)	3 (0.9%)	<0.001
Complex	48 (61.5%)	147 (45.5%)	0.008
Size of mass (cm)	15.1 (11.0, 22.0)	10.0 (6.2, 15.6)	<0.001
Elevated Tumor Markers			
AFP	31 (39.7%)	5 (1.5%)	<0.0001
LDH	42 (53.8%)	90 (27.9%)	0.02
CEA	1 (1.3%)	0 (0.0%)	0.05
CA 125	30 (38.5%)	31 (9.6%)	<0.0001
CA 19–9	2 (2.6%)	12 (3.7%)	0.89
Beta-hCG	28 (35.9%)	60 (18.6%)	0.001
Inhibin A	9 (11.5%)	2 (0.6%)	<0.0001
Inhibin B	10 (12.8%)	5 (1.5%)	0.0005

Other race includes Asian, AI/AN, HI/PI, Multiracial, Self-reported Other

Table 4:

Proportion of Cohort that Received Tumor Marker Testing

	Number tested	Proportion Tested
AFP	376	94%
Beta-hCG	314	78%
CA 125	218	54%
LDH	157	39%
CEA	103	26%
Inhibin A	99	25%
Inhibin B	92	23%
CA 19–9	52	13%

Table 5.

Sensitivity, specificity, positive predictive value, and negative predictive values for elevated tumor markers for any type of malignancy

Tumor Marker	Sensitivity [95% CI]	Specificity [95%CI]	Positive Predictive Value [95% CI]	Negative Predictive Value [95%CI]
AFP	42% [31%, 54%]	98% [97%, 99%]	86% [75%, 97%]	88% [84%, 91%]
LDH	95% [89%, 100%]	13% [6%, 19%]	32% [24%, 40%]	92% [81%, 100%]
CEA	5% [0%, 13%]	100% [100%, 100%]	100% [100%,100%]	78% [70%, 86%]
CA 125	59% [45%, 72%]	81% [76%, 87%]	49% [27%, 62%]	87% [81%, 92%]
CA 19–9	25% [0%, 55%]	73% [60%, 86%]	14% [0%, 33%]	84% [73%,96%]
Beta-hCG	44%[32%,57%]	76% [71%,81%]	32% [22%, 42%]	85% [80%, 89%]
Inhibin A	32% [15%,49%]	97% [93%,100%	82% [59%, 100%]	80% [71%, 88%]
Inhibin B	37% [19%,55%]	92%[86%,99%]	67% [43%, 91%]	79% [70%, 88%]