

# Initial Evaluation and Referral Guidelines for Management of Pelvic/Ovarian Masses

This clinical practice guideline has been prepared and approved by the Society of Obstetricians and Gynaecologists of Canada/Gynecologic Oncologists of Canada/Society of Canadian Colposcopists Policy and Practice Guidelines Committee and the SOGC Diagnostic Imaging Committee. The guideline has been approved by the Executive Council of the Society of Gynecologic Oncologists of Canada, the Executive Council of the Society of Canadian Colposcopists, and the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada. The Society of Obstetricians and Gynaecologists of Canada acknowledges advisory input from the Canadian Association of Radiologists pertaining to imaging guidelines in the creation of this standard.

## PRINCIPAL AUTHORS

Tien Le, MD, Ottawa ON

Christopher Giede, MD, Saskatoon SK

## CONTRIBUTING AUTHOR

Shia Salem, MD, Toronto ON

## SOGC/GOC/SCC POLICY AND PRACTICE GUIDELINES COMMITTEE

Tien Le (Chair), MD, Ottawa ON

Guyline Lefebvre, MD, Toronto ON

Barry Rosen, MD, Toronto ON

James Bentley, MB, ChB, Halifax NS

Christopher Giede, MD, Saskatoon SK

Rachel Kupets, MD, Toronto ON

Patti Power, MD, St. John's NL

Marie-Claude Renaud, MD, Quebec QC

Peter Bryson, MD, Kingston ON

Donald B. Davis, MD, Medicine Hat AB

Susie Lau, MD, Montreal QC

Robert Lotocki, MD, Winnipeg MB

Vyta Senikas, MD, Ottawa ON

## SOGC DIAGNOSTIC IMAGING COMMITTEE

Lucie Morin (Chair), MD, Outremont QC

Stephen Bly, MD, Ottawa ON

Kimberly Butt, MD, Fredericton NB

Yvonne M. Cargill, MD, Ottawa ON

Nanette Denis, RDMS, CRGS, Saskatoon SK

Robert Gagnon, MD, Montreal QC

Marja Anne Hietala-Coyle, RN, Halifax NS

Kenneth Ian Lim, MD, Vancouver BC

Annie Ouellet MD, Sherbrooke QC

Maria-Hélène Racicot, MD, Montreal QC

Shia Salem, MD, Toronto ON

Disclosure statements have been received from all members of the committees.

## Abstract

**Objectives:** To optimize the management of adnexal masses and to assist primary care physicians and gynaecologists determine which patients presenting with an ovarian mass with a significant risk of malignancy should be considered for gynaecologic oncology referral and management.

**Options:** Laparoscopic evaluation, comprehensive surgical staging for early ovarian cancer, or tumour debulking for advanced stage ovarian cancer.

**Outcomes:** To optimize conservative versus operative management of women with possible ovarian malignancy and to optimize the involvement of gynaecologic oncologists in planning and delivery of treatment.

**Evidence:** Published literature was retrieved through searches of PubMed or MEDLINE, CINAHL, and the Cochrane Library, using

appropriate controlled vocabulary and key words. Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. Grey (unpublished) literature was identified by searching the web sites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

## Recommendations

1. Primary care physicians and gynaecologists should always consider the possibility of an underlying ovarian cancer in patients in any age group who present with an adnexal or ovarian mass. (II-2B)
2. Appropriate workup of a perimenopausal or postmenopausal woman presenting with an adnexal mass should include evaluation of symptoms and signs suggestive of malignancy, such as persistent pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size/bloating, and difficulty eating. In addition, CA125 measurement should be considered. (II-2B)

**Key Words:** Pelvic mass, ultrasound evaluation, surgical management

This document reflects emerging clinical and scientific advances on the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the SOGC.

**Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care**

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

\*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.<sup>33</sup>

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.<sup>33</sup>

- Transvaginal or transabdominal ultrasound examination is recommended as part of the initial workup of a complex adnexal/ovarian mass. (II-2B)
- Ultrasound reports should be standardized to include size and unilateral/bilateral location of the adnexal mass and its possible origin, thickness of septations, presence of excrescences and internal solid components, vascular flow distribution pattern, and presence or absence of ascites. This information is essential for calculating the risk of malignancy index II score to identify pelvic mass with high malignant potential. (IIIC)
- Patients deemed to have a high risk of an underlying malignancy should be reviewed in consultation with a gynaecologic oncologist for assessment and optimal surgical management. (II-2B)

J Obstet Gynaecol Can 2009;31(7):668–673

## INTRODUCTION

Ovarian cancer is relatively uncommon, yet it is the deadliest of all gynaecologic malignancies, often affecting perimenopausal and postmenopausal women.<sup>1</sup> According to the Canadian Cancer Society statistics, there were 2300 new cases and 1600 deaths due to ovarian cancer in 2006. In the same report, the estimated five-year survival rate for patients with ovarian cancer (1995–1997) was 38% (95% CI 37%–40%).<sup>2</sup> This rate has not changed significantly over the past few decades despite significant advances in surgical techniques, chemotherapeutic options, and supportive care that have, however, improved the median survival.<sup>3,4</sup> Standard management for patients with tumour clinically localized to the ovary(ies) includes comprehensive surgical staging to guide subsequent need for further adjuvant treatment and to provide prognostic information. For patients with metastatic disease, numerous ret-

rospective and prospective studies have shown that the extent of residual disease after radical surgical debulking is a significant predictor of both progression-free and overall survival.<sup>5,6</sup> More recently, intraperitoneal chemotherapy has shown significant survival benefits over standard intravenous chemotherapy in metastatic disease that has been optimally debulked at time of initial surgical exploration, confirming the importance of aggressive surgical tumour resection at the time of initial diagnosis.<sup>7</sup>

A number of case series have shown that patients with ovarian cancer whose initial surgery is performed by gynaecologic oncologists are more likely to be appropriately staged and optimally debulked than those managed initially by general gynaecologists and general surgeons.<sup>8,9</sup> Despite this, data from a large population-based study suggested that only approximately one third of patients with ovarian cancer were initially managed by gynaecologic oncologists.<sup>8</sup> Likely this is secondary to human resource constraints as well as to the challenges facing physicians in diagnosing cancer preoperatively so appropriate referrals can be made. This guideline is meant to assist physicians in the identification of patients with increased likelihood of underlying malignancy so appropriate referrals can be made to optimize patients' outcomes in the context of the current Canadian health care system.

## OVARIAN MASS INITIAL ASSESSMENTS

Ovarian cancer often remains asymptomatic in its early phase because of the anatomic location of the ovaries deep

in the pelvis. Even when metastases are present, only persistent, mild, vague abdominal symptoms would cause patients to seek medical attention. Physicians should consider the diagnosis of ovarian cancer in all patients presenting with ovarian masses, especially in women in the perimenopausal or postmenopausal age group. In women of reproductive age, the majority of ovarian masses will be of functional origin and these will respond well to an expectant management protocol. A careful history should include the nature, progression, and duration of the presenting symptoms. Specific signs and symptoms suggestive of an underlying malignancy such as pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size/bloating, and difficulty in eating/feeling full should be specifically sought, especially when these symptoms have been persistent (present for <1 year and occurred > 12 days per month).<sup>10</sup> Any significant family history of neoplasia, such as breast, ovarian, endometrial, colorectal, and pancreatic carcinoma should be noted. Family or personal history of endometriosis may be of value in better defining the potential differential diagnosis.

When a woman presents with a unilateral adnexal mass of probable functional origin, it is appropriate to repeat the ultrasound following the next menses to ensure resolution. Cysts or masses that continue to enlarge, become increasingly symptomatic, or attain a more worrisome appearance on ultrasound would then justify further investigation and management.

If the patient has had previous gynaecologic surgery, it is appropriate to obtain previous operative notes and pathology reports. Previous cystectomy for dermoid cyst, for example, or extensive endometriosis, may help predict the nature of the present disease, although it is important to remember that malignancy can occur in the presence of previous benign disease.

When history and/or imaging findings suggest the possibility of an underlying malignancy, a comprehensive physical examination should be carried out that includes assessments of the supraclavicular and inguinal nodal areas, auscultation of the chest, breast examination, and abdominal examination to detect ascites or abnormal masses. A combined pelvic and rectal examination should be done in the presence of any pelvic mass to assess the contour and consistency of the pelvic mass as well as the presence of pelvic nodularities. The presence of any of these signs or symptoms is suggestive of an underlying malignancy. Serum CA125 level measurement should be considered prior to surgical intervention, especially in a situation where the risk of underlying malignancy is elevated.<sup>11</sup> It is important to be aware of the range of normal CA125 in each specific

laboratory used, as many different assays are currently in use with different upper limit of the normal range.

### **ULTRASOUND EXAMINATION**

Transvaginal pelvic/transabdominal ultrasound is a readily available investigation that can provide information to assist physicians in assessing the malignant potential of an adnexal/ovarian mass. Because of the proximity of the ovaries to the transvaginal probe, detailed examination of the appearance and internal structure of the ovarian/adnexal mass can be performed. The size of the mass should be reported, whether it is unilateral or bilateral, and the origin (ovarian or extra ovarian) determined, if possible. A complex multilocular mass, thick septations, presence of papillary excrescences and solid components, increased central vascularity within the mass, and evidence of ascites and peritoneal nodularities have been shown to be predictive of an increased risk of malignancy.<sup>12,13</sup>

### **RISK OF MALIGNANCY INDEX**

A risk of malignancy index (RMI) has been proposed and validated to identify patients at high risk of ovarian cancer.<sup>14,15</sup> Two scoring schemes exist, RMI I and RMI II, each of which derives scores using ultrasound features, menopausal status, and preoperative CA125 level (using assays with a normal CA125 being less than 35 U/mL) according to the following equation:

$$\text{RMI score} = \text{ultrasound score} \times \text{menopausal score} \times \text{CA125 level in U / mL}$$

The original RMI I scoring system and the revised RMI II system are both outlined in Table 2. Three studies have compared the two RMI scoring schemes, using cut-off RMI score above 200 to indicate high malignancy risk.<sup>15-17</sup> The RMI II score was more sensitive than the RMI I system, with a specificity of 89% to 92% and positive predictive values around 80%. Because of its simplicity and reproducibility, the RMI II scoring system is recommended to provide an objective assessment of the underlying malignant potential, using a cut-off score of 200. To facilitate computation of the RMI II score, it is recommended that each ultrasound report done for assessment of an ovarian mass is standardized to include the required variables to compute the RMI score. In patients with an abnormal RMI score based on ultrasound findings and suggestive clinical signs and symptoms of malignancy, further radiographic evaluations such as CT/MRI prior to subspecialty referral are unlikely to be beneficial.

**Table 2. The risk of malignancy index (RMI) scoring system**

Ultrasound features	RMI I score	RMI II score
Multilocular cyst	0 = no abnormality	1 = no or one abnormality
Presence of solid areas	1 = one abnormality	4 = two or more abnormalities
Bilaterality of lesions	3 = two or more abnormalities	
Presence of ascites		
Presence of intra-abdominal metastasis		
Premenopausal	1	1
Postmenopausal	3	4
CA125 level	U/mL	U/mL

Example: A postmenopausal woman with a multilocular cyst with solid areas with ascites and a CA125 level of 100 has a RMI II score of  $4 \times 4 \times 100 = 1600$ .

## **FUTURE DIRECTIONS**

Active research is ongoing to develop better screening tests to detect early ovarian cancers and improve diagnostic accuracy of existing imaging modalities.<sup>18,19</sup>

## **ROLE OF THE GYNAECOLOGIC ONCOLOGIST IN THE MANAGEMENT OF OVARIAN CANCER**

Over the past few decades, there has been an increased emphasis on subspecialty training in the management of various cancers. For ovarian cancer, both centralized care<sup>20,21</sup> and initial surgery by a gynaecologic oncologist resulted in improved outcomes.<sup>22,23</sup> The management of ovarian cancer can be broken down into early (stage I/II) and advanced (stage III/IV) disease.

### **Early Stage Disease**

The management of patients with clinically confined disease to the ovary centres on comprehensive surgical staging to rule out occult metastatic disease. Patients thought to have disease clinically confined to the ovaries are upstaged approximately 30% of the time when further comprehensive surgical staging is performed.<sup>24</sup>

Comprehensive surgical staging should include the following:

1. Bilateral salpingo-oophorectomy and hysterectomy in postmenopausal women. A more limited surgery may be acceptable in young women wishing fertility preservation.
2. Infra-colic omentectomy
3. Peritoneal fluid sampling or pelvic washings
4. Biopsy of any suspicious peritoneal nodules/adhesions or random peritoneal biopsies from all intra-abdominal serosal surfaces
5. Bilateral diaphragmatic scraping/biopsies

6. Retroperitoneal lymph node evaluations to include both bilateral pelvic and para-aortic nodal areas

The contributions of the gynaecologic oncologist to the management of early ovarian cancer can be assessed in the following clinical situations:

### **1. Lower recurrence rates**

In a retrospective review, Le et al.<sup>25</sup> compared recurrence rate in patients who had minimal surgical staging and liberal use of adjuvant chemotherapy with a similar group of patients who had comprehensive staging with more stringent criteria used for adjuvant therapy based on surgical findings. The odds ratio for recurrence was 2.62 (95% CI, 1.09–6.32) in patients not comprehensively staged.

### **2. Improved overall survival**

Studies looking at a relationship between surgeon and survival in early stage ovarian cancer show a trend towards improved survival when gynaecologic oncologists are performing the surgery.<sup>26</sup> One study involving 47 patients by Mayer et al.<sup>27</sup> found patients operated on by gynaecologic oncologists had a 24% improvement in five-year overall survival when compared with those patients operated on by general surgeons and general gynaecologists ( $P < 0.05$ ).

When patients with clinically apparent early ovarian cancer are not staged, consideration is often given to repeat surgery to assist with the decision regarding needs for subsequent adjuvant treatment. The prospect of two surgeries increases the risk for surgical morbidity and increases cost to the health care system. Elit et al.<sup>28</sup> reported the relative risk of re-operation to be significantly decreased when gynaecologic oncologists were present at time of initial surgery. The significance of comprehensive staging was demonstrated recently in the ACTION trial,<sup>29</sup> conducted in Europe. Patients who are optimally staged according to strict protocol and who are proven to truly have surgically stage I disease have a low recurrence rate and high overall

survival even without adjuvant chemotherapy. Patients who are sub-optimally staged are more likely to require adjuvant chemotherapy.<sup>30</sup>

### Advanced Disease

The inverse relationship between residual tumour volume and survival in patients with ovarian cancer was first described by Griffiths in 1975,<sup>31</sup> and several studies have shown an improved rate of optimal debulking and improved overall survival when patients with ovarian cancer whose initial surgery is performed by gynaecologic oncologists. An evidence-based review looking at the relationship between surgical specialty and survival in patients with ovarian cancer found a six- to nine-month median survival benefit in patients managed initially by gynaecologic oncologists.<sup>32</sup>

### Recommendations

The quality of evidence reported in this document has been assessed using the Evaluation of Evidence criteria in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

1. Primary care physicians and gynaecologists should always consider the possibility of an underlying ovarian cancer in patients in any age group presenting with an adnexal or ovarian mass. (II-2B)
2. Appropriate workup of a perimenopausal or post menopausal woman presenting with an adnexal mass should include evaluation of symptoms and signs suggestive of malignancy, such as persistent pelvic/ abdominal pain, urinary urgency/frequency, increased abdominal size/bloating, and difficulty eating. In addition, CA125 measurement should be considered. (II-2B).
3. Transvaginal or transabdominal ultrasound examination is recommended as part of the initial workup of a complex adnexal/ovarian mass. (II-2B)
4. Ultrasound reports should be standardized to include size and unilateral/bilateral location of the adnexal mass and its possible origin, thickness of septations, presence of excrescences and internal solid components, vascular flow distribution pattern, and presence or absence of ascites. This information is essential for calculating the risk of malignancy index II score to identify pelvic mass with high malignant potential. (IIIC)
5. Patients deemed to have a high risk of an underlying malignancy should be reviewed in consultation with a gynaecologic oncologist for assessment and optimal surgical management. (II-2B)

### REFERENCES

1. Zhang J, Ugnat AM, Clarke K, Mao Y. Ovarian cancer histology-specific incidence trends in Canada 1969–1993: age-period-cohort analyses. *Br J Cancer* 1999;81(1):152–8.
2. Canadian Cancer Society. Canadian cancer statistics, 2006. Available at: <http://www.cancer.ca>. Accessed May 8, 2009.
3. Chan JK, Cheung MK, Husain A, Teng NN, West D, Whitemore AS, et al. Patterns and progress in ovarian cancer over 14 years. *Obstet Gynecol* 2006;108(3 Pt 1):521–8.
4. Tingulstad S, Skjeldestad FE, Halvorsen TB, Hagen B. Survival and prognostic factors in patients with ovarian cancer. *Obstet Gynecol* 2003;101(5 Pt 1):885–91.
5. Chan JK, Loizzi V, Lin YG, Osann K, Brewster WR, DiSaia PJ. Stages III and IV invasive epithelial ovarian carcinoma in younger versus older women: what prognostic factors are important? *Obstet Gynecol* 2003;102(1):156–61.
6. Bristow RE, Montz FJ, Lagasse LD, Leuchter RS, Karlan BY. Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. *Gynecol Oncol* 1999;72(3):278–87.
7. Jaaback K, Johnson N. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst Rev* 2006 Jan 25;(1):CD005340.
8. Earle CC, Schrag D, Neville BA, Yabroff KR, Topor M, Fahey A, et al. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. *J Natl Cancer Inst* 2006 ;98(3):172–80.
9. Engelen MJ, Kos HE, Willemse PH, Aalders JG, de Vries EG, Schaapveld M, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. *Cancer* 2006;106(3):589–98.
10. Goff BA, Mandel LS, Drescher CW, Urban N, Gough S, Schurman KM, et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. *Cancer* 2007;109(2):221–7.
11. Milojkovic M, Hrgovic Z, Hrgovic I, Jonat W, Maass N, Bukovic D. Significance of CA 125 serum level in discrimination between benign and malignant masses in the pelvis. *Arch Gynecol Obstet* 2004;269(3):176–80.
12. Valentin L, Ameye L, Testa A, Lécuru F, Bernard JP, Paladini D, et al. Ultrasound characteristics of different types of adnexal malignancies. *Gynecol Oncol* 2006;102(1):41–8.
13. Brown DL, Doubilet PM, Miller FH, Frates MC, Laing FC, DiSalvo DN, et al. Benign and malignant ovarian masses: selection of the most discriminating gray-scale and Doppler sonographic features. *Radiology* 1998;208(1):103–10.
14. 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(3):128–31.
15. Tingulstad S, Hagen B, Skjeldestad FE, Onsrud M, Kiserud T, Halvorsen T, 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(8):826–31.
16. 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(6):524–7.
17. Aslam N, Tailor A, Lawton F, Carr J, Savvas M, Jurkovic D. Prospective evaluation of three different models for the pre-operative diagnosis of ovarian cancer. *BJOG* 2000;107(11):1347–53.
18. Moore RG, Brown AK, Miller MC, Skates S, Allard WJ, Verch T, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecol Oncol* 2008;108(2):402–8.
19. 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(1):40–8.

20. Ioka A, Tsukuma H, Ajiki W, Oshima A. Influence of hospital procedure volume on ovarian cancer survival in Japan, a country with low incidence of ovarian cancer. *Cancer Sci* 2004 Mar;95(3):233–7.
21. Paulsen T, Kjaerheim K, Kaern J, Tretli S, Trope C. Improved short term survival for advanced ovarian, tubal, and peritoneal cancer patients operated at teaching hospitals. *Int J Gynecol Cancer* 2006;16(Suppl 1):11–7.
22. Eisenkop SM, Spirtos NM, Montag TW, Nalick RH, Wang HJ. The impact of subspecialty training on the management of advanced ovarian cancer. *Gynecol Oncol* 1992 Nov;47(2):203–9.
23. Junor EJ, Hole DJ, McNulty L, Mason M, Young J. Specialist gynaecologists and survival outcome in ovarian cancer: a Scottish national study of 1866 patients. *Br J Obstet Gynaecol* 1999 Nov;106(11):1130–6.
24. Young RC, Decker DG, Wharton JT, Piver MS, Sindelar WF, Edwards BK, et al. Staging laparotomy in early ovarian cancer. *JAMA* 1983;250:3072–6.
25. Le T, Adolph A, Krepart GV, Lotocki R, Heywood MS. The benefits of comprehensive surgical staging in the management of early-stage epithelial ovarian carcinoma. *Gynecol Oncol* 2002 May;85(2):351–5.
26. Nguyen HN, Averette HE, Hoskins W, Penalver M, Sevin BU, Steren A. National survey of ovarian carcinoma. Part V. The impact of physician's specialty on patients' survival. *Cancer* 1993;72(12):3663–70.
27. Mayer AR, Chambers SK, Graves E, Home C, Tseng PC, Nelson GE, et al. Ovarian cancer staging: does it require a gynecologic oncologist? *Gynecol Oncol* 1992;47:223–7.
28. Elit L, Bondy SJ, Paszat L, Przybysz R, Levine M. Outcomes in surgery for ovarian cancer. *Gynecol Oncol* 2002;87:260–7.
29. Trimbos JB, Parmar M, Vergote I, Guthrie D, Bolis G, Colombo N, et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst* 2003;95:105–12.
30. Trimbos JB, Vergote I, Bolis G, Vermorken JB, Mangioni C, Madronal C, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. *J Natl Cancer Inst* 2003 95(2):113–25.
31. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst Monogr* 1975;42:101–4.
32. Giede KC, Kieser K, Dodge J, Rosen B. Who should operate on patients with ovarian cancer? An evidence based review. *Gynecol Oncol* 2005;99(2):447–61.
33. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. *CMAJ* 2003;169(3):207–8.