Evidence-Based Series 4-15 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Management of a Suspicious Adnexal Mass

Members of the Gynecology Cancer Disease Site Group

Evidence-based Series 4-15 was reviewed and ENDORSED by the Gynecology Disease Site Group (DSG). See Section 4: Document Assessment and Review for details.

The reviewed EBS report consists of
Section 1: Guideline Recommendations (ENDORSED)
Section 2: Evidentiary Base
Section 3: Guideline Development Methods and External Review Process
Section 4: Document Assessment and Review
and is available on the CCO website on the PEBC Gynecology Cancer DSG page

September 9, 2016

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Guideline Report History

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Management of a Suspicious Adnexal Mass:
Guideline Recommendations

J Dodge, A Covens, C Lacchetti, L Elit, T Le, M Devries-Aboud, M Fung Kee Fung
and the Gynecology Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

September 9, 2016

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.

Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2009 and 2016, and for details on how this Clinical Practice Guideline was ENDORSED

QUESTIONS
1. What is the optimal strategy for preoperative identification of the adnexal mass suspicious for ovarian cancer?
2. What is the most appropriate surgical procedure for a woman who presents with an adnexal mass suspicious for ovarian cancer?

TARGET POPULATION
The target population of this guideline is adult women presenting with a suspicious adnexal mass, either symptomatic or asymptomatic.

INTENDED USERS
This guideline is targeted for clinicians managing the care of women with a suspicious adnexal mass, specifically general gynecologists and gynecologic oncologists.

RECOMMENDATIONS
Identification of an Adnexal Mass Suspicious for Ovarian Cancer
Sonography, particularly three-dimensional (3D) sonography, magnetic resonance imaging (MRI), and computerized tomography (CT) imaging are each recommended for differentiating malignant from benign ovarian masses. However, the working group offers the following further recommendations, based on their expert consensus opinion and the consideration of availability, access, and harm:

- Transvaginal sonography should be the first modality of choice, where technically feasible, in patients with a suspicious, isolated ovarian mass.
- MRI is the most appropriate test to help clarify the malignant potential in patients where ultrasound may be unreliable.
- CT is most useful in cases where metastatic disease is suspected or needs to be ruled out.

Key Evidence
- The diagnostic performance of each diagnostic technology was compared and contrasted based on the summary data on sensitivity and specificity obtained from the meta-analysis.
- A meta-analysis of six cohort studies that investigated 3D sonography (1-6) indicated an enhanced sensitivity of 93.5% and specificity of 91.5% with 3D technology (Section 2, Figure 2A).
- A meta-analysis of 22 cohort studies with 24 data sets that investigated the effectiveness of MRI in the diagnosis of adnexal masses (7-28) found an overall sensitivity of 91.9% and specificity of 88.4% (Section 2, Figure 2A).
- A meta-analysis of seven studies with eight data sets considering CT technology (2,10,12,14,22,29-30) yielded an overall sensitivity of 87.2% and specificity of 84.0% (Section 2, Figure 2A).

Evaluation of an adnexal mass by Doppler technology alone is not recommended. Doppler technology should be combined with a morphological assessment.

Key Evidence
- This recommendation is based on the results of several meta-analyses on Doppler indices, but not direct comparisons between them. Rather, the summary data from these meta-analyses were inspected and reasonable sensitivities and specificities were noted.
- A meta-analysis of the resistance index (RI) included 35 cohort studies (2,5,17,30-61) with 42 data sets and yielded an overall sensitivity of 77.2% and specificity of 89.8% (Section 2, Figure 2C).
- A meta-analysis of 21 cohort studies with 22 data sets that evaluated the Pulsatility Index (PI) found an overall sensitivity of 80.6% and specificity of 79.9% (Section 2, Figure 2C).
- A meta-analysis of the peak systolic velocity (PSV) included seven cohort studies (32-33,37,42,50-51,62) and found an overall sensitivity of 80.0% and specificity of 84.2% (Section 2, Figure 2C).

Qualifying Statement
- Assessment of an adnexal mass by colour Doppler technology, using the RI, PI, and PSV indices, was neither as sensitive nor specific as simple ultrasonography. Furthermore, because of the overlap of vascular parameters between malignant and benign masses, a firm diagnosis based on Doppler evaluation alone can be problematic.
Ultrasound-based morphological scoring systems can be used to differentiate benign from malignant adnexal masses. These systems are based on specific ultrasound parameters, each with several scores according to determined features. All evaluated scoring systems were found to have an acceptable level of sensitivity and specificity; therefore, the choice of scoring system may be made based on clinician preference. More information on the characteristics of these scoring systems can be found in Appendix 1.

**Key Evidence**
- Direct comparisons between ultrasound-based morphological scoring systems were not performed in this review. Instead, the assessment was based on summary data on sensitivity and specificity obtained from the meta-analyses conducted. The meta-analyses found summary sensitivities ranging from 83.5% (Finkler) (63) to 91% (DePriest) (64) and specificities ranging from 63% (Lerner) (65) to 85.9% (Ferrazzi) (66) (Section 2, Figure 2B).
- The Risk of Malignancy Index (RMI) (67) is a clinical prediction rule that includes CA-125 and menopausal status, in addition to ultrasound-based morphology. In a meta-analysis of data from the 13 RMI studies (67-79), with 15 data sets, employing a cutoff of 200 to be indicative of malignancy, the summary sensitivity and specificity were 79.2% and 91.7%, respectively (Section 2, Figure 2B). RMI2 (74) and RMI3 (80) are newer versions of this tool, with comparable levels of sensitivity and specificity. The choice of version of RMI should be based on clinician preference.

**Qualifying Statement**
- Ultrasound diagnostic criteria using a set of simple rules to distinguish between benign and malignant masses, and the IOTA (International Ovarian Tumour Analysis) predictive adnexal model had been extensively studied with acceptable sensitivity and specificity. This can serve as potential alternative diagnostic strategy to the RMI score. (81-83)

As a stand-alone modality, serum CA-125 is not recommended for distinguishing between benign and malignant adnexal masses.

**Key Evidence**
- This recommendation is based on a meta-analysis of 49 cohort studies (17,31,35,39,52,62-63,70,72,77-78,84-121) and two case-control studies (122-123) with a total of 52 data sets that found, at a threshold of 35 U/mL, an overall sensitivity of 78.7% and specificity of 77.9% (Section 2, Figure 2D).

**Qualifying Statement**
- Elevated serum CA-125 levels have been reported in a variety of benign conditions. Because the incidence of ovarian cancer relative to benign gynecologic conditions is lower in premenopausal women, CA-125 values are of limited use in this population (124). CA-125 levels are elevated in only 50% of early stage ovarian cancers (125). Caution should be used in interpreting values in such patients.

Frozen section for the intraoperative diagnosis of a suspicious adnexal mass is recommended in settings where availability and patient preferences allow.
Section 1: Guideline Recommendations

**Key Evidence**
- This recommendation is based on a meta-analysis of frozen section diagnoses that included 15 cohort studies (7,126-139) and yielded an overall sensitivity of 89.2% and specificity of 97.9% (Section 2, Figure 2D).

**Surgical Procedures for an Adnexal Mass Suspicious for Malignancy**

- **Comprehensive surgical staging with lymphadenectomy is recommended for the surgical management of patients with early-stage ovarian cancer to improve survival.**

**Key Evidence**
- This recommendation is based on the results of five retrospective cohort studies (140-144).
- Two large population-based studies (140,141) found that surgical staging with lymphadenectomy was associated with improved three-year (p<0.001) (141) and five-year disease specific survival (p<0.001) (140) compared to staging procedures without lymphadenectomy.
- Oksefjell et al (142) reported a statistically significant improvement in five-year overall survival rates in patients undergoing a lymphadenectomy versus those that did not (87% versus [vs.] 64%, respectively; p=0.02).
- Survival analyses performed by both Skirnisdottir et al (143) and Hornung et al (144) also demonstrated a statistically significant benefit in disease-free survival (p=0.004 and p=0.0007, respectively) for patients undergoing a lymphadenectomy versus those that did not.
- Hornung and colleagues (144) also considered overall survival and reported a statistically significant difference (p=0.0008) in the two patient groups in favour of the patients undergoing a lymphadenectomy.
- One randomized controlled trial (RCT) (145) was identified and reported no statistically significant effect of lymphadenectomy on progression-free (hazard ratio [HR]= 0.72; 95% confidence interval [CI], 0.46 to 1.14) or overall (HR=0.85; 95% CI, 0.49 to 1.47) survival. However, this study was underpowered to detect a difference in survival, the study’s secondary outcome. Rather, the sample-size calculation for this RCT was undertaken to detect a difference in prevalence of lymph node positivity. It was deemed inadequate to inform the recommendation.

- **Laparoscopy is a reasonable alternative to laparotomy, provided appropriate surgery and/or staging can be done. The choice between laparoscopy and laparotomy should be based on patient and clinician preferences. Discussion with a gynecologic oncologist is recommended.**

**Key Evidence**
- This recommendation is based on the results of six retrospective cohort studies (146-151).
- In the three studies (146,147,150) that considered patients with early epithelial ovarian cancer, no statistical difference in survival rates was detected between patients undergoing a laparoscopy versus laparotomy.
- In the management of patients with early borderline ovarian tumours, Romangnolo et al (149), Park et al (151) and Desfeux et al (148) found that a laparoscopic versus laparotomic surgical approach did not appear to influence survival rates.
Fertility-preserving surgery is an acceptable alternative to more extensive surgery in patients with low-malignant potential (LMP) tumours and those with well-differentiated surgically staged 1 ovarian cancer. Discussion with a gynecologic oncologist is recommended.

Key Evidence
- This recommendation is based on two cohort studies that compared the impact of conservative fertility-sparing surgeries versus more radical surgical approaches. Yinon et al (152) specifically compared rates of recurrence in 40 patients who underwent unilateral salpingo-oophorectomy versus 22 patients who underwent cystectomy only. No statistical difference in recurrence rates was detected (27.5% vs. 22.7%, respectively; p=0.8). Similarly, in a larger study of 360 women with LMP tumours, Park et al (151) found no difference in disease-free survival between patients who underwent radical or fertility-sparing surgery (p=0.651).

Qualifying Statement
- The Gynecology Cancer Disease Site Group (DSG) acknowledges that, despite definitions and criteria, it is unrealistic to expect that 100% of ovarian cancers will be identified as suspicious preoperatively. Pathology remains the gold standard.

RELATED GUIDELINES
- PEBC EBS 4-4 2004 Update. Management Options for Women with a Hereditary Predisposition to Ovarian Cancer.
- PEBC EBS 4-6a 2004 Update. Screening Postmenopausal Women for Ovarian Cancer
- PEBC EBS 4-6b 2004. Screening High Risk Women for Ovarian Cancer

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REFERENCES

11. Booth SJ, Turnbull LW, Poole DR, Richmond I. The accurate staging of ovarian cancer using 3T magnetic resonance imaging--a realistic option. BJOG. 2008;115(7):894-901.


Section 1: Guideline Recommendations


Section 1: Guideline Recommendations


147. Lecuru F, Desfeux P, Camatte S, Bissery A, Blanc B, Querleu D. Impact of initial surgical access on staging and survival of patients with stage I ovarian cancer. Int J Gynecol Cancer. 2006;16(1):87-94.


Appendix 1. Scoring systems for distinguishing benign from malignant adnexal masses.

**Ultrasound-based morphological scoring systems**

**Table 1. Detailed description of ultrasound scoring systems (121).**

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sassone et al., 1991 (153)</strong></td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>1</td>
</tr>
<tr>
<td>Inner wall structure</td>
<td>Smooth</td>
</tr>
<tr>
<td>Wall thickness (mm)</td>
<td>Thin (≤ 3)</td>
</tr>
<tr>
<td>Septa (mm)</td>
<td>None</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Sonolucent</td>
</tr>
<tr>
<td><strong>DePriest et al., 1993 (64)</strong></td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>0</td>
</tr>
<tr>
<td>Cystic wall structure</td>
<td>Smooth (&lt;3 mm thick)</td>
</tr>
<tr>
<td>Volume (cm³)</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Septum structure</td>
<td>No septa</td>
</tr>
<tr>
<td><strong>Ferrazzi et al., 1997 (66)</strong></td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>1</td>
</tr>
<tr>
<td>Wall</td>
<td>≤ 3 mm</td>
</tr>
<tr>
<td>Septa</td>
<td>None</td>
</tr>
<tr>
<td>Vegetations</td>
<td>None</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Sonolucent</td>
</tr>
<tr>
<td><strong>Lerner et al., 1994 (65)</strong></td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>0</td>
</tr>
<tr>
<td>Wall structure</td>
<td>Smooth or small irregularities &lt;3 mm</td>
</tr>
<tr>
<td>Shadowing</td>
<td>Yes</td>
</tr>
<tr>
<td>Septa</td>
<td>None or thin (&lt;3 mm)</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Sonolucent or low-level echo or echogenic core</td>
</tr>
</tbody>
</table>

**Cutoffs suggestive of malignancy:** Sassone: >9, DePriest: ≥5, Ferrazzi: >9. Lerner: ≥3
Table 2. Finkler ultrasound-based morphological scoring system (63).*

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cyst and smooth borders or fibroid (ovaries normal), or tubular cyst such as hydrosalpinx</td>
<td>1</td>
</tr>
<tr>
<td>Clear cyst with slightly irregular border; cyst with smooth walls but low-level echoes (i.e., endometrioma)</td>
<td>2</td>
</tr>
<tr>
<td>Cyst with low-level echoes with slightly irregular border but no nodularity (i.e. endometrioma); clear cyst in postmenopausal patient</td>
<td>3</td>
</tr>
<tr>
<td>Equivocal, nonspecific ultrasound appearance: solid ovarian enlargement or small cyst with irregular borders and internal echoes (hemorrhagic cyst or benign ovarian tumour)</td>
<td>4-6</td>
</tr>
<tr>
<td>Multiseptated or irregular cystic mass consistent in appearance with ovarian tumour (7 = less nodularity, 8-9 = more nodularity)</td>
<td>7-9</td>
</tr>
<tr>
<td>Pelvic mass as above, with ascites</td>
<td>10</td>
</tr>
</tbody>
</table>

*1 = benign, 10 = malignant, ≥7 indicative of probable malignancy

**Risk of Malignancy Index (RMI)**

The RMI (67, 124), is a clinical prediction rule that calculates a numeric score based on the tumour marker CA-125, which may be elevated in the blood of some cancer patients, multiplied by a menopausal score and an ultrasound morphology score. The most common threshold for probability of malignancy is 200. Scores are calculated as follows:

\[
\text{RMI} = U \times M \times CA-125
\]

where ultrasound (transabdominal) is scored 1 point for each of the following characteristics: multilocular cyst, evidence of solid areas, evidence of metastases, presence of ascites, and bilateral lesions.

\[
U = 0 \text{ for ultrasound score of 0} = 1 \text{ for ultrasound score of 1} = 3 \text{ for ultrasound score of } \geq 2
\]

\[
CA-125 = \text{serum CA-125 in U/ml}
\]

And menopausal status is defined as:

\[
M = 1 \text{ if premenopausal} = 3 \text{ if postmenopausal}
\]

RMI2 (74) is calculated in the same way as the original RMI, except that new weights were used for the ultrasound and menopause components:

\[
U = 1 \text{ for ultrasound score of 0-1} = 4 \text{ for ultrasound score of } \geq 2
\]

\[
M = 1 \text{ if premenopausal} = 4 \text{ if postmenopausal}
\]
RMI3 (80) is a further refinement to the RMI and RMI2, using the same definitions, but with an adjustment to the ultrasound and menopause components:

\[ U = \begin{cases} 
1 & \text{for ultrasound score of } 0-1 \\
3 & \text{for ultrasound score of } \geq 2 
\end{cases} \]

\[ M = \begin{cases} 
1 & \text{if premenopausal} \\
3 & \text{if postmenopausal} 
\end{cases} \]