Curr Oncol, Vol. 19, pp. e244-257; doi: http://dx.doi.org/10.3747/co.19.980

Management of a suspicious adnexal mass: a clinical practice guideline

J.E. Dodge MD, A.L. Covens MD,† C. Lacchetti MHSc,‡ L.M. Elit MD,§ T. Le MD,|| M. Devries–Aboud PhD,# M. Fung-Kee-Fung MD|| and the Gynecology Cancer Disease Site Group*

ABSTRACT

Questions

What is the optimal strategy for preoperative identification of the adnexal mass suspicious for ovarian cancer?

What is the most appropriate surgical procedure for a woman who presents with an adnexal mass suspicious for malignancy?

Perspectives

In Canada in 2010, 2600 new cases of ovarian cancer were estimated to have been diagnosed, and of those patients, 1750 were estimated to have died, making ovarian cancer the 7th most prevalent form of cancer and the 5th leading cause of cancer death in Canadian women. Women with ovarian cancer typically have subtle, nonspecific symptoms such as abdominal pain, bloating, changes in bowel frequency, and urinary or pelvic symptoms, making early detection difficult. Thus, most ovarian cancer cases are diagnosed at an advanced stage, when the cancer has spread outside the pelvis. Because of late diagnosis, the 5-year relative survival ratio for ovarian cancer in Canada is only 40%. Unfortunately, because of the low positive predictive value of potential screening tests (cancer antigen 125 and ultrasonography), there is currently no screening strategy for ovarian cancer.

The purpose of this document is to identify evidence that would inform optimal recommended protocols for the identification and surgical management of adnexal masses suspicious for malignancy.

Outcomes

Outcomes of interest for the identification question included sensitivity and specificity. Outcomes of interest for the surgical question included optimal surgery, overall survival, progression-free or disease-free survival, reduction in the number of surgeries, morbidity, adverse events, and quality of life.

Methodology

After a systematic review, a practice guideline containing clinical recommendations relevant to patients in Ontario was drafted. The practice guideline was reviewed and approved by the Gynecology Disease Site Group and the Report Approval Panel of the Program in Evidence-based Care. External review by Ontario practitioners was obtained through a survey, the results of which were incorporated into the practice guideline.

Practice Guideline

These recommendations apply to adult women presenting with a suspicious adnexal mass, either symptomatic or asymptomatic.

Identification of an Adnexal Mass Suspicious for Ovarian Cancer

Sonography (particularly 3-dimensional sonography), magnetic resonance imaging (MRI), and computed tomography (CT) imaging are each recommended for differentiating malignant from benign ovarian masses. However, the working group offers the following further recommendations, based on

Cancer Care Ontario's Program in Evidence-based Care is sponsored by Cancer Care Ontario and the Ministry of Health and Long-term Care. Please see the Program in Evidence-Based Care section of Cancer Care Ontario's Web site for a complete list of current Gynecology Cancer Disease Site Group members (http://www.cancercare.on.ca/cms/one.aspx?pageId=10245)

their expert consensus opinion and a consideration of availability, access, and harm:

- Where technically feasible, transvaginal sonography should be the modality of first choice in patients with a suspicious isolated ovarian mass.
- To help clarify malignant potential in patients in whom ultrasonography may be unreliable, MRI is the most appropriate test.
- In cases in which extra-ovarian disease is suspected or needs to be ruled out, CT is the most useful technique.
- Evaluation of an adnexal mass by Doppler technology alone is not recommended. Doppler technology should be combined with a morphology assessment.
- Ultrasonography-based morphology scoring systems can be used to differentiate benign from malignant adnexal masses. These scoring systems are based on specific ultrasound parameters, each with several scores base on determined features. All evaluated scoring systems were found to have an acceptable level of sensitivity and specificity; the choice of scoring system may therefore be made based on clinician preference.
- As a standalone modality, serum cancer antigen 125 is not recommended for distinguishing between benign and malignant adnexal masses.
- Frozen sections for the intraoperative diagnosis of a suspicious adnexal mass is recommended in settings in which availability and patient preference allow.

Surgical Procedures for an Adnexal Mass Suspicious for Malignancy

To improve survival, comprehensive surgical staging with lymphadenectomy is recommended for the surgical management of patients with early-stage ovarian cancer.

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

Fertility-preserving surgery is an acceptable alternative to more extensive surgery in patients with low-malignant-potential tumours and those with well-differentiated surgical stage I ovarian cancer. Discussion with a gynecologic oncologist is recommended.

KEY WORDS

Adnexal mass, identification, ultrasonography, surgery

1. QUESTIONS

What is the optimal strategy for preoperative identification of an adnexal mass suspicious for ovarian cancer?

What is the most appropriate surgical procedure for a woman who presents with an adnexal mass suspicious for malignancy?

2. BACKGROUND

In Canada in 2010, 2600 new cases of ovarian cancer were estimated to have been diagnosed, and of those patients, 1750 were estimated to have died, making ovarian cancer the 7th most prevalent form of cancer and the 5th leading cause of cancer death in Canadian women[1]. Women with ovarian cancer typically have subtle, nonspecific symptoms such as abdominal pain, bloating, changes in bowel frequency, and urinary or pelvic symptoms[2], making early detection difficult. Thus, most ovarian cancer cases are diagnosed at an advanced stage, when the cancer has spread outside the pelvis[3]. Because of late diagnosis, the 5-year relative survival ratio for ovarian cancer in Canada is only 40%[1]. Unfortunately, because of the low positive predictive value of potential screening tests [cancer antigen 125 (CA125) and ultrasonography], there is currently no screening strategy for ovarian cancer[4].

The purpose of the present document is to identify evidence that can inform optimal recommended protocols for the identification and surgical management of adnexal masses suspicious for malignancy.

3. METHODS

3.1 Guideline Development

The evidence-based series guidelines developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC) use the methods of the practice guidelines development cycle[5]. For the present project, the core methodology used to develop the evidentiary base was an update of two previously published systematic reviews: the Agency for Healthcare Research and Quality (AHRQ) report, 2006[3], and the Australian Cancer Network Clinical Practice Guideline, 2004[6]. Evidence was selected and reviewed by 5 members of the PEBC Gynecology Disease Site Group (DSG) and 1 methodologist.

This practice guideline is a convenient and up-to-date source of the best available evidence on the management of an adnexal mass suspicious for malignancy. It was developed by systematic review, data synthesis, internal review by a clinician and a methodologist, and external review by clinical experts and Ontario practitioners. The systematic review evidence (manuscript under development) forms the basis of the recommendations developed by the Gynecology DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of

Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent of its funding source.

3.2 Literature Search Strategy

As a first step, an Internet search of Canadian and international health organizations and the National Guidelines Clearinghouse was conducted for existing guidelines and systematic reviews relevant to the research question. Guidelines were included if they had been published since 1999 in English. This initial environmental scan yielded eleven practice guidelines; however, one guideline was excluded because the full guideline was available only in French, and another guideline was excluded because only the National Guidelines Clearinghouse summary was available. One evidence report and technology assessment and one clinical practice guideline identified through the environmental scan were deemed to be the most appropriate to answer the guideline questions. The 2006 AHRQ report[3] addresses the identification question concerning an adnexal mass suspicious for malignancy. The 2004 Australian Cancer Network Clinical Practice Guideline[6] addresses the surgical management question concerning an adnexal mass suspicious for malignancy.

The literature search from the AHRQ report was updated using MEDLINE (Ovid: January 2004 through week 3, March 2009). Because an exact search strategy for the Australian Cancer Network report was not available, an update of that literature search (using the key words provided in the report) was approximated using MEDLINE (Ovid: January 2004 through week 3, April 2009). This literature search combined disease-specific terms ("pelvic mass," "adnexal mass," "pelvic neoplasms," "ovarian cancer," "ovarian neoplasm," "ovarian carcinoma," "epithelial ovarian cancer," "borderline ovarian tumours," and "tumours of low malignant potential") with surgery-specific terms ("intraoperative pathological examination," "frozen section," "debulking surgery," "fertility sparing," "surgical staging," "bilateral salpingo-oophorectomy," "total hysterectomy," "node or nodal dissection," "surgical management," "treatment," "cytoreduction," "secondary cytoreduction," "interval cytoreduction," "laparotomy," and "laparoscopy") for all study designs.

Relevant articles and abstracts were selected and reviewed by 2 reviewers. The reference lists of included studies, together with the personal reference lists of the guideline working group, were searched for additional studies.

4. RESULTS

Four meta-analyses[7–10] and sixty-seven primary studies pertaining to the identification of an adnexal mass suspicious for malignancy met the inclusion criteria and were included in the review. A total of 1809 articles were identified in the updated search for the most appropriate surgical procedure, of which sixteen met the inclusion criteria[11–26].

5. DSG CONSENSUS PROCESS

The draft guideline and systematic review were circulated to the Gynecology DSG for review and approval. The DSG consists of medical oncologists, radiation oncologists, surgical oncologists, and a methodologist.

6. INTERNAL REVIEW

Before submission of this evidence-based series draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of 2 members, including an oncologist with expertise in clinical and methodology issues. The key issues raised by the Report Approval Panel are noted below. Modifications to the guideline were made accordingly.

- If pathology is still the "gold standard," what is the role of the other diagnostic technologies?
- The authors' first recommendation concludes that 3-dimensional ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are "all recommended," with considerations of more "local factors" then suggested as determinants of the modality of choice. The authors should reconsider whether they have missed an opportunity to make a more definitive recommendation that accounts for the "equality" in diagnostic efficacy and what can be reasonably assumed about cost, access, harm (for example, radiation exposure), and patient inconvenience.
- The authors consider various diagnostic tools separately (for example, imaging, CA125). Is there a risk that, in practice, these modalities are used in combination and in doing so, diagnostic properties are changed? Related to this theme, are there important differences in the eligibility of patients included in any analysis of a single modality in which a second-modality criterion was required for inclusion?
- In contrast to the diagnostic efficacy section, the section that deals with "therapy" does not include conventional guideline methodology or reporting. The authors should reconsider their approach to that question.
- The authors might wish to clarify whether the post-diagnostic therapeutic pathway includes multiple modalities that require systematic review to assess linkage.

7. EXTERNAL REVIEW

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to

obtain direct feedback on the draft report from a small number of specified content experts, and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

7.1 Methods

7.1.1 Targeted Peer Review

During the guideline development process, 2 targeted peer reviewers from Ontario and 1 from the United States considered to be clinical or methodological experts (or both) on the topic were identified by the working group. Several weeks before completion of the draft report, the nominees were contacted by e-mail and asked to serve as reviewers. The 3 reviewers agreed, and the draft report and a questionnaire were sent by e-mail for review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent April 8, 2011. Follow-up reminders were sent at 2 weeks (e-mail) and at 4 weeks (telephone call). One reviewer of the invited 3 provided a response to the questionnaire. A score of 5 out of 5 was assigned to the guideline by that reviewer on all 8 questions.

7.1.2 Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Gynecologists and gynecologic oncologists in the PEBC database were contacted by e-mail to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and recommend it. Written comments were invited. Participants were contacted by e-mail and directed to the survey Web site, where they were provided with access to the survey, the guideline recommendations (Section 1), and the evidentiary base (Section 2). The notification e-mail was sent April 13, 2011. The consultation period ended June 10, 2011. The working group reviewed the results of the survey.

7.2 Results

7.2.1 Summary of Written Comments from the Targeted Peer Review

Of the 3 invited reviewers, 1 provided a response. The responding reviewer advised that references by L. Cohen and A. Fleischer be added to the evidence base. The authors were not able to gather more information from the reviewer regarding exactly which publications had been missed. The authors examined whether references by Cohen and Fleischer (independently or together) had been considered at any time during the guideline development process. Cohen *et al.* (2001)[27] was considered by the AHRQ review and reported in Section 2 under "Other Scoring Systems." One Fleischer paper (Wilson *et al.,* 2006[28]) was included in the evidence base for the guideline. In the end, no modifications to the evidence base were made on the basis of the reviewer's comment.

7.2.2 Summary of Written Comments from the Professional Consultation

As a result of the professional consultation, 60 responses were received. Table I summarizes key results of the feedback survey. Modifications to the guideline were made accordingly.

Of the 60 responders, 20 provided additional written comments. Most indicated that the document was of high quality and would be of use to practitioners. Suggestions for improvements or additions to the document included several comments relating to the scoring systems described in the report. The feedback generally indicated that many practitioners in the province are not aware of the scoring systems. A direct link from the recommendations to the scoring systems was requested. It was also suggested that the guideline recommend one scoring system that would be the most reliable. Other comments related to scoring systems include making the Risk of Malignancy Index (RMI) available as an appendix to the guideline. There was also a request for an appendix setting out the ultrasonography features of malignancy and the definitions of resistance index, pulsatility index, and peak systolic velocity.

8. PRACTICE GUIDELINE

The present report integrates the feedback obtained through the external review process, with final approval given by the Gynecology DSG and the Report Approval Panel of the PEBC.

8.1 Recommendations and Key Evidence

8.1.1 Identification of an Adnexal Mass Suspicious for Ovarian Cancer

Recommendation: Sonography (particularly 3-dimensional sonography), magnetic resonance imaging (MRI), and computed 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 a consideration of availability, access, and harm:

- Where technically feasible, transvaginal sonography should be the modality of first choice in patients with a suspicious isolated ovarian mass.
- To help clarify malignant potential in patients in whom ultrasonography may be unreliable, MRI is the most appropriate test.

TABLE I Responses to four items on the professional consultation survey

	Quality				
General questions: overall guideline assessment	*Lowest* *1*	*2*	*3*	*4*	*Highest* *5*
Rate the overall quality of the guideline report [n (%)]	0 (0)	0 (0)	6 (11)	31 (54)	23 (41)
	Strongly disagree *1*	*2*	*3*	*4*	*Strongly agree* *5*
I would make use of this guideline in my professional decisions [n (%)]	2 (4)	0 (0)	6 (11)	21 (38)	31 (55)
I would recommend this guideline for use in practice [n (%)]	0 (0)	0 (0)	7 (13)	22 (39)	31 (55)

- In cases in which extra-ovarian disease is suspected or needs to be ruled out, CT is the most useful technique.

This recommendation is based on results of a meta-analysis of six cohort studies that investigated 3-dimensional sonography[29–34] and indicated an enhanced sensitivity of 93.5% and a specificity of 91.5% with 3-dimensional technology. Furthermore, a meta-analysis of twenty-two cohort studies with 24 datasets that investigated the effectiveness of MRI in the diagnosis of adnexal masses[35–56] found an overall sensitivity of 91.9% and a specificity of 88.4%. Finally, a meta-analysis of seven studies with 8 datasets considering CT technology[30,38,40,42,50,57,58] yielded an overall sensitivity of 87.2% and a specificity of 84.0%.

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

This recommendation is based on the results of several meta-analyses on Doppler indices, but not on direct comparisons between them. Rather, the summary data from the meta-analyses were inspected, and reasonable sensitivities and specificities were noted. A meta-analysis of the resistance index included thirty-five cohort studies [30,33,45,58–89] with 42 datasets and yielded an overall sensitivity of 77.2% and a specificity of 89.8%. A meta-analysis of twenty-one cohort studies with 22 datasets that evaluated the pulsatility index found an overall sensitivity of 80.6% and a specificity of 79.9%. A meta-analysis of the peak systolic velocity included seven cohort studies[60,61,65,70,78,79,90] and found an overall sensitivity of 80.0% and a specificity of 84.2%.

Qualifying Statement: Assessment of an adnexal mass by colour Doppler technology using the resistance, pulsatility, and peak systolic velocity indices was neither as sensitive nor as 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.

Recommendation: Ultrasonography-based morphology scoring systems can be used to differentiate benign from malignant adnexal masses. These scoring systems are based on specific ultrasound parameters, each with several scores base on determined features. All evaluated scoring systems were found to have an acceptable level of sensitivity and specificity; the choice of scoring system may therefore be made based on clinician preference. More information on the characteristics of these scoring systems can be found in Appendix A.

Ultrasonography-based morphology scoring systems were not directly compared in this review. Instead, the assessment was based on summary data of the sensitivity and specificity obtained from the meta-analyses. The meta-analyses found summary sensitivities ranging from 83.5% (Finkler *et al.*[95]) to 91% (DePriest *et al.*[92]) and specificities ranging from 63% (Lerner *et al.*[94]) to 85.9% (Ferrazzi *et al.*[93]). The Risk of Malignancy Index (RMI)[96] is a clinical prediction rule that includes CA125 and menopausal status in addition to ultrasonography-based morphology. In a meta-analysis of data from the thirteen RMI studies[96,97,99–109] with 15 datasets, which used a cut-off of 200 as indicative of malignancy, the summary sensitivity and specificity were 79.2% and 91.7% respectively. The newer versions of this tool, RMI2[97] and RMI3[98], have comparable levels of sensitivity and specificity. The choice of RMI version should be based on clinician preference.

Recommendation: As a standalone modality, serum cancer antigen 125 is not recommended for

distinguishing between benign and malignant adnexal masses.

This recommendation is based on a meta-analysis of forty-nine cohort studies [45,59,63,67,80,90,95,101,103,107,108,110–147] and two case–control studies [148,149] with a total of 52 datasets that found, at a threshold of 35 U/mL, an overall sensitivity of 78.7% and a specificity of 77.9%.

Qualifying Statement: Elevated serum CA125 has been reported in a variety of benign conditions. Because the incidence of ovarian cancer relative to benign gynecologic conditions is lower in premenopausal women, serum CA125 is of limited use in that population[3]. Serum CA125 is elevated in only 50% of early-stage ovarian cancers[150]. Caution should be used in interpreting values in such patients.

Recommendation: Frozen sections for the intraoperative diagnosis of a suspicious adnexal mass is recommended in settings in which availability and patient preference allow.

This recommendation is based on a meta-analysis of frozen section diagnoses that included fifteen cohort studies [35,151–164] and yielded an overall sensitivity of 89.2% and a specificity of 97.9%.

8.1.2 Surgical Procedures for an Adnexal Mass Suspicious for Malignancy

Recommendation: To improve survival, comprehensive surgical staging with lymphadenectomy is recommended for the surgical management of patients with early-stage ovarian cancer.

This recommendation is based on the results of five retrospective cohort studies[11,12,14,16,17]. Two large population-based studies[11,12] found improved 3-year ($p < 0.001$)[12] and 5-year disease-specific survival ($p < 0.001$)[11] for surgical staging with lymphadenectomy compared with staging procedures without lymphadenectomy. Oksefjell *et al.*[16] reported a statistically significant improvement in 5-year overall survival rates in patients that underwent lymphadenectomy compared with those that did not (87% vs. 64%; $p = 0.02$). Survival analyses performed by both Skirnisdottir *et al.*[17] and Hornung *et al.*[14] also demonstrated a statistically significant benefit in disease-free survival ($p = 0.004$ and $p = 0.0007$ respectively) for patients that underwent lymphadenectomy compared with patients that did not. Hornung and colleagues[14] also considered overall survival and reported a statistically significant difference ($p = 0.0008$) between the groups in favour of the patients undergoing a lymphadenectomy. The one randomized controlled trial[15] that was identified reported no statistically significant effect of lymphadenectomy on progression-free survival (hazard ratio: 0.72; 95% confidence interval: 0.46 to 1.14) or overall survival (hazard ratio: 0.85; 95% confidence interval: 0.49 to 1.47). However, the study was underpowered to detect a difference in survival, the study's secondary outcome. Rather, the sample size calculation was undertaken to detect a difference in the prevalence of lymph node positivity. The study was deemed inadequate to inform the recommendation.

Recommendation: Laparoscopy is a reasonable alternative to laparotomy, provided that appropriate surgery and staging can be done. The choice between laparoscopy and laparotomy should be based on patient and clinician preference. Discussion with a gynecologic oncologist is recommended.

This recommendation is based on the results of six retrospective cohort studies[20–25]. In the three studies[21–23] that considered patients with early epithelial ovarian cancer, no statistical difference in survival rates was detected between patients undergoing laparoscopy and those undergoing laparotomy. In the management of patients with early borderline ovarian tumours, Romangnolo *et al.*[24], Park *et al.*[25], and Desfeux *et al.*[20] found that the surgical approach—laparoscopic or laparotomic—did not appear to influence survival rates.

Recommendation: Fertility-preserving surgery is an acceptable alternative to more extensive surgery in patients with low malignant-potential tumours and those with well-differentiated surgical stage I ovarian cancer. Discussion with a gynecologic oncologist is recommended.

This recommendation is based on two cohort studies that compared the impacts of conservative fertility-sparing surgeries and more radical surgical approaches. Yinon *et al.*[26] specifically compared rates of recurrence in 40 patients who underwent unilateral salpingo-oophorectomy with those in 22 patients who underwent cystectomy only. No statistical difference in recurrence rates was detected (27.5% vs. 22.7%, $p = 0.8$). Similarly, in a larger study of 360 women with low malignant-potential tumours, Park *et al.*[25] found no difference in disease-free survival between patients who underwent radical or fertility-sparing surgery ($p = 0.651$).

Qualifying Statement: The Gynecology Cancer 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 clinical standard.

9. CONFLICT OF INTEREST DISCLOSURES

The authors declare that there are no financial conflicts of interest.

10. REFERENCES

1. Canadian Cancer Society's Steering Committee. *Canadian Cancer Statistics 2010.* Toronto, ON: Canadian Cancer Society; 2010.

2. Scottish Intercollegiate Guidelines Network (SIGN). *Epithelial Ovarian Cancer: A National Clinical Guideline*. No. 75. Edinburgh, Scotland: SIGN; 2003.
3. Myers ER, Bastian LA, Havrilesky LJ, *et al.* Management of adnexal mass. *Evid Rep Technol Assess (Full Rep)* 2006;:1–145.
4. Fung Kee Fung M, Bryson P, Johnston M, Chambers A, and the members of the Gynecology Cancer Disease Site Group. *Screening Postmenopausal Women for Ovarian Cancer*. Evidence summary report no. 4–6a. Toronto, ON: Cancer Care Ontario; 2004.
5. Browman GP, Levine MN, Mohide EA, *et al.* The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502–12.
6. Australia, Department of Health and Ageing, Australian Cancer Network, National Breast Cancer Centre (NBCC). *Clinical Practice Guidelines for the Management of Women with Epithelial Ovarian Cancer*. Camperdown, Australia: NBCC; 2004.
7. Geomini P, Bremer G, Kruitwagen R, Mol BW. Diagnostic accuracy of frozen section diagnosis of the adnexal mass: a metaanalysis. *Gynecol Oncol* 2005;96:1–9.
8. Liu J, Xu Y, Wang J. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis of ovarian carcinoma. *Eur J Radiol* 2007;62:328–34.
9. Geomini P, Kruitwagen R, Bremer GL, Cnossen J, Mol BW. The accuracy of risk scores in predicting ovarian malignancy: a systematic review. *Obstet Gynecol* 2009;113:384–94.
10. Medeiros LR, Rosa DD, Edelweiss MI, *et al.* Accuracy of frozen-section analysis in the diagnosis of ovarian tumors: a systematic quantitative review. *Int J Gynecol Cancer* 2005;15:192–202.
11. Chan JK, Munro EG, Cheung MK, *et al.* Association of lymphadenectomy and survival in stage I ovarian cancer patients. *Obstet Gynecol* 2007;109:12–19.
12. Chan J, Fuh K, Shin J, *et al.* The treatment and outcomes of early-stage epithelial ovarian cancer: have we made any progress? *Br J Cancer* 2008;98:1191–6.
13. Cho YH, Kim DY, Kim JH, *et al.* Is complete surgical staging necessary in patients with stage I mucinous epithelial ovarian tumors? *Gynecol Oncol* 2006;103:878–82.
14. Hornung R, Urs E, Serenella E, *et al.* Analysis of potential prognostic factors in 111 patients with ovarian cancer. *Cancer Lett* 2004;206:97–106.
15. Maggioni A, Benedetti Panici P, Dell'Anna T, *et al.* Randomised study of systematic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis. *Br J Cancer* 2006;95:699–704.
16. Oksefjell H, Sandstad B, Tropé C. Is the watch and wait approach adequate after comprehensive surgical staging in invasive stage I epithelial ovarian cancer? The Norwegian Radium Hospital experience. *Eur J Gynaecol Oncol* 2008;29:583–9.
17. Skírnisdóttir I, Sorbe B. Lymph node sampling is of prognostic value in early stage epithelial ovarian carcinoma. *Eur J Gynaecol Oncol* 2005;26:181–5.
18. Suzuki S, Kajiyama H, Shibata K, *et al.* Is there any association between retroperitoneal lymphadenectomy and survival benefit in ovarian clear cell carcinoma patients? *Ann Oncol* 2008;19:1284–7.
19. Wong HF, Low JJ, Chua Y, Busmanis I, Tay EH, Ho TH. Ovarian tumors of borderline malignancy: a review of 247 patients from 1991 to 2004. *Int J Gynecol Cancer* 2007;17:342–9.
20. Desfeux P, Camatte S, Chatellier G, Blanc B, Querleu D, Lécuru F. Impact of surgical approach on the management of macroscopic early ovarian borderline tumors. *Gynecol Oncol* 2005;98:390–5.
21. Ghezzi F, Cromi A, Uccella S, *et al.* Laparoscopy versus laparotomy for the surgical management of apparent early stage ovarian cancer. *Gynecol Oncol* 2007;105:409–13.
22. Lécuru 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;16:87–94.
23. Park JY, Bae J, Lim MC, *et al.* Laparoscopic and laparotomic staging in stage I epithelial ovarian cancer: a comparison of feasibility and safety. *Int J Gynecol Cancer* 2008;18:1202–9.
24. Romagnolo C, Gadducci A, Sartori E, Zola P, Maggino T. Management of borderline ovarian tumors: results of an Italian multicenter study. *Gynecol Oncol* 2006;101:255–60.
25. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Surgical management of borderline ovarian tumors: the role of fertility-sparing surgery. *Gynecol Oncol* 2009;113:75–82.
26. Yinon Y, Beiner ME, Gotlieb WH, Korach Y, Perri T, Ben-Baruch G. Clinical outcome of cystectomy compared with unilateral salpingo-oophorectomy as fertility-sparing treatment of borderline ovarian tumors. *Fertil Steril* 2007;88:479–84.
27. Cohen LS, Escobar PF, Scharm C, Glimco B, Fishman DA. Three-dimensional power Doppler ultrasound improves the diagnostic accuracy for ovarian cancer prediction. *Gynecol Oncol* 2001;82:40–8.
28. Wilson WD, Valet AS, Andreotti RF, Green–Jarvis B, Lyshchik A, Fleischer AC. Sonographic quantification of ovarian tumor vascularity. *J Ultrasound Med* 2006;25:1577–81.
29. Geomini PM, Kluivers KB, Moret E, Bremer GL, Kruitwagen RF, Mol BW. Evaluation of adnexal masses with three-dimensional ultrasonography. *Obstet Gynecol* 2006;108:1167–75.
30. Laban M, Metawee H, Elyan A, Kamal M, Kamel M, Mansour G. Three-dimensional ultrasound and three-dimensional power Doppler in the assessment of ovarian tumors. *Int J Gynaecol Obstet* 2007;99:201–5.
31. Alcázar JL, Galán MJ, García–Manero M, Guerriero S. Three-dimensional sonographic morphologic assessment in complex adnexal masses: preliminary experience. *J Ultrasound Med* 2003;22:249–54.
32. Kurjak A, Kupesić S. Three dimensional ultrasound and power Doppler in assessment of uterine and ovarian angiogenesis: a prospective study. *Croat Med J* 1999;40:413–20.
33. Kurjak A, Kupesic S, Sparac V, Kosuta D. Three-dimensional ultrasonographic and power Doppler characterization of ovarian lesions. *Ultrasound Obstet Gynecol* 2000;16:365–71.
34. Alcázar JL, Castillo G. Comparison of 2-dimensional and 3-dimensional power-Doppler imaging in complex adnexal masses for the prediction of ovarian cancer. *Am J Obstet Gynecol* 2005;192:807–12.

35. Bazot M, Nassar–Slaba J, Thomassin–Naggara I, Cortez A, Uzan S, Daraï E. MR imaging compared with intraoperative frozen-section examination for the diagnosis of adnexal tumors; correlation with final histology. *Eur Radiol* 2006;16:2687–99.
36. Chen M, Wang WC, Zhou C, *et al.* Differentiation between malignant and benign ovarian tumors by magnetic resonance imaging. *Chin Med Sci J* 2006;21:270–5.
37. Guerra A, Cunha TM, Félix A. Magnetic resonance evaluation of adnexal masses. *Acta Radiol* 2008;49:700–9.
38. Tsili AC, Tsampoulas C, Argyropoulou M, *et al.* Comparative evaluation of multidetector CT and MR imaging in the differentiation of adnexal masses. *Eur Radiol* 2008;18:1049–57.
39. Booth SJ, Turnbull LW, Poole DR, Richmond I. The accurate staging of ovarian cancer using 3T magnetic resonance imaging—a realistic option. *BJOG* 2008;115:894–901.
40. Umemoto M, Shiota M, Shimono T, Hoshiai H. Preoperative diagnosis of ovarian tumors, focusing on the solid area based on diagnostic imaging. *J Obstet Gynaecol Res* 2006;32:195–201.
41. Scoutt LM, McCarthy SM, Lange R, Bourque A, Schwartz PE. MR evaluation of clinically suspected adnexal masses. *J Comput Assist Tomogr* 1994;18:609–18.
42. Buist MR, Golding RP, Burger CW, *et al.* Comparative evaluation of diagnostic methods in ovarian carcinoma with emphasis on CT and MRI. *Gynecol Oncol* 1994;52:191–8.
43. Fenchel S, Grab D, Nuessle K, *et al.* Asymptomatic adnexal masses: correlation of FDG PET and histopathologic findings. *Radiology* 2002;223:780–8.
44. Grab D, Flock F, Stöhr I, *et al.* Classification of asymptomatic adnexal masses by ultrasound, magnetic resonance imaging, and positron emission tomography. *Gynecol Oncol* 2000;77:454–9.
45. Hata K, Hata T, Manabe A, Sugimura K, Kitao M. A critical evaluation of transvaginal Doppler studies, transvaginal sonography, magnetic resonance imaging, and CA125 in detecting ovarian cancer. *Obstet Gynecol* 1992;80:922–6.
46. Hricak H, Chen M, Coakley FV, *et al.* Complex adnexal masses: detection and characterization with MR imaging—multivariate analysis. *Radiology* 2000;214:39–46.
47. Huber S, Medl M, Baumann L, Czembirek H. Value of ultrasound and magnetic resonance imaging in the preoperative evaluation of suspected ovarian masses. *Anticancer Res* 2002;22:2501–7.
48. Jain KA, Friedman DL, Pettinger TW, Alagappan R, Jeffrey RB Jr, Sommer FG. Adnexal masses: comparison of specificity of endovaginal US and pelvic MR imaging. *Radiology* 1993;186:697–704.
49. Komatsu T, Konishi I, Mandai M, *et al.* Adnexal masses: transvaginal US and gadolinium-enhanced MR imaging assessment of intratumoral structure. *Radiology* 1996;198:109–15.
50. Kurtz AB, Tsimikas JV, Tempany CM, *et al.* Diagnosis and staging of ovarian cancer: comparative values of Doppler and conventional US, CT, and MR imaging correlated with surgery and histopathologic analysis—report of the Radiology Diagnostic Oncology Group. *Radiology* 1999;212:19–27.
51. Medl M, Kulenkampff KJ, Stiskal M, Peters–Engl C, Leodolter S, Czembirek H. Magnetic resonance imaging in the preoperative evaluation of suspected ovarian masses. *Anticancer Res* 1995;15:1123–5.
52. Reuter M, Steffens J, Schüppler U, *et al.* Critical evaluation of the specificity of MRI and TVUS for differentiation of malignant from benign adnexal lesions. *Eur Radiol* 1998;8:39–44.
53. Yamashita Y, Torashima M, Hatanaka Y, *et al.* Adnexal masses: accuracy of characterization with transvaginal US and precontrast and postcontrast MR imaging. *Radiology* 1995;194:557–65.
54. Kawahara K, Yoshida Y, Kurokawa T, *et al.* Evaluation of positron emission tomography with tracer 18-fluorodeoxyglucose in addition to magnetic resonance imaging in the diagnosis of ovarian cancer in selected women after ultrasonography. *J Comput Assist Tomogr* 2004;28:505–16.
55. Sohaib SA, Mills TD, Sahdev A, *et al.* The role of magnetic resonance imaging and ultrasound in patients with adnexal masses. *Clin Radiol* 2005;60:340–8.
56. Rieber A, Nüssle K, Stöhr I, *et al.* Preoperative diagnosis of ovarian tumors with MR imaging: comparison with transvaginal sonography, positron emission tomography, and histologic findings. *AJR Am J Roentgenol* 2001;177:123–9.
57. Kitajima K, Murakami K, Yamasaki E, *et al.* Diagnostic accuracy of integrated FDG-PET/contrast-enhanced CT in staging ovarian cancer: comparison with enhanced CT. *Eur J Nucl Med Mol Imaging* 2008;35:1912–20.
58. Lin JY, Angel C, DuBeshter B, Walsh CJ. Diagnoses after laparotomy for a mass in the pelvic area in women. *Surg Gynecol Obstet* 1993;176:333–8.
59. Alcázar JL, Errasti T, Zornoza A, Mínguez JA, Galán MJ. Transvaginal color Doppler ultrasonography and CA-125 in suspicious adnexal masses. *Int J Gynaecol Obstet* 1999;66:255–61.
60. Alcázar JL, Ruiz–Perez ML, Errasti T. Transvaginal color Doppler sonography in adnexal masses: which parameter performs best? *Ultrasound Obstet Gynecol* 1996;8:114–19.
61. Alcázar JL, López–García G. Transvaginal color Doppler assessment of venous flow in adnexal masses. *Ultrasound Obstet Gynecol* 2001;17:434–8.
62. Anandakumar C, Chew S, Wong YC, Chia D, Ratnam SS. Role of transvaginal ultrasound color flow imaging and Doppler waveform analysis in differentiating between benign and malignant ovarian tumors. *Ultrasound Obstet Gynecol* 1996;7:280–4.
63. Berlanda N, Ferrari MM, Mezzopane R, *et al.* Impact of a multiparameter, ultrasound-based triage on surgical management of adnexal masses. *Ultrasound Obstet Gynecol* 2002;20:181–5.
64. Bromley B, Goodman H, Benacerraf BR. Comparison between sonographic morphology and Doppler waveform for the diagnosis of ovarian malignancy. *Obstet Gynecol* 1994;83:434–7.
65. Buy JN, Ghossain MA, Hugol D, *et al.* Characterization of adnexal masses: combination of color Doppler and conventional sonography compared with spectral Doppler analysis alone and conventional sonography alone. *AJR Am J Roentgenol* 1996;166:385–93.
66. Carter JR, Lau M, Fowler JM, Carlson JW, Carson LF, Twiggs LB. Blood flow characteristics of ovarian tumors: implications for ovarian cancer screening. *Am J Obstet Gynecol* 1995;172:901–7.
67. Chou CY, Chang CH, Yao BL, Kuo HC. Color Doppler ultrasonography and serum CA125 in the differentiation of

benign and malignant ovarian tumors. *J Clin Ultrasound* 1994;22:491–6.

68. Franchi M, Beretta P, Ghezzi F, Zanaboni F, Goddi A, Salvatore S. Diagnosis of pelvic masses with transabdominal color Doppler, CA125 and ultrasonography. *Acta Obstet Gynecol Scand* 1995;74:734–9.
69. Guerriero S, Ajossa S, Piras S, *et al.* Three-dimensional quantification of tumor vascularity as a tertiary test after B-mode and power Doppler evaluation for detection of ovarian cancer. *J Ultrasound Med* 2007;26:1271–8.
70. Hata K, Hata T, Kitao M. Intratumoral peak systolic velocity as a new possible predictor for detection of adnexal malignancy. *Am J Obstet Gynecol* 1995;172:1496–500.
71. Jain KA. Prospective evaluation of adnexal masses with endovaginal gray-scale and duplex and color Doppler US: correlation with pathologic findings. *Radiology* 1994;191:63–7.
72. Kurjak A, Zalud I, Alfirevic Z. Evaluation of adnexal masses with transvaginal color ultrasound. *J Ultrasound Med* 1991;10:295–7.
73. Kurjak A, Predanić M. New scoring system for prediction of ovarian malignancy based on transvaginal color Doppler sonography. *J Ultrasound Med* 1992;11:631–8.
74. Leeners B, Schild RL, Funk A, *et al.* Colour Doppler sonography improves the pre-operative diagnosis of ovarian tumours made using conventional transvaginal sonography. *Eur J Obstet Gynecol Reprod Biol* 1996;64:79–85.
75. Marchesini AC, Magrio FA, Berezowski AT, Neto OB, Nogueira AA, Candido dos Reis FJ. A critical analysis of Doppler velocimetry in the differential diagnosis of malignant and benign ovarian masses. *J Womens Health (Larchmt)* 2008;17:97–102.
76. Marret H, Sauget S, Giraudeau B, *et al.* Contrast-enhanced sonography helps in discrimination of benign from malignant adnexal masses. *J Ultrasound Med* 2004;23:1629–39.
77. Mercé LT, Caballero RA, Barco MJ, Bau S, López G. B-Mode, utero-ovarian and intratumoural transvaginal colour Doppler ultrasonography for differential diagnosis of ovarian tumours. *Eur J Obstet Gynecol Reprod Biol* 1998;76:97–107.
78. Mousavi AS, Borna S, Moeinoddini S. Estimation of probability of malignancy using a logistic model combining color Doppler ultrasonography, serum CA125 level in women with a pelvic mass. *Int J Gynecol Cancer* 2006;16(suppl 1):92–8.
79. Prömpeler HJ, Madjar H, Sauerbrei W. Classification of adnexal tumors by transvaginal color Doppler. *Gynecol Oncol* 1996;61:354–63.
80. Schneider VL, Schneider A, Reed KL, Hatch KD. Comparison of Doppler with two-dimensional sonography and CA 125 for prediction of malignancy of pelvic masses. *Obstet Gynecol* 1993;81:983–8.
81. Stein SM, Laifer–Narin S, Johnson MB, *et al.* Differentiation of benign and malignant adnexal masses: relative value of gray-scale, color Doppler, and spectral Doppler sonography. *AJR Am J Roentgenol* 1995;164:381–6.
82. Takac I. Analysis of blood flow in adnexal tumors by using color Doppler imaging and pulsed spectral analysis. *Ultrasound Med Biol* 1998;24:1137–41.
83. Tekay A, Jouppila P. Validity of pulsatility and resistance indices in classification of adnexal tumors with transvaginal color Doppler ultrasound. *Ultrasound Obstet Gynecol* 1992;2:338–44.
84. Tepper R, Lerner–Geva L, Altaras MM, *et al.* Transvaginal color flow imaging in the diagnosis of ovarian tumors. *J Ultrasound Med* 1995;14:731–4.
85. Timor–Tritsch LE, Lerner JP, Monteagudo A, Santos R. Transvaginal ultrasonographic characterization of ovarian masses by means of color flow-directed Doppler measurements and a morphologic scoring system. *Am J Obstet Gynecol* 1993;168:909–13.
86. Valentin L. Comparison of Lerner score, Doppler ultrasound examination, and their combination for discrimination between benign and malignant adnexal masses. *Ultrasound Obstet Gynecol* 2000;15:143–7.
87. Valentin L. Pattern recognition of pelvic masses by gray-scale ultrasound imaging: the contribution of Doppler ultrasound. *Ultrasound Obstet Gynecol* 1999;14:338–47.
88. Wu CC, Lee CN, Chen TM, Lai JI, Hsieh CY, Hsieh FJ. Factors contributing to the accuracy in diagnosing ovarian malignancy by color Doppler ultrasound. *Obstet Gynecol* 1994;84:605–8.
89. Zanetta G, Vergani P, Lissoni A. Color Doppler ultrasound in the preoperative assessment of adnexal masses. *Acta Obstet Gynecol Scand* 1994;73:637–41.
90. Hillaby K, Aslam N, Salim R, Lawrence A, Raju KS, Jurkovic D. The value of detection of normal ovarian tissue (the "ovarian crescent sign") in the differential diagnosis of adnexal masses. *Ultrasound Obstet Gynecol* 2004;23:63–7.
91. Sassone AM, Timor–Tritsch IE, Artner A, Westhoff C, Warren WB. Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. *Obstet Gynecol* 1991;78:70–6.
92. DePriest PD, Shenson D, Fried A, *et al.* A morphology index based on sonographic findings in ovarian cancer. *Gynecol Oncol* 1993;51:7–11.
93. Ferrazzi E, Zanetta G, Dordoni D, Berlanda N, Mezzopane R, Lissoni AA. Transvaginal ultrasonographic characterization of ovarian masses: comparison of five scoring systems in a multicenter study. *Ultrasound Obstet Gynecol* 1997;10:192–7.
94. Lerner JP, Timor–Tritsch IE, Federman A, Abramovich G. Transvaginal ultrasonographic characterization of ovarian masses with an improved, weighted scoring system. *Am J Obstet Gynecol* 1994;170:81–5.
95. Finkler NJ, Benacerraf B, Lavin PT, Wojciechowski C, Knapp RC. Comparison of serum CA125, clinical impression, and ultrasound in the preoperative evaluation of ovarian masses. *Obstet Gynecol* 1988;72:659–64.
96. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol* 1990;97:922–9.
97. Tingulstad S, Hagen B, Skjeldestad FE, *et al.* Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. *Br J Obstet Gynaecol* 1996;103:826–31.
98. Tingulstad S, Hagen B, Skjeldestad FE, Halvorsen T, Nustad K, Onsrud M. The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. *Obstet Gynecol* 1999;93:448–52.

99. Bensaid C, Le Frère Belda MA, *et al.* Performance of laparoscopy in identifying malignant ovarian cysts. *Surg Endosc* 2006;20:1410–14.
100. Van Holsbeke C, Van Calster B, Valentin L, *et al.* External validation of mathematical models to distinguish between benign and malignant adnexal tumors: a multicenter study by the International Ovarian Tumor Analysis Group. *Clin Cancer Res* 2007;13:4440–7.
101. Asif N, Sattar A, Dawood MM, Rafi T, Aamir M, Anwar M. Pre-operative evaluation of ovarian mass: risk of malignancy index. *J Coll Physicians Surg Pak* 2004;14:128–31.
102. Davies AP, Jacobs I, Woolas R, Fish A, Oram D. The adnexal mass: benign or malignant? Evaluation of a risk of malignancy index. *Br J Obstet Gynaecol* 1993;100:927–31.
103. Manjunath AP, Pratapkumar, Sujatha K, Vani R. Comparison of three risk of malignancy indices in evaluation of pelvic masses. *Gynecol Oncol* 2001;81:225–9.
104. Morgante G, la Marca A, Ditto A, De Leo V. Comparison of two malignancy risk indices based on serum CA125, ultrasound score and menopausal status in the diagnosis of ovarian masses. *Br J Obstet Gynaecol* 1999;106:524–7.
105. Aslam N, Tailor A, Lawton F, Carr J, Savvas M, Jurkovic D. Prospective evaluation of three different models for the preoperative diagnosis of ovarian cancer. *BJOG* 2000;107:1347–53.
106. Mol BW, Boll D, De Kanter M, *et al.* Distinguishing the benign and malignant adnexal mass: an external validation of prognostic models. *Gynecol Oncol* 2001;80:162–7.
107. Timmerman D, Bourne TH, Tailor A, *et al.* A comparison of methods for preoperative discrimination between malignant and benign adnexal masses: the development of a new logistic regression model. *Am J Obstet Gynecol* 1999;181:57–65.
108. Engelen MJ, Bongaerts AH, Sluiter WJ, *et al.* Distinguishing benign and malignant pelvic masses: the value of different diagnostic methods in everyday clinical practice. *Eur J Obstet Gynecol Reprod Biol* 2008;136:94–101.
109. Obeidat BR, Amarin ZO, Latimer JA, Crawford RA. Risk of malignancy index in the preoperative evaluation of pelvic masses. *Int J Gynaecol Obstet* 2004;85:255–8.
110. Patsner B, Mann WJ. The value of preoperative serum CA 125 levels in patients with a pelvic mass. *Am J Obstet Gynecol* 1988;159:873–6.
111. Adonakis GL, Paraskevaidis E, Tsiga S, Seferiadis K, Lolis DE. A combined approach for the early detection of ovarian cancer in asymptomatic women. *Eur J Obstet Gynecol Reprod Biol* 1996;65:221–5.
112. Benjapibal M, Neungton C. Pre-operative prediction of serum CA125 level in women with ovarian masses. *J Med Assoc Thai* 2007;90:1986–91.
113. Romagnolo C, Trivella G, Bonacina M, Fornalè M, Maggino T, Ferrazzi E. Preoperative diagnosis of 221 consecutive ovarian masses: scoring system and expert evaluation. *Eur J Gynaecol Oncol* 2006;27:487–9.
114. Zhang Z, Yu Y, Xu F, *et al.* Combining multiple serum tumor markers improves detection of stage I epithelial ovarian cancer. *Gynecol Oncol* 2007;107:526–31.
115. Milojkovic M, Hrgovic Z, Hrgovic I, Jonat W, Maass N, Buković D. Significance of CA125 serum level in discrimination between benign and malignant masses in the pelvis. *Arch Gynecol Obstet* 2004;269:176–80.
116. Erdoğan N, Ozçelik B, Serin IS, Akgün M, Oztürk F. Doppler ultrasound assessment and serum cancer antigen 125 in the diagnosis of ovarian tumors. *Int J Gynaecol Obstet* 2005;91:146–50.
117. Balbi GC, Musone R, Menditto A, *et al.* Women with a pelvic mass: indicators of malignancy. *Eur J Gynaecol Oncol* 2001;22:459–62.
118. Chalas E, Welshinger M, Engellener W, Chumas J, Barbieri R, Mann WJ. The clinical significance of thrombocytosis in women presenting with a pelvic mass. *Am J Obstet Gynecol* 1992;166:974–7.
119. Chen DX, Schwartz PE, Li XG, Yang Z. Evaluation of CA125 levels in differentiating malignant from benign tumors in patients with pelvic masses. *Obstet Gynecol* 1988;72:23–7.
120. Doed JR, Quinn MA, Rome R, Koh H. Women with a pelvic mass—when to perform an ultrasound. *Aust N Z J Obstet Gynaecol* 1993;33:404–7.
121. Einhorn N, Bast RC Jr, Knapp RC, Tjernberg B, Zurawski VR Jr. Preoperative evaluation of serum CA 125 levels in patients with primary epithelial ovarian cancer. *Obstet Gynecol* 1986;67:414–16.
122. Gadducci A, Capriello P, Bartolini T, *et al.* The association of ultrasonography and CA-125 test in the preoperative evaluation of ovarian carcinoma. *Eur J Gynaecol Oncol* 1988;9:373–6.
123. Gadducci A, Ferdeghini M, Prontera C, *et al.* The concomitant determination of different tumor markers in patients with epithelial ovarian cancer and benign ovarian masses: relevance for differential diagnosis. *Gynecol Oncol* 1992;44:147–54.
124. Gadducci A, Ferdeghini M, Rispoli G, Prontera C, Bianchi R, Fioretti P. Comparison of tumor-associated trypsin inhibitor (TATI) with CA125 as a marker for diagnosis and monitoring of epithelial ovarian cancer. *Scand J Clin Lab Invest Suppl* 1991;207:19–24.
125. Hogdall EV, Høgdall CK, Tingulstad S, *et al.* Predictive values of serum tumour markers tetranectin, OVX1, CASA and CA125 in patients with a pelvic mass. *Int J Cancer* 2000;89:519–23.
126. Woolas RP, Conaway MR, Xu F, *et al.* Combinations of multiple serum markers are superior to individual assays for discriminating malignant from benign pelvic masses. *Gynecol Oncol* 1995;59:111–16.
127. Zhang Z, Barnhill SD, Zhang H, *et al.* Combination of multiple serum markers using an artificial neural network to improve specificity in discriminating malignant from benign pelvic masses. *Gynecol Oncol* 1999;73:56–61.
128. Hurteau JA, Woolas RP, Jacobs IJ, *et al.* Soluble interleukin-2 receptor alpha is elevated in sera of patients with benign ovarian neoplasms and epithelial ovarian cancer. *Cancer* 1995;76:1615–20.
129. Kawai M, Kikkawa F, Ishikawa H, *et al.* Differential diagnosis of ovarian tumors by transvaginal color-pulse Doppler sonography. *Gynecol Oncol* 1994;54:209–14.
130. Maggino T, Gadducci A, D'Addario V, *et al.* Prospective multicenter study on CA125 in postmenopausal pelvic masses. *Gynecol Oncol* 1994;54:117–23.
131. Malkasian GD Jr, Knapp RC, Lavin PT, *et al.* Preoperative evaluation of serum CA 125 levels in premenopausal and postmenopausal patients with pelvic masses: discrimination

of benign from malignant disease. *Am J Obstet Gynecol* 1988;159:341–6.
132. Mancuso A, De Vivo A, Triolo O, Irato S. The role of transvaginal ultrasonography and serum CA 125 assay combined with age and hormonal state in the differential diagnosis of pelvic masses. *Eur J Gynaecol Oncol* 2004;25:207–10.
133. O'Connell GJ, Ryan E, Murphy KJ, Prefontaine M. Predictive value of CA125 for ovarian carcinoma in patients presenting with pelvic masses. *Obstet Gynecol* 1987;70:930–2.
134. Pyrgiotis E, Salamalekis E, Loghis C, Dima C, Zourlas PA. CA 125 in preoperative evaluation of pelvic masses. *Eur J Gynaecol Oncol* 1993;14:279–82.
135. Roman LD, Muderspach LI, Stein SM, Laifer–Narin S, Groshen S, Morrow CP. Pelvic examination, tumor marker level, and gray-scale and Doppler sonography in the prediction of pelvic cancer. *Obstet Gynecol* 1997;89:493–500.
136. Schutter EM, Davelaar EM, van Kamp GJ, Verstraeten RA, Kenemans P, Verheijen RH. The differential diagnostic potential of a panel of tumor markers (CA125, CA 15-3, and CA 72-4 antigens) in patients with a pelvic mass. *Am J Obstet Gynecol* 2002;187:385–92.
137. Schutter EM, Kenemans P, Sohn C, *et al.* Diagnostic value of pelvic examination, ultrasound, and serum CA125 in postmenopausal women with a pelvic mass. An international multicenter study. *Cancer* 1994;74:1398–406.
138. Schutter EM, Sohn C, Kristen P, *et al.* Estimation of probability of malignancy using a logistic model combining physical examination, ultrasound, serum CA125, and serum CA 72-4 in postmenopausal women with a pelvic mass: an international multicenter study. *Gynecol Oncol* 1998;69:56–63.
139. Sengoku K, Satoh T, Saitoh S, Abe M, Ishikawa M. Evaluation of transvaginal color Doppler sonography, transvaginal sonography and CA125 for prediction of ovarian malignancy. *Int J Gynaecol Obstet* 1994;46:39–43.
140. Smikle CB, Lunt CC, Hankins GD. Clinical predictors in the evaluation of a pelvic mass. *Mil Med* 1995;160:233–5.
141. Soper JT, Hunter VJ, Daly L, Tanner M, Creasman WT, Bast RC Jr. Preoperative serum tumor-associated antigen levels in women with pelvic masses. *Obstet Gynecol* 1990;75:249–54.
142. Tay SK, Chua EK. Correlation of serum, urinary and salivary CA125 levels in patients with adnexal masses. *Ann Acad Med Singapore* 1994;23:311–14.
143. Tian J, Zhang J, Jiao L, Li Y, Cao L. A prospective study of Tc-99m MIBI in the differential diagnosis of pelvic masses in female patients. *Clin Nucl Med* 2000;25:614–18.
144. Torres JC, Derchain SF, Faundes A, Gontijo RC, Martinez EZ, Andrade LA. Risk-of-malignancy index in preoperative evaluation of clinically restricted ovarian cancer. *Sao Paulo Med J* 2002;120:72–6.
145. Vasilev SA, Schlaerth JB, Campeau J, Morrow CP. Serum CA 125 levels in preoperative evaluation of pelvic masses. *Obstet Gynecol* 1988;71:751–6.
146. Wakahara F, Kikkawa F, Nawa A, *et al.* Diagnostic efficacy of tumor markers, sonography, and intraoperative frozen section for ovarian tumors. *Gynecol Obstet Invest* 2001;52:147–52.
147. Weiner Z, Thaler I, Beck D, Rottem S, Deutsch M, Brandes JM. Differentiating malignant from benign ovarian tumors with transvaginal color flow imaging. *Obstet Gynecol* 1992;79:159–62.
148. El-Shalakany A, Abou-Talib Y, Shalaby HS, Sallam M. Preoperative serum inhibin levels in patients with ovarian tumors. *J Obstet Gynaecol Res* 2004;30:155–61.
149. Nakae M, Iwamoto I, Fujino T, *et al.* Preoperative plasma osteopontin level as a biomarker complementary to carbohydrate antigen 125 in predicting ovarian cancer. *J Obstet Gynaecol Res* 2006;32:309–14.
150. NIH consensus conference. Ovarian cancer. Screening, treatment, and follow-up. NIH Consensus Development Panel on Ovarian Cancer. *JAMA* 1995;273:491–7.
151. Naik R, Cross P, Lopes A, Godfrey K, Hatem MH. "True" versus "apparent" stage I epithelial ovarian cancer: value of frozen section analysis. *Int J Gynecol Cancer* 2006;16(suppl 1):41–6.
152. Boriboonhirunsarn D, Sermboon A. Accuracy of frozen section in the diagnosis of malignant ovarian tumor. *J Obstet Gynaecol Res* 2004;30:394–9.
153. Brun JL, Cortez A, Rouzier R, *et al.* Factors influencing the use and accuracy of frozen section diagnosis of epithelial ovarian tumors. *Am J Obstet Gynecol* 2008;199:244.e1–7.
154. Wootipoom V, Dechsukhum C, Hanprasertpong J, Lim A. Accuracy of intraoperative frozen section in diagnosis of ovarian tumors. *J Med Assoc Thai* 2006;89:577–82.
155. Yarandi F, Eftekhar Z, Izadi–Mood N, Shojaei H. Accuracy of intraoperative frozen section in the diagnosis of ovarian tumors. *Aust N Z J Obstet Gynaecol* 2008;48:438–41.
156. Ghaemmaghami F, Fakour F, Karimi Zarchi M, *et al.* Clinical assessment, gross examination, frozen section of ovarian masses: do patients benefit? *Arch Gynecol Obstet* 2008;278:209–13.
157. Wasinghon P, Suthippintawong C, Tuipae S. The accuracy of intraoperative frozen sections in the diagnosis of ovarian tumors. *J Med Assoc Thai* 2008;91:1791–5.
158. Ilvan S, Ramazanoglu R, Ulker Akyildiz E, Calay Z, Bese T, Oruc N. The accuracy of frozen section (intraoperative consultation) in the diagnosis of ovarian masses. *Gynecol Oncol* 2005;97:395–9.
159. Stewart CJ, Brennan BA, Hammond IG, Leung YC, McCartney AJ. Intraoperative assessment of ovarian tumors: a 5-year review with assessment of discrepant diagnostic cases. *Int J Gynecol Pathol* 2006;25:216–22.
160. Geomini PM, Zuurendonk LD, Bremer GL, de Graaff J, Kruitwagen RF, Mol BW. The impact of size of the adnexal mass on the accuracy of frozen section diagnosis. *Gynecol Oncol* 2005;99:362–6.
161. Fanfani F, Zannoni GF, Fagotti A, *et al.* Importance of a specialized pathologist for the examination of frozen sections of adnexal masses. *Int J Gynecol Cancer* 2007;17:1034–9.
162. Tangjitgamol S, Jesadapatrakul S, Manusirivithaya S, Sheanakul C. Accuracy of frozen section in diagnosis of ovarian mass. *Int J Gynecol Cancer* 2004;14:212–19.
163. Taskiran C, Erdem O, Onan A, *et al.* The role of frozen section evaluation in the diagnosis of adnexal mass. *Int J Gynecol Cancer* 2008;18:235–40.
164. Canis M, Mashiach R, Wattiez A, *et al.* Frozen section in laparoscopic management of macroscopically suspicious ovarian masses. *J Am Assoc Gynecol Laparosc* 2004;11:365–9.

Correspondence to: Michael Fung-Kee-Fung, Cancer Care Ontario's Program in Evidence-based Care, c/o Christina Lacchetti, McMaster University–Henderson Site, 60(G) Wing, 2nd Floor, Room 227, 711 Concession Street, Hamilton, Ontario L8V 1C3.
E-mail: lacchet@mcmaster.ca

* Division of Gynaecologic Oncology, Princess Margaret Hospital, University Health Network, Department of Obstetrics and Gynaecology, Toronto, ON.

† Division of Gynecologic Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON.

‡ Cancer Care Ontario, Program in Evidence-Based Care, McMaster University, Hamilton, ON.

§ Department of Obstetrics and Gynecology, McMaster University, Hamilton, ON.

‖ Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Ottawa, Ottawa, ON.

Guelph Family Health Team, Guelph, ON.

APPENDIX A
SCORING SYSTEMS FOR DISTINGUISHING BENIGN FROM MALIGNANT ADNEXAL MASSES

Ultrasonography-Based Morphology Scoring Systems

TABLE A.I Detailed description of ultrasonography-based scoring systems[3]

Scoring system	*Score*				
Sassone et al., *1991*[91]					
Morphology	1	2	3	4	5
Inner wall structure (mm)	Smooth	Irregularities ≤3	Papillarities >3	NA, mostly solid	—
Wall thickness (mm)	Thin (≤3)	Thick (>3)	NA, mostly solid	—	—
Septa (mm)	None	Thin (≤3)	Thick (>3)	—	—
Echogenicity	Sonolucent	Low echogenicity	Low echogenicity with echogenic core; mixed echogenicity	—	High echogenicity
Cut-off suggestive of malignancy: >9					
DePriest et al., *1993*[92]					
Morphology	0	1	2	3	4
Cystic wall structure (mm)	Smooth (<3 thick)	Smooth (>3 thick)	Papillary projection (<3)	(≥3)	Predominately solid
Volume (cm^3)	<10	10 to 50	>50 to 200	>200 to 500	>500
Septa structure (mm)	None	Thin septa (<3)	Thick septa (3 to 10)	Solid area (≥10)	Predominately solid
Cut-off suggestive of malignancy: ≥5					
Ferrazzi et al., *1997*[93]					
Morphology	1	2	3	4	5
Wall (mm)	≤3	>3	—	Irregular, mostly solid	Irregular, NA
Septa (mm)	None	≤3	>3	—	—
Vegetations	None	—	—	≤3	>3
Echogenicity	Sonolucent	Low echogenicity	—	With echogenic areas	With heterogeneous echogenic areas, solid
Cut-off suggestive of malignancy: >9					
Lerner et al., *1994*[94]					
Morphology	0	1	2	3	—
Wall structure (mm)	Smooth or small irregularities (<3)	—	Solid or NA	Papillarities (≥3)	— —
Shadowing	Yes	No	—	—	—
Septa (mm)	None or thin (<3)	Thick (≥3)	—	—	—
Echogenicity	Sonolucent or low-level echo or echogenic core	—	—	Mixed or high	—
Cut-off suggestive of malignancy: ≥3					

TABLE A.II Finkler ultrasonography-based morphology scoring system[95]

Clear cyst and smooth borders, or fibroid (ovaries normal), or tubular cyst such as hydrosalpinx	1
Clear cyst with slightly irregular border; cyst with smooth walls but low-level echoes (that is, endometrioma)	2
Cyst with low-level echoes with slightly irregular border but no nodularity (that is, endometrioma); clear cyst in postmenopausal patient	3
Equivocal, nonspecific appearance: solid ovarian enlargement or small cyst with irregular borders and internal echoes (hemorrhagic cyst or benign ovarian tumour)	4–6
Multiseptate or irregular cystic mass consistent in appearance with ovarian tumour (7 = less nodularity; 8–9 = more nodularity)	7–9
Pelvic mass as above, with ascites	10

1 = benign; 10 = malignant; ≥7 = indicative of probable malignancy.

TABLE A.III Risk of Malignancy Index (RMI)

RMI[3,96]

The RMI is a clinical prediction rule that calculates a numeric score based on the tumour marker cancer antigen 125 (CA125), which may be elevated in the blood of some cancer patients, multiplied by a menopausal score (M) and an ultrasonography-based morphology score (U). The most common threshold for probability of malignancy is 200. Scores are calculated as follows:

$$\text{RMI} = U \times M \times \text{CA125}$$

where U is 0, 1, or 3 (see explanation, next); M is 1 (premenopausal) or 3 (postmenopausal); and CA125 is the serum CA125 in units per millilitre.

The transabdominal ultrasound imaging is scored 1 point for each of these characteristics:

- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions

If the score is 0, then U = 0; if the score is 1, then U = 1; if the score is 2 or more, then U = 3.

RMI2[97]

The RMI2 is calculated in the same way as the original RMI, except that the U and M components are differently weighted:

- M is 1 (premenopausal) or 4 (postmenopausal).
- If the transabdominal ultrasound imaging score is 0 or 1, then U = 1; if the score is 2 or more, then U = 4.

RMI3[98]

The RMI3 further refines the RMI and RMI2, using the same definitions, but adjusting the U and M components:

- M is 1 (premenopausal) or 3 (postmenopausal).
- If the transabdominal ultrasound imaging score is 0 or 1, then U = 1; if the score is 2 or more, then U = 3.