Featured Articles

Ovarian masses in the child and adolescent: An American Pediatric Surgical Association Outcomes and Evidence-Based Practice Committee systematic review

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A R T I C L E  I N F O

Article history:
Received 26 September 2017
Received in revised form 13 August 2018
Accepted 29 August 2018

Key words:
Ovarian mass
Pediatric
Adolescent
Diagnosis
Management

A B S T R A C T

Background: The treatment of ovarian masses in pediatric patients should balance appropriate surgical management with the preservation of future reproductive capability. Preoperative estimation of malignant potential is essential to planning an optimal surgical strategy.

Methods: The American Pediatric Surgical Association Outcomes and Evidence-Based Practice Committee drafted three consensus-based questions regarding the evaluation and treatment of ovarian masses in pediatric patients. A search of PubMed, the Cochrane Library, and Web of Science was performed and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to identify articles for review.

Results: Preoperative tumor markers, ultrasound malignancy indices, and the presence or absence of the ovarian crescent sign on imaging can help estimate malignant potential prior to surgical resection. Frozen section also plays a role in operative strategy. Surgical staging is useful for directing chemotherapy and for prognostication. Both unilateral oophorectomy and cystectomy have been used successfully for germ cell and borderline ovarian tumors, although cystectomy may be associated with higher rates of local recurrence.

Conclusions: Malignant potential of ovarian masses can be estimated preoperatively, and fertility-sparing techniques may be appropriate depending on the type of tumor. This review provides recommendations based on a critical evaluation of recent literature.

Type of study: Systematic review of level 1–4 studies.
Level of evidence: Level 1–4 (mainly 3–4).

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https://doi.org/10.1016/j.jpedsurg.2018.08.058
0022-3468/© 2018 Published by Elsevier Inc.
Pediatric and adolescent patients who present with ovarian masses pose multiple challenges for the surgical provider. In addition to performing proper staging when malignancy is suspected, the surgeon must weigh the risks and benefits of ovarian preservation and must balance the best options for cure with those supporting future fertility and hormonal health. Often, insufficient clinical information is available preoperatively to assess malignant potential adequately. Preoperative risk assessment of ovarian malignancy is essential to balance fertility pres-ervation with more aggressive cancer treatment. Unilateral oophorectomy in a patient with a nonmalignant mass may lead to future infertility; however, inadequate resection or staging in the setting of a malignancy may place the patient at risk for unnecessary adjuvant therapy or recurrent disease. Surgeons treating patients with suspected malignant lesions must be familiar with current guidelines and procedures for accurate staging in order to best serve the patient for cure and preservation of fertility [1,2].

The goal of this systematic review was to evaluate the published literature and derive recommendations regarding the preoperative evaluation and operative management of pediatric and adolescent patients with ovarian masses.

1. Materials and methods

1.1. Research questions

The members of the American Pediatric Surgical Association (APSA) Outcomes and Evidence Based Practice (OEBP) Committee drafted and iteratively refined the following three questions for this review: (1) Which patients with benign-appearing ovarian lesions are candidates for ovarian preservation? (2) In what situations are formal staging procedures or more extensive resections (e.g. omentectomy, lymph node dissection) warranted?; and (3) Is ovarian preservation safe in the setting of suspected malignant disease?

This review was originally part of a larger project which also included questions regarding ovarian torsion; the results of the review for these additional research questions were published in a separate study [3].

1.2. Search methods

An initial search of PubMed, the Cochrane Library, and Web of Science was performed using the Medical Subject Headings (MeSH) terms “ovary,” “ovarian,” “tumor,” “mass,” “malignancy,” “lesion,” and “preservation.” Results were restricted to English language publications of human subjects aged 0 to 18 years and to articles published from 1980 to July, 2015.

1.3. Study selection

The authors followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to generate the final list of articles used in this review [4]. Two authors (ER and RD)
independently reviewed abstracts and references and chose articles pertinent to the study questions. Some studies with only adult populations were chosen if they contained significant findings relevant to tumors also seen in pediatric patients.

Titles without full text available were excluded from review. Publications reviewed included prospective and retrospective clinical studies as well as large case series and prior systematic reviews. Case reports or opinion papers were excluded.

278 articles underwent full review. Bibliographies were searched for additional titles. On final review, an additional online search was performed to capture more recent articles. The final result was 64 articles which pertained to at least one of the three study questions regarding ovarian masses. (Prisma chart, Fig. 1).

1.4. Review process

Articles were assessed for study design, patient population, sample size, comparison and outcome measures, findings, and level of evidence according to Oxford Centre for Evidence-Based Medicine (OCEBM) guidelines (Table 1) [5].

2. Pediatric ovarian tumors

2.1. Background

Overall, pediatric and adolescent ovarian masses have a low likelihood of malignancy. Approximately 1.5% of all childhood cancers are

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**Table 1**

<table>
<thead>
<tr>
<th>Oxford Centre for Evidence-based Medicine levels of evidence and grades of recommendation (Adapted from <a href="http://www.cebm.net">www.cebm.net</a>) (RCT: Randomized Control Trial).</th>
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<tr>
<td><strong>Level of Evidence</strong></td>
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<td>I. Systematic Review of RCTs or RCT with a narrow confidence interval</td>
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<td>II. Cohort studies, low quality RCTs, outcomes research</td>
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<td>III. Case-control studies</td>
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<td>IV. Case series</td>
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<td>V. Expert Opinion</td>
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ovarian in origin; the reported frequency of malignancy found in pediatric ovarian masses varies greatly but ranges from 4% to 22% [1,2,6,7], with a malignancy incidence between 0.102 and 1.072 per 100,000 per year, depending on patient age [8]. In general, survival is high. Germ cell tumors are the most common type of ovarian malignancy found in the pediatric population. Epithelial tumors occur primarily in adolescent patients and are mostly borderline or low malignant potential; poorly differentiated epithelial tumors are rare [6,9].

2.1. Which patients with benign-appearing ovarian lesions are candidates for ovarian preservation?

2.1.1. Screening for malignancy: signs, symptoms, patient characteristics. Six studies (5 pediatric, 1 pediatric and adult) of level 4 evidence evaluated the association between particular signs and symptoms with the risk of malignancy in a newly diagnosed ovarian tumor; the results were inconsistent. [8,10–14] Pediatric patients with ovarian masses often present with nonspecific complaints. While four studies found some association of malignancy with abdominal pain, distention, mass on exam, or precocious puberty [8,10,13,14], two other studies found no association between malignancy and presenting symptoms [11,12]. Therefore, symptomatology at presentation is not an accurate indicator of the risk of preoperative malignancy.

2.1.1.2. Screening for malignancy: tumor markers. Different tumor markers are associated with specific types of ovarian tumors: α-fetoprotein (αFP), β-human chorionic gonadotropin (βHCG), and lactate dehydrogenase (LDH) can be elevated in the presence of germ cell tumors, while cancer antigen 125 (CA-125) is elevated in epithelial tumors. Estradiol and testosterone may be elevated in the presence of sex cord tumors.

Three studies evaluated the use of tumor markers in preoperative evaluation for malignancy [8,11,15]. These studies examined the predictive discrimination of these markers as panels and not individually. A prospective study of 53 patients 19 years and under with either germ cell or epithelial tumors found that a positive result for any one of six markers in a tumor marker panel (αFP, βHCG, LDH, Ca-125, estradiol, and testosterone) had a 0.76 positive predictive value (PPV), 0.86 negative predictive value (NPV), and 0.83 accuracy for malignancy [15]. In two retrospective studies of germ cell tumors, one found that elevations of βHCG, αFP, and Ca-125 were associated with malignancy [8], and a second noted a greater likelihood of malignancy with elevations of αFP, βHCG, and LDH [11]. Therefore, tumor markers may be most useful in the determination of malignancy when ordered as a standard panel preoperatively.

2.1.1.3. Screening for malignancy: imaging characteristics. All studies meeting inclusion criteria for this review evaluated ultrasound as the primary imaging modality; there were no high quality studies which evaluated CT or MRI.

2.2. Tumor size

Three studies found that tumor size was a helpful preoperative predictor of malignancy for pediatric patients [8,11,16]. Two retrospective studies found that a larger diameter was associated with an increased likelihood of malignancy [8,11]. In the first study (11% of tumors malignant), a tumor diameter ≥ 8 cm had an odds ratio of 19 for malignancy (95% CI, 4.42–81.69) [8]; in the second study (12% malignancy) a diameter ≥ 10 cm had an odds ratio of 9.6 for malignancy (95% CI, 2.12–43.42) [11]. A third study noted that larger tumor volume (calculated with the “prolate ellipsoid formula” which measures the volume of a nonuniform spheroid structure) was associated with malignant potential. This method demonstrated that a cutoff of 184 mL had 100% sensitivity, 54% specificity, NPV of 100% and PPV of 13% to rule out malignancy [16].

2.3. Tumor characteristics

2.3.1. Screening for malignancy: scoring systems and the “ovarian crescent sign”

Ultrasound scoring systems which combine size and intrinsic mass characteristics have been developed to increase the sensitivity, specificity, and accuracy of ultrasound as a preoperative screening modality for malignancy. Five studies evaluated ovarian scoring systems applicable to a pediatric population (Table 2) [17–21]. In a retrospective study of 121 pediatric and adult patients, DePriest et al. described and validated an ultrasound morphology index which included descriptions of the volume, wall structure, and septations. By this index, an ovarian mass with a score of ≥5 or more had a PPV of 0.45 for malignancy while those with scores <5 were uniformly benign [17]. In 2003, Ueland conducted a prospective study of adult patients and modified the DePriest scoring system to focus on size and characteristics as a two factor system. With this modification a score of ≥5 had a 0.981 sensitivity, 0.808 specificity, 0.409 PPV, and 0.997 NPV for malignancy [18]. In an additional prospective study of 98 patients less than 20 years of age with both epithelial and germ cell tumors, a Ueland index ≥7 had a 90% sensitivity, 94% specificity, and positive likelihood ratio of 35.870 for malignancy [19]. One final study of only pediatric patients developed a pediatric risk of malignancy index. A combination of maximum diameter of the largest solid component, the presence of enhancement of flow in a septum or solid papillary projection, and the presence of sex hormone-related symptoms predicted the presence of a benign or nonbenign lesion with an accuracy of 96.4% [20]. Unfortunately, additional validation of this index showed poorer performance with an accuracy of 82.1% and a PPV of 57.1% and NPV of 91.2% [21]. Therefore, as with other preoperative indicators, malignancy indices are a helpful adjunct in preoperative risk stratification but do have limitations and should be used with other assessment measures.

Another radiological indicator of malignancy is the ovarian crescent sign (OCS). This finding said to be present (or “positive”), indicating a benign lesion, when a rim of healthy ovarian tissue is seen on the ipsilateral ovary in the presence of an ovarian mass. Two prospective adult studies of mostly epithelial tumors demonstrated that the absence of an OCS is associated with malignancy with a high sensitivity (96% and 100%) and a high specificity (92% and 93%) [22,23]. In the pediatric literature, one prospective study found that the ovarian crescent sign compared favorably with the Ueland index; OCS absence was 90% sensitive and 72% specific for predicting malignancy [19]. It was less predictive in premenarchal patients, who have smaller ovaries, and also in the setting of ovarian torsion.

One final prospective study used both the Ueland index and the ovarian crescent sign to develop a decision tree system for pediatric patients [24]. If the index was 7 or more with no crescent sign, a mass was classified as malignant; the system showed a 93% sensitivity, 97% specificity, PPV of 85.7% and NPV of 98.9% for malignancy. The use of a combination of radiologic findings and scoring systems appears to be the safest means of screening for malignancy.

2.3.2. Torsion and malignancy

The overall rate of malignancy in torsed ovaries is low. Three recent studies (2 retrospective, 1 prospective) have demonstrated a malignancy rate of 3.5%–5.4% in torsed ovaries [24–26]. The study which
developed a decision tree for masses, referenced in the last section, demonstrated that the tree was effective at distinguishing between malignant and nonmalignant masses in patients that needed emergent surgical treatment including those with torsion, and allowed for a higher rate of preservation of ovarian tissue [24]. Therefore, while malignancy may be present in a torsed ovary, the overall rate is low and available ultrasound indexes can help estimate the likelihood of malignancy preoperatively.

2.3.3. Borderline ovarian tumors
Borderline ovarian tumors (BOT) are epithelial tumors with increased mitotic activity and nuclear atypia but generally without stromal invasion. They share biochemical and radiological characteristics with both benign and malignant tumors but present early in early stage and have a good prognosis, and can be found in adolescent patients [27]. As these tumors can be difficult to diagnose preoperatively, they should be in the differential diagnosis when preoperative tests or scoring systems do not strongly favor a diagnosis of either a benign or malignant lesion.

3. Recommendation

3.1. Which patients with benign-appearing ovarian lesions are candidates for ovarian preservation? Screening for malignancy

Symptoms and signs are not reliable preoperative predictors of malignancy.

Preoperative tumor markers, used as a panel and not individually, may aid in predicting malignant potential.

GRADE C, extrapolation from level 3 and 4 studies

Ultrasound malignancy indices such as the Ueland index and the ovarian crescent sign are useful for distinguishing benign from malignant lesions.

GRADE B, consistent level 2 and 3 studies

3.1.1. Screening for malignancy, role of frozen section

Eight studies addressed the role of frozen section in the intraoperative diagnosis of ovarian malignancy [28–35]. Most of these studies were of level 3 or 4 evidence and focused primarily on adult patients and on epithelial tumors. In 6 studies reporting tumor histology, 43.4%–56% were epithelial [28–33]. The accuracy of frozen section for a combination of tumor histology types was 92% to 97.1% [29–33]. For BOT, underdiagnosis could occur; frozen section for BOT had a sensitivity of 60% to 71% and an accuracy of 55% to 78.6% [28–30,32]. This finding was supported by the single pediatric-only study (~20 years of age) of borderline ovarian tumors in which the rate of agreement between permanent and frozen section was only 55.1% [34]. Pure cystic nature and size > 17 cm in diameter decreased frozen section accuracy owing to sampling error [29,35]. Mucinous tumors also increased sampling error owing to larger size and increased heterogeneity, as single mucinous lesions could contain benign, borderline, and malignant areas [28,30].

4. Recommendation

4.1. Which patients with benign-appearing ovarian lesions are candidates for ovarian preservation? Role of frozen section

Studies in adults demonstrate that frozen section can accurately distinguish benign from malignant tumors; data in the pediatric population are limited. Frozen section is less accurate for borderline ovarian tumors, large tumors, purely cystic lesions, and those of mucinous histology, and should be used with caution for these masses.

GRADE C recommendations, level 3 and 4 studies

5. Surgical staging

5.1. Background

Current guidelines for surgical staging of adult epithelial tumors are derived from the International Federation of Gynecology and Obstetrics (FIGO) [36,37]. In addition to intact tumor removal, optimal staging practice includes the "assessment of peritoneal fluid volume, and fluid cytology...biopsies should be taken from the pelvic side walls, cul-de-sac, and paracolic gutters. The infra-diaphragmatic surface should be evaluated by cytology or biopsy. Bowel serosa and mesentery should be evaluated for tumor. The infra-colic omentum should be removed...Pelvic and para-aortic lymph node sampling is part of surgical staging."

This protocol allows for the preservation of the uterus and the contralateral ovary in the case of a young patient with early disease who wishes to preserve reproductive potential [36,37].

The current surgical staging procedure for pediatric ovarian germ cell tumors has been outlined by the Children's Oncology Group (COG). These guidelines recommend:

"(1) Collection of ascites or washings on entering the peritoneal cavity; (2) examination of the peritoneal surfaces with biopsy or excision of any nodules; (3) examination and palpation of lymph nodes in the retroperitoneum with sampling of any firm or enlarged nodes; (4) inspection and palpation of the omentum with removal of any adherent or abnormal areas noted; (5) inspection and palpation of the opposite ovary with biopsy of any normal areas; and (6) complete resection of the tumor-containing ovary with sparing of the fallopian tube if not involved." [9]

5.1.1. In what situations are formal staging procedures or more extensive resections (e.g. omentectomy, lymph node dissection) warranted?

5.1.1.1. Germ cell tumors. Four articles of level 3 and 4 evidence quality addressed the role of formal staging for germ cell tumors [9,38–40]. Three studies including adult and pediatric patients concluded that conservative surgery, defined as preservation of the contralateral ovary and the uterus, yielded outcomes similar to more radical resections. Overall, recurrences were low, occurred in the setting of both radical surgery
and contralateral preservation, and were generally salvageable with either additional surgery or chemotherapy. [38–40] In an additional study of pediatric patients with germ cell tumors, the Pediatric Intergroup, a combination of Pediatric Oncology Group and Children’s Cancer Study Group, evaluated the outcomes of 131 patients between 1.4 and 20 years of age with ovarian germ cell tumors [9]. Only 3 patients underwent an initial exploration according to the traditional FIGO staging. This study reported excellent survival for all stages of disease with the use of conservative surgery in combination with platinum-based chemotherapy. It was concluded, therefore, that survival appeared to have been unaffected by deviations from traditional surgical guidelines. This paper was the basis for the current COG surgical staging guidelines [9].

Based on the above, the use of more conservative surgery, in particular contralateral ovarian preservation, appears safe in the treatment of germ cell tumors. However, tumor biology and appropriate use of chemotherapy have a direct effect on recurrence, and adherence to staging recommendations aids in directing adjuvant therapy and determining prognosis.

5.1.1.2. Epithelial neoplasms. Only two studies in pediatric patients addressed the extent of initial surgery for the treatment of epithelial neoplasms [6,41]. The paucity of reports is likely owing to the rarity of malignant epithelial ovarian lesions in patients less than 18 years of age. The first study, a retrospective review of 69 epithelial neoplasms (4.7% malignant, 37.5% of low malignant potential), found an overall low recurrence rate and argued that pathological diagnosis should be definitively established before proceeding to extensive resection. [6]. A second study evaluated whether the COG germ cell tumor guidelines could be applied to all pediatric ovarian tumors, regardless of histology. This study included 424 patients less than 19 years of age, of whom 46 had malignancies (11%), and evaluated surgeon adherence to current COG staging practices. The results demonstrated that COG germ cell tumor staging guidelines were followed in only 24% of cases. This cohort experienced two recurrences and four deaths; all were in individuals who had undergone complete staging at their original procedure. The authors concluded that a worse outcome was associated with inherent tumor biology and not secondary to protocol deviation [41].

5.1.1.3. Borderline ovarian tumors. Although BOT have some properties similar to malignant lesions, these tumors may not require extensive staging procedures. Six articles of level 3 evidence addressed the need for extensive surgery in borderline ovarian tumors; five of these included adolescent patients [42–47]. The definitions of a “complete” staging procedure varied among the studies and, therefore, limited their comparability. The studies also reported conflicting results in terms of recurrence: three [42–44] noted an increase in recurrence with incomplete staging, while two showed no difference [45,46]. In all studies relapse did not affect overall survival. The presence of malignant transformation in a recurrence was associated with age greater than 40 years at initial presentation and not completeness of staging [43]. Restaging surgery after initial incomplete staging did not affect recurrence or survival [45,46]. All studies recommended against biopsy of the contralateral ovary in the absence of a visible abnormality owing to the low likelihood of detecting occult disease [42–47].

6. Recommendations

6.1. In what situations are formal staging procedures or more extensive resections (e.g. omentectomy, lymph node dissection) warranted?

6.1.1. Germ cell tumors

Providers should adhere to the COG guidelines when conducting and reporting a staging procedure for patients with suspected germ cell malignancy.

Grade C, consistent level 3 and 4 studies.

6.1.2. Epithelial and borderline neoplasms

There is a lack of literature regarding staging protocols for epithelial malignancies in the pediatric population. Current pediatric staging reflects recommendations for adults, although COG staging practices rather than more extensive FIGO standards may be sufficient for pediatric patients with low grade tumors and BOT. Patients who are incompletely staged at the time of diagnosis should be followed closely for recurrence.

Grade C, extrapolations from level 3 studies.

7. Ovarian preservation

7.1. Background

The primary goal of surgery for a malignant mass is cure. However, owing to the age and expected lengthy disease-free survival of many pediatric and adolescent patients with ovarian tumors, the potential for fertility as well as future hormonal health must also be considered in their care. In terms of fertility, unilateral oophorectomy may have negative effects on later oocyte production and may result in earlier menopause. Large cohort studies from Norway and Japan of women previously undergoing unilateral oophorectomy demonstrate a tendency towards earlier menopause and premature ovarian failure [48,49]. Earlier menopause may also affect the overall health of a patient in terms of earlier cardiovascular disease, osteoporosis, and other effects of aging [50,51]. Concerns such as these have resulted in a focus on safe strategies which preserve fertility by retaining the contralateral undiseased ovary or possibly the affected ovary itself without compromising the oncologic completeness of the tumor resection.

7.1.1. Is ovarian preservation safe in the setting of suspected malignant disease?

7.1.1.1. Contralateral ovarian conservation, germ cell tumor. This review found five articles of level 3 or 4 evidence quality which addressed contralateral ovarian preservation for germ cell tumors; all articles included at least some pediatric patients in their study populations [39,52–55]. These studies agreed that for lower stage disease, preservation of the uterus and contralateral ovary did not increase the rate of recurrence or affect prognosis [39,52–55]. Unilateral oophorectomy can also be performed with more advanced disease: two studies demonstrated that recurrence was higher with advanced disease whether or not bilateral oophorectomy was performed [53,55]. Three studies which reported the outcome of intraoperative contralateral ovarian biopsy found that no biopsy of a normal-appearing ovary revealed occult disease [52,53,55]. Therefore, the sacrifice or biopsy of a normal appearing contralateral ovary is not necessary during operations for germ cell tumors.

7.1.1.2. Contralateral ovarian conservation, epithelial ovarian neoplasm. Four studies of level 3 and 4 evidence addressed fertility-conserving procedures in the setting of epithelial neoplasms [12,56–58]. Only one study exclusively examined patients younger than 21 years of age [12]. This report was a case series of 19 patients treated at a single institution; the patients had a combination of low malignant potential and more invasive tumors. Of those with invasive carcinoma, 4 underwent unilateral salpingo-oophorectomy with staging only; none developed a recurrence. Of the 5 who underwent hysterectomy with bilateral salpingo-oophorectomy, two died of their disease. Both had small cell, anaplastic tumors which are known to portend a poorer prognosis [12].

The three other studies included some pediatric patients. In two of these studies, recurrences occurred in the contralateral ovary, but overall recurrence was low (7/31 and 2/56) [56,57]. Most recurrences were in patients with initial tumors of stage greater than I. None of the three studies recommended attempting contralateral ovarian preservation in patients who presented with greater than stage I disease [57,58], and one study did not recommend contralateral conservation for tumors.
over stage Ia [56]. Therefore, contralateral conservation may be safe for low stage epithelial neoplasms.

7.1.1.3. Contralateral ovarian conservation, borderline ovarian tumor. Two concerns exist regarding ovarian preservation in the setting of BOT: the risk of recurrence in the remaining ovary, and the risk of that recurrence as an invasive tumor. Four articles of level 3 evidence, including 3 with adolescent patients, compared outcomes between patients undergoing radical or fertility-preserving (unilateral oophorectomy) procedures [43,47,59,60]. Recurrence after radical surgery ranged from 0% to 4.5% among all studies; recurrence after fertility preserving procedures ranged from 5.1% to 7.7% [43,47,59,60]. The most common site of recurrence for those undergoing unilateral oophorectomy was in the contralateral retained ovary. Three studies reported stage as a risk factor associated with recurrence [43,47,60], and one reported that the fertility-preserving approach was a negative predictive factor on multivariable analysis [43]. However, all of the studies reported no difference in overall survival between groups, despite the higher rate of recurrence in some studies. Recurrences of BOT were generally effectively treated with a second surgery, which in some cases was again ovary-preserving.

The frequency of invasive cancer at the time of recurrence varied by study. The study by Boran [59], which included some adolescent patients, found no invasive disease at the time of recurrence. In the study by Park of 360 patients [47], there were 18 recurrences, 5 of which consisted of an invasive cancer. Four of these were in patients who had undergone radical surgery. In the study by Song [60], there were 4 recurrences with invasive cancer with one death from disease. Overall, the likelihood of recurrence of BOT as an invasive cancer was low.

8. Recommendations

8.1. Is contralateral ovarian preservation safe in the setting of suspected malignant disease? Conservative surgery

8.1.1. Germ cell tumors

Conservation of the contralateral ovary and the uterus is safe in the setting of germ cell tumors if postoperative chemotherapy guidelines are followed, and may therefore be considered in this subset of patients. Grade C, consistent level 4 studies.

8.1.2. Epithelial ovarian neoplasms

As there is limited literature regarding contralateral ovarian presentation in pediatric patients with epithelial ovarian neoplasms, treatment should follow adult guidelines; contralateral ovarian preservation may be appropriate for low stage tumors.

8.1.3. Borderline ovarian tumor

Patients undergoing unilateral oophorectomy for borderline ovarian tumor are at higher risk for recurrence; these recurrences may be salvaged without an effect on overall survival. Unilateral oophorectomy may therefore be considered for these patients with caution and with close follow up. Grade C, extrapolation from level 3 studies.

8.1.3.1. Cystectomy, germ cell. The risk of metachronous ovarian tumors in patients with germ cell tumors varies from 5% to 15% among studies; therefore, even patients undergoing unilateral oophorectomy may still be at risk of later sterility if a new mass arises in the contralateral organ. Cystectomy can help reduce this risk. Five articles addressed the use of cystectomy in the setting of a germ cell tumor [14,40,61–63]. One study of 31 benign ovarian teratomas found in pediatric patients and treated with cystectomy or unilateral oophorectomy demonstrated five recurrences. Four were in the contralateral ovaries of patient who had undergone unilateral oophorectomy and one in the ipsilateral ovary of a patient who had undergone cystectomy. All recurrences were benign teratomas without malignant transformation [61].

The other four studies of both pediatric and adult patients included an array of germ cell tumors, including immature teratoma, dysgerminoma, endodermal sinus tumor, yolk sac tumor, and mixed germ cell tumor [14,40,62,63]. Three studies were level 4 evidence, and one was level 3. In three series, while only a small number in each study underwent cystectomy, there were no recurrences. Most patients underwent chemotherapy in addition to cystectomy. The authors concluded that cystectomy was an option in the setting of adjuvant chemotherapy, although they could not comment on cystectomy as monotherapy [14,40,62]. The only retrospective comparative study demonstrated that only use of nonplatinum based chemotherapy and AFP > 1000 were associated with increased relapse. The extent of surgery was included in this analysis and was not found to be associated with recurrence [63].

8.1.3.2. Cystectomy, borderline ovarian tumor. Patients presenting with BOTs are often younger than those presenting with epithelial neoplasms and tend to have more favorable long term outcomes. Preservation of fertility has, therefore, become a focus for this lower risk group. In addition, as the risk of synchronous or metachronous tumors ranges from 20% to 40%, patients undergoing unilateral oophorectomy may still be at risk for future sterility [64].

Eight studies explored the potential of cystectomy as a treatment for borderline ovarian tumors [43,59,64–69]. Two articles, an initial report and a follow up, evaluated a randomized control study (Level 1) of cystectomy for adult patients presenting with bilateral borderline ovarian tumors. The first study randomized patients to unilateral salpingo-oophorectomy (USO) with contralateral cystectomy or bilateral cystectomy and found no statistically significant difference in the rate of recurrence between the two groups (58.8% in the bilateral cystectomy group vs. 60% in the USO with cystectomy group). Patients undergoing bilateral cystectomy did have a shorter time to recurrence [64]. The follow up study confirmed these findings [65]. All recurrences were in the ovaries that had undergone cystectomy; however, none were invasive cancer. These patients were treated with repeat surgical resection. In addition, there was an improvement in fertility in the bilateral cystectomy group compared to the USO with cystectomy group. This improvement was reflected in a significantly shorter time to conceive, higher cumulative pregnancy rate, and consistently stable follicle stimulating hormone (FSH) levels for those undergoing bilateral cystectomy, while those undergoing USO with cystectomy demonstrated increases in FSH during the first two years after surgery [64].

In the remaining studies, all of level 3 or 4 evidence, recurrence after cystectomy ranged from 15% to 36.3%, in contrast to recurrence after USO which ranged from 2.4% to 15.1% [59,66]. Of those studies reporting site, all recurrences were in retained ovarian tissue, whether ipsilateral or contralateral [59,67,68]. One database study reported a 30% rate of malignant transformation in recurrences; this study did not specify the type of initial operation [42]. In evaluating factors related to recurrence, two articles included cystectomy in their analysis and did not find an association [68,69]. One study recommended that cystectomy be performed only if a margin of normal ovarian tissue was visible [59]; this recommendation was supported by the finding of another study that involvement of the resection margin and removal of more than one cyst from an ovary were associated with persistence or recurrence [68]. All articles recommended that if cystectomy was chosen as a treatment modality, patients must have close follow up with appropriate surveillance and aggressive treatment of any suspected recurrence [59,64–69].

9. Recommendations

9.1. Is ovarian preservation safe in the setting of suspected malignant disease? Cystectomy

9.1.1. Germ cell tumors

While there is limited literature evaluating cystectomy for germ cell tumors, it is likely safe for benign teratomas depending on size of lesion
and ovary. Cystectomy alone in the setting of immature or malignant germ cell tumors is not supported by the current literature, and is not considered standard of care even when utilizing platinum based chemotherapy.

Grade C, extrapolations from level 4 studies.

9.1.2. Borderline ovarian tumors

The risk of recurrence is higher after cystectomy than after conservative surgery for BOT. Recurrence can be salvaged with additional surgery with a limited effect on survival. Cystectomy may therefore be considered when treating these patients.

Grade B, consistent level 3 and 4 studies.

10. Conclusions

Malignant ovarian masses are rare but treatable tumors in children and adolescents. Although the literature for this patient population regarding their management is limited by the lack of prospective and randomized trials and the dependence on retrospective studies, this review found that some preoperative indicators, including select ultrasound characteristics and a panel of tumor markers, can guide the surgeon when evaluating the preoperative likelihood of malignancy (Ovarian Mass Decision Pathway, Fig. 2). In the setting of malignancy, proper staging determines the need for subsequent adjunctive therapy which can greatly increase a patient’s likelihood of cure. Preservation of future fertility may be possible in cases of malignant tumors, but this option must be evaluated on an individual basis with close follow up owing to a higher risk of recurrence. Further research regarding the best surgical management of these tumors may benefit from a prospective evaluation of outcomes according to tumor histology, stage, and method of treatment. Overall, physicians treating ovarian malignancies in children can be optimistic in counseling patients and families about the possibility of long term survival and potential for future fertility.

Acknowledgments

The authors would like to thank Elizabeth Irish MLS, AHIP for her assistance with the searches required for this review.

References


