



Evidence-Based Series #4-11 REQUIRES UPDATING

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

Organizational Guideline for Gynecologic Oncology Services in Ontario

*M. Fung-Kee-Fung, E.B. Kennedy, J. Biagi, T. Colgan, D. D'Souza, L. Elit, A. Hunter, J. Irish,
R. McLeod, B. Rosen and members of the
Gynecologic Oncology Organizational Guideline Expert Panel*

Report Date: June 6, 2013

An assessment conducted in February 2021 indicated that Evidence-based Series (EBS) 4-11 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

Evidence-Based Series 4-11 is comprised of 3 sections. You can access the summary and full report here:

<https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/446>

Section 1:	Guideline Recommendations
Section 2:	Evidentiary Base
Section 3:	Development Methods, Recommendations Development and External Review Process

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Fung-Kee-Fung M, Kennedy EB, Biagi J, Colgan T, D'Souza D, Elit L, et al. Organizational guideline for gynecological services in Ontario. Toronto (ON): Cancer Care Ontario; 2013 June 6 [REQUIRES UPDATING]. Program in Evidence-based Care Evidence-based Series No.: 4-11 REQUIRES UPDATING.

Journal Citations: Fung-Kee-Fung M, Kennedy EB, Biagi J, Colgan T, D'Souza D, Elit LM, et al. The optimal organization of gynecologic oncology services: a systematic review. *Curr Oncol.* 2015;22(4):e282-93.

Fung-Kee-Fung M, Kennedy EB, Biagi J, Colgan T, D'Souza D, Elit LM, et al. An organizational guideline for gynecologic oncology services. *Int J Gynecol Cancer.* 2015;25(4):551-8.

IN REVIEW

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Organizational Guideline for Gynecologic Oncology Services in Ontario:
Guideline Recommendations

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IN REVIEW

Evidence-Based Series #4-11: Section 1

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Guideline Recommendations

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**A Quality Initiative of the
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Guideline Recommendations**

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Report Date: June 6, 2013

A. GUIDELINE OBJECTIVE

To determine the optimal organization of gynecologic oncology services in Ontario for patients who have been diagnosed with a gynecologic malignancy in order to ensure high-quality care and optimal cancer treatment outcomes.

B. RESEARCH QUESTIONS

1. Does treatment by a gynecologic oncologist result in better outcomes than treatment by a gynecologist (GYN) or general surgeon (GS)?
2. Are there better outcomes for patients with gynecologic cancer treated in designated centres compared to non-designated centres?
3. Is there a volume-outcome relationship between number of procedures by a physician/hospital and patient surgical or survival outcomes?

In addition, the Gynecologic Oncology Organizational Guideline Development Group (the Guideline Development Group) agreed to use the evidentiary base generated by the research questions above to provide consensus-based guidance regarding implementation of the optimal system of organization for gynecologic oncology in Ontario. Questions related to implementation/organization include:

1. How will services be regionally organized? Will specialized gynecologic oncology centres be designated?
2. If designated centres are recommended:
 - What is the optimal relationship or network of care between designated and non-designated centres?
 - What are the human and physical resources requirements of a designated (specialized) centre?

The general consensus at this time is that multidisciplinary care is the standard for all cancer types (1), and Cancer Care Ontario supports the use of regularly scheduled multidisciplinary cancer conferences (MCCs) to prospectively review individual cancer patients and make recommendations on management (2). The following questions specific to gynecologic oncology multidisciplinary teams (MDTs) were also asked by the Guideline Development Group:

1. What are the recommended staff requirements for a gynecologic oncology MDT?
2. What expertise/formal training is required by the members of the MDT?

C. PATIENT POPULATION

The target patient population is women in Ontario who have been diagnosed with gynecologic cancer or have an ovarian mass with Risk of Malignancy Index (RMI) >200. The scope does not include the following non-invasive cases:

- Cervical intraepithelial neoplasia & carcinoma in situ (\leq Stage T1a1);
- Vaginal intraepithelial neoplasia;
- Vulvar intraepithelial neoplasia;
- Ovarian masses with an RMI score of less than 200, as these cases are less likely to be invasive (3);
- Low-risk gestational trophoblastic neoplasia (GTN) that resolves spontaneously.

D. INTENDED USERS

This guideline is intended for use by Ontario policy makers and clinicians involved in the care of gynecologic cancer patients.

E. INTRODUCTION

Rationale for a Guideline

A system-level organizational guideline has been identified by the PEBC Gynecologic Oncology Disease Site Group and the Surgical Oncology Program, through consultation with stakeholders in Ontario, as a key priority. The purpose of the guideline is to provide recommendations for the optimal organization of gynecologic oncology services in Ontario in order to improve access to multidisciplinary care and appropriate treatment, thereby improving outcomes for patients. Designation of this topic as a key priority was based on data suggesting a gap in quality of care in Ontario, including data showing many patients are receiving care in lower volume hospitals and, are therefore, less likely to have access to multidisciplinary care, and that many ovarian and endometrial cancer patients are not receiving adequate surgical staging, which has independently been associated with survival. There are also issues in Ontario with wait times for gynecologic oncology surgery, with only 69% and 67% of surgeries being completed within the wait time target for the first and second quarter of 2012/2013, respectively (4). At the same time, a 16% increase in gynecologic malignancies is projected between 2011 and 2018 (5,6). With an increase in the patient population, there is a need to examine ways to establish a network that will facilitate the flow of these patients through the care continuum. Furthermore, the lower rates of staging in Ontario by both specialists and non-specialists indicate that there is a need for recommendations that will allow a collaborative community of practice to evolve in order to facilitate adherence to guidelines and best practices at a system-wide level (7).

Scope of the Report

The scope of the report is defined by the research questions and includes recommendations for the optimal organizational of gynecologic oncology services in Ontario, including whether patients should receive subspecialty care in designated hospitals, the human and physical resources associated with the delivery of care, and the characteristics of the relationship between designated and non-designated hospitals. The guideline also addresses some aspects of the working of the multidisciplinary team.

Development of the Guidance Document

The recommendations in this document are based on a systematic review of existing guidance documents and primary literature found in electronic databases. Overall, the

evidence base was determined to be of lower quality, based on study design, conflicting findings, and the lack of generalizability of results due to heterogeneity of comparison groups and outcome measures. Thus, the Guideline Development Group, which included expertise in gynecologic oncology, radiation oncology, medical oncology, methodology, and representation from CCO's Surgical Oncology Program, used an informal consensus-based approach to develop a consensus-based guideline, relying on trends found in the evidence, recommendations from other jurisdictions, and personal opinion based on knowledge of the current situation in the province. The recommendations were reviewed by an Expert Panel (EP) that included the specialties represented on the Guideline Development Group and additional expertise in gynecology, pathology, and nursing as well as a regional vice president. The comments of the EP were incorporated into the draft, which subsequently received EP approval. The document was also disseminated widely to professionals from relevant specialties across Ontario, and to three peer reviewers from outside of the province for their review and feedback, which was incorporated into the guideline draft. A summary of the development process, including the feedback from reviewers is provided in Section 3 of this EBS document.

Overview of Guideline Recommendations

Specific recommendations are outlined in the Recommendations and Key Evidence section below. In summary, the Guideline Development Group's consensus is a vision for gynecologic cancer care in the province that includes:

- Access to treatment for all invasive cancer at Gynecologic Oncology Centres and affiliated centres, effectively creating networks of care;
- Strong, well-defined accountable partnerships between gynecologic oncology centres and affiliated centres;
- Consistent high-quality treatment provision within and between regional networks, regardless of geographic location;
- Access to multidisciplinary care for all gynecologic oncology patients.

More resources may be needed in order to meet the recommendations outlined in this guidance document, as we are recommending that some cases be shifted to subspecialty care and more comprehensive pathology reviews. We hope that these recommendations will result in improvements in practice for individuals who are already practicing in higher volume teaching centres, including better adherence to existing guidance, and greater collaboration among specialties, resulting in improved access to treatment and better outcomes for gynecologic oncology patients in Ontario throughout the patient journey from diagnosis to treatment, recovery, and palliative care.

F. RECOMMENDATIONS AND KEY EVIDENCE

I. GYNECOLOGIC ONCOLOGISTS

Recommendation

Definitive surgical treatment of the following invasive cancers should be performed by gynecologic oncologists:

- cervical cancer (Stage \geq T1A2);
- endometrial cancer (grade 2 or 3), including high-risk histology i.e., uterine clear cell or papillary serous carcinoma, malignant mixed Mullerian tumour;
- ovarian cancer, including germ cell, epithelial cell and stromal cancers, and all suspicious ovarian masses with a Risk of Malignancy Index score greater than 200 (3);
- vulvar cancer;
- vaginal cancer.

Recommendation

Patients who have intermediate to high GTN and low-risk GTN in need of chemotherapy need to be assessed and treated by gynecologic oncologists.

Recommendation

Definitive surgical treatment of grade 1 endometrial cancer may be performed by a GYN or gynecologic oncologist.

Recommendation

Definitive surgical treatment of gynecologic malignancies is not within the domain of general surgery.

Qualifying statements

- As evidence has shown that adherence to recommended clinical practice guidelines can be sub-optimal for gynecologic oncologists at teaching centres, it will be important to implement initiatives that improve adherence to accepted clinical practice guidelines and to identify and fill gaps in guidance for the Ontario context (7).
- The correlation between preoperative biopsy for endometrial adenocarcinoma and the final tumour grade determined by the hysterectomy specimen has been found to range from 15% to 30% in several studies (8-10). A large population-based study from Ontario, using data from 1996-2000, found that the discordance between pre- and postoperative diagnosis of grade 1 tumours was 27% (11). These data suggest that the capacity of the preoperative biopsy to identify lower risk patients is limited. The Guideline Development Group recognizes this limitation and provides further recommendations below, including multidisciplinary care and optimization of the quality of initial pathology reporting in order to ensure that as many patients as possible receive surgery from the appropriate recommended specialty.

Key Evidence

Evidence for an advantage with treatment by a gynecologic oncologist was mixed. In a systematic review that included ovarian cancer patients, 7 of 15 studies that compared treatment by a gynecologic oncologist to a GYN found a survival advantage with treatment by a gynecologic oncologist; however, the significant effects were found only for selected subgroups according to particular FIGO stages, with the positive effect more pronounced in patients with a poorer prognosis (12). They also found that survival was worse for patients treated by GYN, compared to GS in 7 of 11 studies that assessed this comparison, with the differences limited to specific FIGO stages in three studies. Surgery by gynecologic oncologist resulted in a significant advantage compared to surgery by GYN according to various measures of optimal debulking in 6 of 11 studies of patients with advanced disease. Surgery by GYN versus GS resulted in a significant advantage when the outcome was degree of cytoreduction in five of nine studies. All studies evaluating physical specialty and completeness of surgical staging found a significant association in favour of gynecologic oncologist compared to GYN or others.

Our systematic review found a significant association between survival for ovarian cancer and physician specialty in one of four studies that met the inclusion criteria; however, this study compared gynecologic oncologist/GYN care to GS care. Two studies assessed the relationship between physician specialty and surgical outcomes. A study that used Ontario data from 1996 to 1998 found no difference in survival for patients by surgical discipline (gynecologic oncologist vs. GYN), after controlling for prognostic factors associated with stage

of disease; however, a significant gynecologic oncologist advantage was found for risk of repeat surgery (13), compared to the categories GYN, GS and other physician type. The second study found that subspecialist gynecologists were significantly more likely to adequately stage patients (14).

Three studies assessed survival difference for endometrial cancer patients with treatment by gynecologic oncologist versus GYN/other (15-17). One found no significant difference for gynecologic oncologist versus GYN in a population with stage IA-IIA disease (17), while another other found a significant advantage for gynecologic oncologist versus other for all stages combined (15). A study that used Ontario data from 1996 to 2000 found that there was no difference in 5-year survival for gynecologic oncologist versus other after controlling for stage and other prognostic variables (16). Three of three studies found that surgery by a gynecologic oncologist involves a more comprehensive assessment of tumour invasion and more accurate determination of stage, compared to surgery by a GYN in both early-stage endometrial cancer and for all stages combined (15,17,18).

No studies were found that looked at outcomes by physician specialty for cervical cancer, vulvar cancer, vaginal cancer or GTN.

Justification

The limited and inconsistent nature of the evidence led the Guideline Development Group to develop the consensus-based recommendation that all invasive ovarian cancer patients receive treatment by a gynecologic oncologist. The Guideline Development Group concluded that the evidence for a link between gynecologic oncologist care and overall survival was not strong, perhaps due to data-quality issues. However, a systematic review did find a strong association between gynecologic oncologist care and completeness of surgical staging (12). Furthermore, a study conducted in Ontario found that repeat surgery, which is associated with increased risk or morbidity, was significantly more likely to occur with treatment by GYNs, GSs or other physicians than by gynecologic oncologists, after controlling for stage and other prognostic factors (13). A second study found that physician specialty (“specialized gynecologists” vs. GYNs) was significantly associated with adequate staging (14). As completeness of staging is important for long-term survival in early ovarian cancer, the Guideline Development Group concluded that these patients should have access to gynecologic oncologist care in Ontario. Optimal debulking is a critical prognostic factor in advanced ovarian cancer. More than half the studies in a systematic review found that optimal debulking was more likely with subspecialty care, providing further rationale for the Guideline Development Group’s recommendation that all invasive ovarian cancer patients receive treatment by gynecologic oncologists.

In Ontario, there is no guideline for surgery for endometrial cancer, and patterns of practice vary across the province. It is the consensus opinion of the Guideline Development Group that all endometrial cancer patients whose biopsy is read as grade >1 preoperatively should be treated by gynecologic oncologists because of the finding that subspecialists provide more-comprehensive staging procedures including appropriate lymph node and upper abdominal assessment (15,17,18). Staging has been found to be a predictor of mortality because, although not of direct survival benefit, it serves as a proxy indicator for overall quality of management (19).

It is the consensus of the Guideline Development Group that endometrial cancer patients whose biopsy is read as grade 1 preoperatively may have surgery performed by gynecologic oncologists or GYNs, because the risk of lymph node metastases in patients with confirmed grade 1 adenocarcinoma is approximately 2.8% (20). Therefore, in the Guideline Development Group’s opinion, the potential value of treatment by a gynecologic oncologist (i.e., comprehensive surgical staging) does not outweigh the considerable increase in human

resources and operating room time that would be required for all patients with endometrial cancer to have surgery performed by a gynecologic oncologist.

The consensus of the Guideline Development Group is that surgical treatment of vulvar cancer should be performed by gynecologic oncologists, due to the relative rarity of this carcinoma (approx. 150 cases per year in Ontario), and the need for meticulous attention to optimizing margins and balancing the risk of local recurrence with the morbidity associated with inguinal lymph node dissection (21). The recommendation that all invasive cervical cancer be treated by a gynecologic oncologist is based on knowledge of the technically demanding nature of the radical hysterectomy procedure and its relatively infrequent performance by most gynecologists.

The consensus of the Guideline Development Group is that treatment of moderate- and high-risk GTN should be performed by gynecologic oncologists or gynecologic oncologists in collaboration with Medical Oncology, due to the relative rarity of this carcinoma, and the need for meticulous attention to timely aggressive treatment in order to obtain cure and to minimize adverse events. The recommendation that all moderate- and high-risk GTN and low-risk GTN that require chemotherapy be treated by a gynecologic oncologist or a gynecologic oncologist in collaboration with a Medical Oncologist is based on the rarity of this tumour, potential high curability if dealt with aggressively, and toxicity of multi-agent chemotherapy.

II. GYNECOLOGIC ONCOLOGY CENTRES

1. Treatment at gynecologic oncology centres

Recommendation

Gynecologic oncologist care should be delivered within designated gynecologic oncology centres.

Recommendation

In addition to surgical care, gynecologic oncology centres will be equipped to provide radiation therapy and systemic therapy for all invasive gynecologic oncology disease sites, and act as the hub for management of all invasive cases.

Qualifying statement

- As evidence has shown that adherence to recommended clinical practice guidelines can be sub-optimal for gynecologic oncologists at designated centres, it will be important to implement initiatives that improve adherence to accepted clinical practice guidelines and to identify and fill gaps in guidance for the Ontario context.

Key Evidence

Six studies that assessed outcomes with centralization or regionalization of gynecological cancer met the inclusion criteria for the systematic review.

The effect of centralization of gynecologic oncology services after the implementation of the 1999 UK National Health Service *Improving Outcomes in Gynecologic Cancer (IOG)* (22) recommendations was assessed in the East Anglia region of the UK. Mortality was reduced significantly for patients with gynecologic cancer in the post-centralization study period compared to pre-centralization (HR: 0.71, 95%CI 0.64-0.79%, $p < 0.001$). Overall, the improvements were attributed to “access to specialized surgery” and “management within a multidisciplinary team” (23); however, as there were known deficiencies in quality of care in the UK prior to the implementation of this guidance in 1999, it is not clear whether or not a comparable improvement could be expected if similar guidelines were implemented in this jurisdiction. Another study looked at outcomes before and after implementation of the IOG

recommendations and found no differences; however, this study included areas where the guidance had not been fully implemented (24). The only study that controlled for clustering of outcomes among facilities found there was no evidence of improved ovarian cancer patient survival with hospital teaching status, although a difference had been found before controlling for clustering (25).

In a study of vulvar cancer in West Midlands, UK (26), 15 different surgical procedures were described before centralization. After centralization, only four types of surgery were performed, and 84% of patients that required lymph node dissection had this procedure, although heterogeneity of surgical technique remained evident. Implementation of centralization that included specialized gynecologic pathology assessment also coincided with improved histology reporting and achievement of adequate excision margins. Although only 52% of case notes had enough information to evaluate 5-year disease-specific survival, survival improved from 51.3% pre-centralization to 73.8% post-centralization ($p=0.055$). Munstedt found that in the population of patients for whom lymphadenectomy is recommended and feasible, it was more likely to be performed in central hospitals; however, even in these centres, adherence to appropriate guidelines was found to be lacking (27). The treatment of ovarian cancer was slowly centralized over a decade in Denmark (28). A significant reduction in mortality for stage IIIC-IV ovarian cancer patients was found for patients treated in tertiary centres compared to others.

Justification

As the evidence for treatment at designated centres was mixed and may have limited applicability to the Ontario context, the recommendation for treatment of most invasive gynecologic cancers by gynecologic oncologists at designated gynecologic oncology centres is the opinion of the Guideline Development Group, based on the consensus that gynecologic oncology centres will be best equipped to provide the resources that are needed to support the work of gynecologic oncologists, including proximity to other members of the multidisciplinary team, and more specialized pathology expertise, capacity to support multidisciplinary cancer conferences, facilitation of accrual to clinical trials, and the necessary human and physical resources outlined in the recommendations below.

2. Human resources at gynecologic oncology centres

Recommendations

The multidisciplinary team at a gynecologic oncology centre should include:

- A minimum of two full-time gynecologic oncologists.
- A minimum of two radiation oncologists.
- A minimum of one specialist in Medical Oncology, with an interest in gynecologic malignancies.
- An adequate number of pathologists with a specialty or special interest in gynecologic pathology.
- Access to molecular scientists for Microsatellite Instability testing, genotyping for placental molar disease and human papillomavirus testing.
- Specialists in Radiology, including one with expertise in gynecologic diagnostic imaging and interventional radiology.
- Access to specialized oncology nursing, and advanced practice nursing

The following medical specialists should be on site:

- Psycho-social-sexual counselling and support.
 - Palliative care physician or specialist, which may include assessment at the

gynecologic oncology centre, with seamless linkage to and coordination with providers in the patient's home community.

- Specialists in general or colorectal surgery, anaesthesia, urology, plastic surgery, or other areas as needed.
- Access to dietitians.

Access to the following medical specialists should be available as required:

- Geneticist/genetic oncology clinic where patients with hereditary predisposition to cancer can receive counselling and appropriate testing when indicated.
- Access to an expert in reproductive medicine.

Key evidence and justification

The detailed requirements for human resources are the opinion of the guideline development group, based on the resources that the group determined would be necessary to support the treatment of patients with invasive gynecologic cancer in gynecologic oncology centres.

3. Physical resources and collaborating services at gynecologic oncology centres

Recommendations

The following physical resources and collaborating services should be available at gynecologic oncology centres:

- Surgery services should be appropriately equipped and resourced to provide:
 - Minimally invasive surgery (laparoscopic/robotic).
 - An intensive care unit (ICU).
 - Dedicated surgical beds for gynecologic oncology patients, with nursing expertise.
 - A fully developed nutrition service, including total parenteral nutrition.
 - Access to specialized stoma care.
- Radiation Therapy services should be appropriately equipped and resourced to provide:
 - On-site services, including capacity for the administration of brachytherapy.
- Systemic Therapy services should be appropriately equipped and resourced to provide:
 - Chemotherapy and biologic agents, and oncology pharmacy support for inpatient and outpatient services.
 - Chemotherapy and biologic agents should be administered by nurses (RNs) who have completed the de Souza Institute Chemotherapy and Biotherapy Provincial Standardized course.
 - Intraperitoneal chemotherapy.
- Pathology services should be appropriately equipped and resourced to provide:
 - Intraoperative frozen-section analysis.
 - Immunohistochemistry (IHC) and molecular testing.
 - Cytopathology/cytology services.
- Radiology services should be appropriately equipped and resourced to provide:
 - A full range of diagnostic imaging, including ultrasound (all modalities, including Doppler), computerized tomography, magnetic resonance imaging, angiography and interventional radiology.
 - Nuclear medicine capabilities to assess sentinel lymph nodes.
- Access to a Community Care Access Centre.

- A formal palliative care service.

Overall, the gynecologic oncology centre should provide:

- High-quality, patient-centred care throughout the patient journey.
- A system for the regular review of the program, including clinical and educational rounds, quality-of-care review, and quality assurance. This includes participation in all quality-improvement programs of Cancer Care Ontario.
- Patient access to clinical trials.
- Teaching, research, quality improvement, and program advancement.

Key evidence and justification

The detailed requirements for physical and collaborating services are the opinion of the guideline development group, based on the resources that the group determined would be necessary to support the treatment of patients with invasive gynecologic cancer in gynecologic oncology centres.

4. Annual volumes at gynecologic oncology centres

Recommendation

A minimum annual volume of 150 new surgical cases is recommended for each gynecologic oncology centre.

Recommendation

A minimum annual volume of 100 new gynecologic oncology radiation therapy cases is recommended for each gynecologic oncology centre.

Qualifying statements

- Volumes for systemic therapy were addressed in PEBC guideline #12-10, which concluded: *“After numerous discussions, the Group determined that [systemic therapy] service volumes should depend on local conditions. A centre should have a sufficient patient volume to maintain competency and safety”* (29).
- If brachytherapy is offered, a minimum of 10 cervical cases should be treated annually, according to PEBC guideline #21-2 (30).

Key evidence

There were no studies specifically designed to test the optimal patient volumes to ensure safe and effective patient care. Furthermore, there is no agreed upon set of criteria for defining safe and effective care. Seventeen studies assessed the relationship between physician and/or hospital volumes and surgical or survival outcomes for one or more disease sites. Higher physician volumes were related to improved survival and surgical outcomes in two (31,32) and four studies (14,21,33,34), respectively. Higher hospital volumes were related to improved survival and surgical outcomes in three (35-37) and five studies (14,31,37-39), respectively. The definition of high volume, when reported, ranged between >4 (33) and at least 100 (40) for physician volumes, and >7 (33) and at least 200 (40) for hospital volumes.

Justification

Although a trend towards improved outcomes with higher volumes was found in some studies, the definitions of “high volume” and “low volume” were highly variable in the literature; therefore, the recommendation for annual volumes of new surgical cases at

gynecologic oncology centres is the opinion of the guideline development group, based on a consensus regarding a reasonable workload for gynecologic oncologists in Ontario, supported by CCO program data (2009-2010). This volume is considered a sufficient caseload to justify the resource investment necessary for a gynecologic oncology centre, and to maintain the skills of the multidisciplinary team.

The recommendation for radiation therapy volumes is the consensus of the Guideline Development Group, based on minimum numbers needed to ensure competency and quality of care (41).

III. AFFILIATED CENTRES

1. Treatment at affiliated centres

Recommendation

Treatment centres that develop a formal affiliation with GOCs may provide any or all of the following services:

- surgery for endometrial cancer patients that are determined preoperatively to be lower risk (i.e., grade 1);
- radiation therapy for all gynecologic oncology disease sites;
- systemic therapy for all gynecologic oncology disease sites.

Recommendation

Appropriate pathology review must be available for all new patients, and access to multidisciplinary team management, including a multidisciplinary cancer conference (MCC) review or documented collaborative discussion between at least two disciplines, or a multidisciplinary clinic appointment at a gynecologic oncology centre must be provided.

Key evidence and justification

As there was no evidence found in the literature search to support the establishment of treatment at affiliated centres, these recommendations are the consensus of the Guideline Development Group, which agreed that, provided a strong linkage was established and maintained with a gynecologic oncology centre, radiation and systemic therapy could be delivered at affiliated centres, in order to allow patients to receive ongoing treatments closer to home.

The recommendation for primary surgery for lower risk endometrial cancer patients is based on the rationale outlined above under Recommendation 1. Gynecologic Oncologists. In the opinion of the Guideline Development Group, appropriate pathology review and access to multidisciplinary consultation are essential for low-grade endometrial patients prior to surgery in order to ensure the best possible accuracy when assigning preoperative grade.

2. Human resources at affiliated centres

Recommendations

It is recommended that affiliated centres have:

- If surgery is offered:
 - a minimum of one gynecologist with a commitment to gynecologic oncology and skills to perform minimally invasive surgery. Centres should strive to have all gynecologic oncology surgeries performed by a small number of gynecologists who discuss grade 1 endometrial cancer patients with a gynecologic oncologist at a gynecologic oncology centre prior to surgery.

- a pathologist with an interest in gynecologic pathology who is networked to gynecologic oncology centre.
- If radiation is offered, a minimum of one radiation oncologist is required.
- If systemic therapy is offered, a medical oncologist [Level 1-3 Regional Systemic Treatment Program (RSTP)], or family physician or nurse (Level 4 RSTP), networked to a gynecologic oncologist or medical oncologists at a gynecologic oncology centre.

Key evidence

The detailed requirements for human resources are the opinion of the guideline development group, based on the resources that the group determined would be necessary to support the treatment of patients with invasive gynecologic cancer in centres that are affiliated with gynecologic oncology centres.

The recommendation for systemic therapy at RSTPs is an endorsed recommendation from previous PEBC guideline #12-10 (29).

3. Physical resources and collaborating services at affiliated centres

Recommendations

It is recommended that physical and collaborating resources at affiliated centres are appropriately equipped and resourced to provide:

- Resources to assess the risk of malignancy of a suspicious adnexal mass, including ultrasound (15) and standardized ultrasound reports (42).
- If surgery is offered:
 - minimally invasive surgery (laparoscopic/robotic).
 - a quality-assurance process to ensure that assignment of the pathologic grade for endometrial cancer patients is reviewed prior to surgery. This may include options such as a quality-assurance program at the affiliated centre, a discussion among pathologists at the affiliated centre, or a review by a gynecologic pathologist at a GOC.
- basic histopathology and IHC testing. Pathology services should be networked to a GOC for non-routine technical testing, as necessary.
- If systemic therapy is offered:
 - chemotherapy and biologic agents, and oncology pharmacy support for inpatient and outpatient services.

Centres offering systemic therapy must be designated RSTPs. Where intra-peritoneal therapy is offered, centres must be Level 1-3 RSTPs (29).

Key Evidence and justification

The detailed requirements for physical and collaborating services, including options for pathology review, are the opinion of the guideline development group, based on the resources that the group determined would be necessary to support the treatment of patients with invasive gynecologic cancer in centres that are affiliated with gynecologic oncology centres.

With respect to pathology review, there is widespread agreement on the benefits of pathology review for the planning of initial management of endometrial cancer patients. Pathology reviews have been performed by body system subspecialists in pathology (e.g., gynecologic pathologists), but in the guideline development group's experience, such subspecialty opinions are not always available in a timely fashion, particularly at anticipated affiliated hospitals; therefore, additional options have been recommended. The issue of which types of specimens may need a secondary review is under further study in a

forthcoming PEBC guideline, which will inform acceptable pathology review procedures for gynecologic pathology.

The recommendation for systemic therapy at RSTPs is an endorsed recommendation from previous PEBC guideline #12-10 (29).

4. Annual volumes at affiliated centres

Recommendations

There is insufficient evidence to specify a target volume for annual number of new surgical, radiation or systemic therapy cases at affiliated centres.

Qualifying statements

- Volumes for systemic therapy were addressed in PEBC guideline #12-10, which concluded: “After numerous discussions, the Group determined that [systemic therapy] service volumes should depend on local conditions. A centre should have a sufficient patient volume to maintain competency and safety” (29).
- If brachytherapy is offered, a minimum of 10 cervical cases should be treated annually, according to PEBC guideline #21-2 (30).

Key evidence

While the guideline development group recognized that a relationship between higher surgical volumes and improvement in outcomes was identified in the systematic review, the inconsistency of the relationship and the variability in defined cut-offs led the guideline development group to conclude that it would not be appropriate to arbitrarily recommend minimum annual volumes at this time for affiliated centres.

As stated above in the section on annual volumes in gynecologic oncology centres, there is no minimum volume specified for systemic therapy, based on PEBC guideline #12-10.

IV. RELATIONSHIP BETWEEN GYNECOLOGIC ONCOLOGY CENTRES and AFFILIATED CENTRES

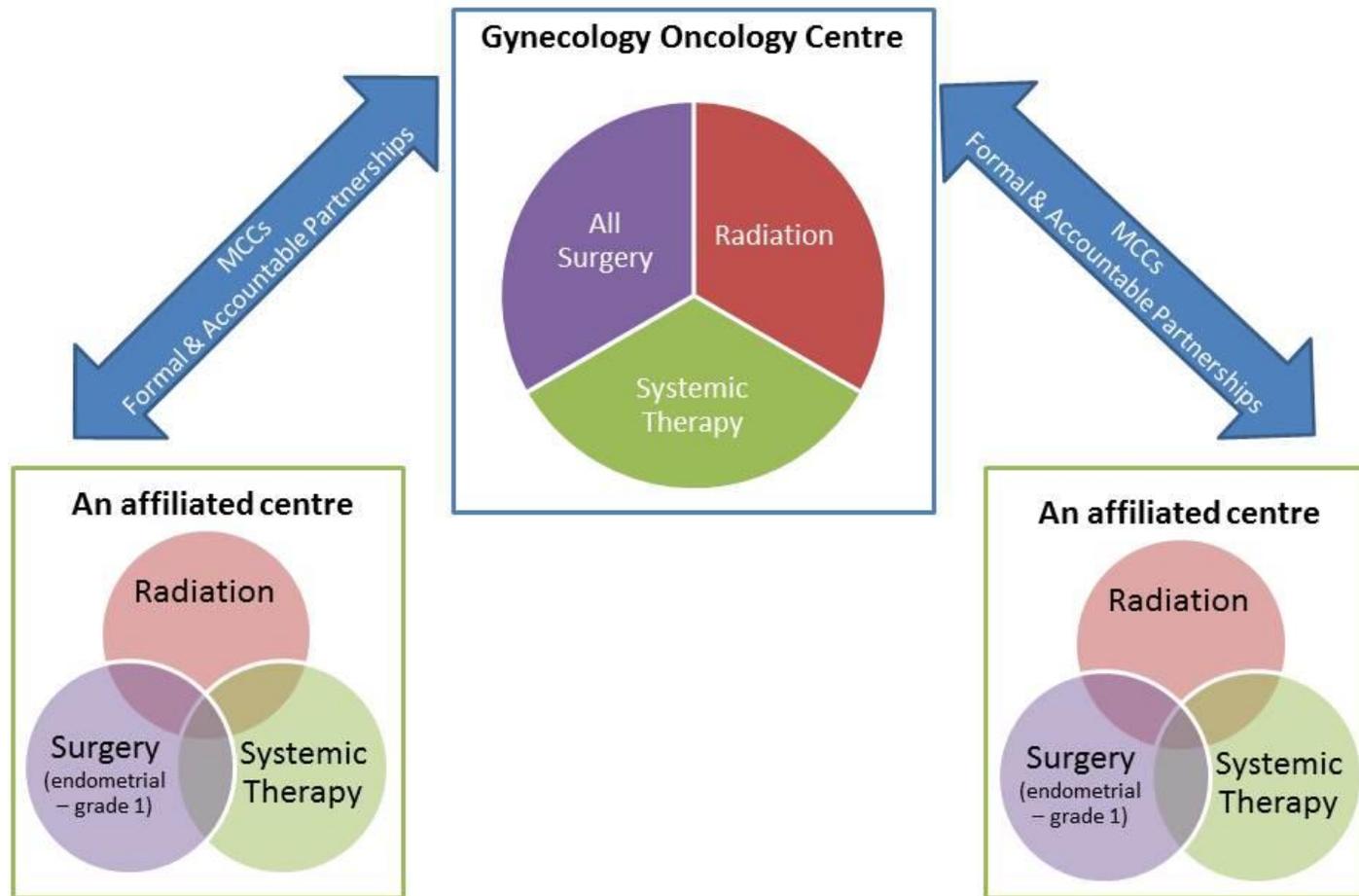
Recommendation

A formal partnership with processes to ensure accountability must be in place between affiliated centres and gynecologic oncology centres (Figure 1). As stated above under affiliated centres, appropriate pathology review must be available for all new patients, and access to multidisciplinary team management, including a multidisciplinary cancer conference (MCC) review or documented collaborative discussion between at least two disciplines, or a multidisciplinary clinic appointment at a gynecologic oncology centre must be provided.

Key evidence

This recommendation is the consensus of the Guideline Development Group.

Figure 1. Model for service provision for gynecologic oncology patients in Ontario, depicting networks of care comprising partnerships between gynecologic oncology centres and affiliated centres.



V. MULTIDISCIPLINARY DISCUSSION/EVALUATION

Recommendation

All patients with newly diagnosed gynecologic malignancy should have access to a GOC, MCC or be the subject of a collaborative discussion, which would include assessment at a multidisciplinary clinic, or a documented discussion with clinicians from at least two disciplines.

The primary purpose of the MCC is to ensure that all appropriate diagnostic tests, treatment options, and treatment recommendations are generated for each cancer patient discussed prospectively in a multidisciplinary forum (2).

Required participants at an MCC include:

- Gynecologic Oncologist
- Radiation Oncologist
- Medical Oncologist
- Pathologist
- Radiologist
- Clinical nurse specialist

Optional members include:

- Gynecologists performing endometrial cancer surgery

Recommendation

Patients who are not discussed in an MCC, but rather are the subject of a collaborative discussion, should also undergo appropriate pathology review. This statement applies in particular to low-grade endometrial cancer patients, as accurate determination of grade will impact their location of treatment and extent of surgery.

Recommendation

Members of the MDT must meet the specialist training required to practice in the province. Non-oncology specialists should have an interest in oncology, and non-gynecology specialists should have an interest in gynecology. GYOs must be certified in gynecologic oncology by the Royal College of Physicians and Surgeons or an equivalent.

Key evidence and justification

The general consensus at this time is that the model of the MDT is the standard of care for all cancer types (1). Several audits in England show that multidisciplinary care, among other factors, is associated with better survival in ovarian, cervical and endometrial cancer (43). A previous review by the PEBC supported the use of regularly scheduled MCCs to prospectively review individual cancer patients and make recommendations on management (2). The Guideline Development Group for this project endorses the 2006 PEBC MCC standards, including MCCs for gynecologic cancers (2).

While it is recommended that all patients have access to an MCC, it is recognized by the Guideline Development Group that MCCs do not have the capacity to discuss every new gynecologic cancer patient prospectively. In the UK, where it is recommended that every cancer patient be discussed, the process has been very time consuming, and insufficient time available to discuss every patient has been identified by others as a problem (44,45). In recognition of this, the Guideline Development Group has provided other options such as the collaborative discussion.

Recommendations for the minimum skill set and experience for MDT members that treat gynecologic malignancies was the consensus of the Guideline Development Group, based on currently accepted definitions for these specialities in Ontario.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Updating

All PEBC documents are maintained and updated as described in the PEBC Document Assessment and Review Protocol.

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Contact Information

For information about the PEBC and the most current version of all reports, please visit the CCO website at <http://www.cancercare.on.ca/> or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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

**Organizational Guideline for Gynecologic Oncology Services in Ontario:
Evidentiary Base**

*M. Fung-Kee-Fung, E.B. Kennedy, J. Biagi, T. Colgan, D. D'Souza, L. Elit, A. Hunter, J. Irish,
R. McLeod, B. Rosen and members of the
Gynecologic Oncology Organizational Guideline Expert Panel*

Report Date: June 6, 2013

RESEARCH QUESTIONS

1. Does treatment by a gynecologic oncologist result in better outcomes than treatment by a GYN or GS?
2. Are there better outcomes for patients with gynecologic cancer treated in designated centres compared to non-designated centres?
3. Is there a volume-outcome relationship between number of procedures by a physician/hospital and patient surgical or survival outcomes?

In addition, the Gynecologic Oncology Organizational Guideline Working Group (the working group) agreed to use the evidentiary base generated by the research questions above to provide consensus-based guidance regarding implementation of the optimal system of organization for gynecologic oncology in Ontario. Questions related to implementation/organization include:

1. How will services be regionally organized? Will specialized gynecologic oncology centres be designated?
2. If designated centres are recommended:
 - What is the optimal relationship or network of care between designated and non-designated centres?
 - What are the human and physical resources requirements of a designated (specialized) centre?

The general consensus at this time is that multidisciplinary care is the standard for all cancer types (1), and the PEBC supports the use of regularly scheduled MCCs to prospectively review individual cancer patients and make recommendations on management (2). The following questions specific to gynecologic oncology multidisciplinary teams (MDTs) were also asked by the working group:

1. What are the recommended staff requirements for a gynecologic oncology MDT?
2. What expertise/formal training is required by the members of the MDT?

INTRODUCTION

Gynecologic oncology is the study of tumours arising in the female reproductive system, including malignancies of the ovaries, endometrium (lining of the uterus), uterine cervix, vulva and vagina. In 2011, there were an estimated 3500 new cases and 1160 deaths due to gynecologic cancers in the province of Ontario (3).

Unpublished preliminary data from Cancer Care Ontario (CCO) show that in 2009-2010, approximately 56% of uterine, 41% of cervical, 34% of ovarian, and 23% of vulvar surgeries were completed in hospitals without a gynecologic oncologist, meaning that many ovarian cancer patients are receiving care in community hospitals. As well, approximately 40 hospitals across the province had a total gynecologic cancer surgical volume of fewer than 10 cases. Patients receiving treatment in low-volume settings are less likely to receive multidisciplinary care, which has been previously identified as a key contributor to quality care (4).

There are other shortcomings in the provision of care for patients in Ontario. Complete tumour resection and staging for early-stage ovarian cancer patients has been identified as important for long-term survival, and optimal debulking surgery is a critical prognostic factor in advanced stage disease (5); however, the most recent data from Ontario show that only 8% of women who received surgery for ovarian cancer had the appropriate extensive surgical staging of their cancers (6). Staging for ovarian cancer is somewhat more common in academic hospitals (11.5%) compared to community hospitals (4.9%) (6).

Surgical staging has been shown to be a predictor of overall survival for endometrial cancer patients in Ontario after controlling for stage and other prognostic variables (7); however, a gap in staging has been found in the province for patients who receive surgery in academic versus community hospitals (34.6% vs. 6.3%, respectively; data not controlled for stage) (8). There is also significant variation in the staging rate across Local Health Integration Networks (LHINs) (range: 6.3% to 58.3%) and when comparing gynecologic oncologists to other surgeons (48.8% vs. 9.4%, respectively; data not controlled for stage) (8). Our research questions for this guideline will explore whether the completeness of surgery for endometrial and ovarian cancer patients could be improved if a greater proportion of these patients were to have access to subspecialty care or treatment in designated or higher volume centres.

In the second fiscal quarter of 2012/2013, 67% of gynecologic oncology surgeries were completed within the target wait times, which is the lowest percentage of all cancer disease sites in Ontario (WTIS). Furthermore, a 20% increase in gynecologic malignancies is projected between 2010 and 2015 (iPort). With an increase in the patient population, there is a need to examine ways to establish a network that will facilitate the flow of these patients through the care continuum (9).

At the present time, approximately 30 gynecologic oncologists are practicing in Ontario in major centres with teaching hospitals; however, a province-wide plan for networks of care or collaboration is lacking. In other areas, such as the UK (10) and Finland (11), there has been a recent trend towards centralization of services. The general model of this type of delivery includes one or more central hospitals receiving referrals from less specialized hospitals within a network, region or defined catchment area. Delivery of services is characterized by the provision of care in comprehensive cancer centres with higher volumes and interdisciplinary collaboration (12). Despite the logic of this model of service delivery for gynecologic oncology, the case for implementation has been controversial (13-15), because data showing effectiveness has not been as strong as for other cancer disease sites (16), and evidence has been limited.

For these reasons, a system-level organizational guideline has been identified by the PEBC Gynecologic Oncology Disease Site Group and the Surgical Oncology Program, through consultation with stakeholders throughout the province, as a priority. Given the historical lack of high-quality evidence addressing the organization of gynecologic oncology services, the working group for this guideline agreed to conduct a systematic review on this topic to ensure that recommendations were based on the most-recent evidence available. Specifically, the review is designed to assess the current evidence related to specific organizational factors, including physician and hospital type and volume, and their relationship to patient survival and surgical outcomes in gynecologic oncology. As multidisciplinary care has been previously established as the standard of care, the review will not address whether or not this type of care is recommended, but rather, how its delivery should be facilitated in the context of gynecologic oncology patient care in Ontario, including the recommended members of the team. The goal is to provide recommendations for best practices in gynecologic oncology service delivery to patients in Ontario in order to improve outcomes among patients. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada, and to improve patient access to timely, high-quality care.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (17). For this project, the core methodology used to develop the evidentiary base was the systematic review. Articles were selected by the project methodologist and reviewed by all members of the Gynecologic Oncology Organizational Guideline Working Group (the working group) (Appendix 1).

The systematic review is a convenient and up-to-date source of the best available evidence on organizational factors affecting gynecologic oncology. The body of evidence in this review is primarily comprised of retrospective observational studies. That evidence forms the basis of the recommendations published in Section 1 of this EBS.

The PEBC is supported by the Ontario Ministry of Health and Long-Term Care (MOHLTC). All work produced by the PEBC is editorially independent of the MOHLTC.

Search for existing guidelines

To identify existing guidelines related to the research questions, a search was conducted of the Inventory of Cancer Guidelines, the National Guidelines Clearinghouse, and the websites of several known high-quality guideline developers, including the UK National Institute for Health and Clinical Excellence, the Scottish Intercollegiate Guidelines Network, the American Society for Clinical Oncology, the National Comprehensive Cancer Network in the US, the Australian National Health and Medical Research Council, and the New Zealand Guidelines Group. Guidelines published between 1995 and 2011 were considered. The working group began with the search year 1995, because this is when changes to the delivery of cancer treatment services, including greater centralization, became more widespread.

The purpose of this search was to identify existing guideline documents that could be adapted or adopted by the working group, or that were based on a systematic review that could be used as part of the evidentiary base for the development of recommendations.

Literature search

A search of the electronic databases MEDLINE and Embase (OVID: 1996 through December 12, 2011) for articles published in any language was conducted, using search terms related to gynecologic malignancies, combined with organization of services, patterns of care, and various facility and physician characteristics. The search terms used and full search strategy are available in Appendix 2. The Cochrane Database of Systematic Reviews was searched for topic-specific reviews up to December Issue 12, 2011. The Cochrane Database of Randomized Trials was not searched, as the working group was aware *a priori* that there are no existing randomized trials on this topic. Reference lists of included articles were scanned for additional citations. In addition, the search engine Google Scholar was used to identify articles using the terms *gyn(a)ecological cancer* and *centralisation* or *centralization* or *volumes*.

An environmental scan using the Google search engine for existing guidance documents or standards for individual Local Health Integration Networks (LHINs) was conducted January 5, 2011, using the words *gynecologic cancer services Ontario* and *LHIN*.

Study selection

Study designs eligible for inclusion were observational studies with a retrospective or prospective assessment of a cohort of patients, or systematic reviews of these study designs, with or without meta-analyses. Studies were eligible for inclusion if they contained an assessment of at least one of the primary outcomes of interest, including:

- overall or disease-specific survival (median and/or 5-year),
- short-term survival,
- adequate staging, and degree of cytoreduction and/or optimal cytoreduction for ovarian cancer patients,
- efficacy of multidisciplinary teams: e.g., rates of major and minor discrepancies.

Case-control studies, case series, letters and editorials were excluded. Non-English-language publications found through the search of electronic databases were included in the title or abstract scanning, but as full-text translation resources for these articles were not available, they were not retained for further assessment.

Data extraction and quality assessment

As an initial screen, guidelines were evaluated to determine whether they were based on a systematic review of the relevant literature. If systematic review methodology was used, then an assessment of the guideline quality was conducted using the Appraisal of Guidelines for Research and Evaluation 2 (AGREE 2) instrument (18). Systematic reviews identified in the search of electronic databases were assessed using the Assessment of Multiple SysTematic Reviews (AMSTAR) tool (19). Important prognostic variables to control for in studies of organizational factors are age, stage and grade of the tumour, and comorbidities (20); therefore, where available, results from analyses adjusted for these variables are reported.

For individual studies, key characteristics including study design, location, number of patients, type of gynecologic malignancy, stage and age, and the intervention and comparison under study were extracted. Determination of study quality was based on an assessment of study design, balance of baseline characteristics, and completeness of follow-up. Funding source and outcomes of interest were also extracted. Data extraction was verified by a project research assistant. All authors reviewed and discussed a draft of the evidence summary. Strengths and weaknesses were evaluated with the aim of characterizing the quality of the evidence base as a whole, without the use of a scoring system or cut-offs, according to the policy of the PEBC.

RESULTS

Search for Existing Guidelines

A guideline published in 1999 by the National Health Service in the UK, entitled *Improving Outcomes in Gynaecological Cancers (IOG) the Manual* (21), was identified. It closely aligned with the objectives of this guideline development group and was based on a systematic review of the literature. It included recommendations for clinical management and organization of services for all gynecologic oncology disease sites. The document scored well on most of the AGREE 2 domains (Appendix 3), including Scope and Purpose, Stakeholder Involvement, Applicability and Clarity of Presentation; however, it scored poorly on the domain of Rigour of Development (50% of quality items deemed inadequate), because the systematic review upon which the guideline was based was not available, either electronically or in print. However, a summary of the systematic review was located (4). The major findings were that survival is improved for ovarian cancer patients who are treated by expert multidisciplinary teams and who undergo surgery by a specialist gynecologic oncologist. The decision to recommend multidisciplinary care was mainly based on a study of ovarian cancer conducted in Scotland that found that follow-up at a multidisciplinary clinic was an independent predictor of survival at five years. The recommendation for treatment by gynecologic oncologists for most patients was based on findings of a prospective study of all patients in Scotland that found that women with stage III cancer who were treated by gynecologic oncologists had a 25% lower death rate at three years, compared to GYNs. Based on these findings, and other lesser quality evidence, centralization of services was advised, with all cases except for stage 1A or B [stage 1A according to the 2009 revised FIGO staging system (22)], grade 1 or 2 endometrial cancer and pelvic masses for which the risk of malignancy is low, recommended for treatment by specialist gynecologic oncologists at designated cancer centres. Cancer units serving smaller populations would refer patients to these centres and be responsible for initial diagnostic procedures and surgery for lower risk cases.

A limitation of the IOG guidance is that, while it is still in use in the UK, the evidence base is current only to 1999. Therefore, the working group agreed to use its evidence base and recommendations to inform its own guideline development process and combine this resource with evidence published between 1999 and 2011.

An environmental scan using the Google search engine for existing guidance documents or standards for LHINs in Ontario did not locate any existing guidelines.

Systematic Reviews

Four systematic reviews were identified in the literature search. One was the NHS *IOG* systematic review (4) summarized previously under the search for existing guidelines. The other three systematic reviews (5,20,23) addressed the organization of services for ovarian cancer. These were assessed with AMSTAR (19) (Appendix 4). The review conducted by du Bois et al. (5) received the highest AMSTAR rating and had the most up-to-date and comprehensive literature search (to July 2007). It included 16 of 18 and 16 of 19 studies from the remaining two systematic reviews, Giede et al. (23) and Vernooij et al. (20), respectively. Therefore, du Bois et al. alone was retained for further consideration, and is described in greater detail in the Results section under ovarian cancer. No systematic reviews or meta-analyses were found for gynecologic cancer disease sites other than ovarian cancer.

As the du Bois et al. (5) systematic review included a comprehensive summary of the ovarian cancer literature relevant to the working group's research questions up to July 2007, the inclusion criteria for ovarian cancer studies were revised from the methods section to include only individual studies published after the final search date used by du Bois et al. (5).

Individual Studies

Three thousand, six hundred and eighty-two unique citations were identified in the search of electronic databases. Of these, 332 were published in a language other than English. A title scan of the non-English-language articles resulted in 10 studies selected for abstract and/or full-text review. As translational capacities were not available, these articles were not given further consideration. Screening of the remaining 3,350 English-language articles resulted in 90 articles being retrieved for full-text review. Two additional articles were identified for full-text review from the scan of reference lists of included articles, Google keyword searching, and files of working group members. Of these, 42 articles met the inclusion criteria and were retained, and are discussed in detail under specific headings in the results sections that follow. See Appendix 5 for a flow diagram of the literature search results.

Centralization

Literature search results

Study characteristics and quality assessment (Table 1)

Six retrospective studies assessed centralization of hospital services for gynecologic malignancies (24-29). Five were conducted in Europe (24,26-29) and one in the USA (25). Three studies looked at all types of gynecologic cancers, (25,28,29), and the others looked at one or more specific disease sites. A variety of data sources were used, including surveys, databases, and a review of clinical notes. Funding sources were not stated for all but one study (29). The number of patients ranged from 124 (27) to almost 50,000 (25). A variety of outcomes was reported including various survival measures and surgical outcomes such as rate of lymphadenectomy. All but one study failed to correct for clustering of outcomes within facilities (25), but in two studies, treatment occurred in only one or two centres, thereby eliminating clustering as a concern (27,28). Overall, the evidence evaluating the feasibility of centralization of gynecologic oncology services was of lower quality due to the lack of consistency in study comparisons, outcomes, time periods and geographic locations, making it difficult to make conclusions and apply them to the Ontario context. However, some trends were noted, as outlined in more detail below.

Table 1. Study characteristics and quality assessment, centralization of gynecologic oncology services.

Study	Location	Comparison of interest	Study design	Data source	Years of diagnosis/operative procedure	Follow-up	Correction for clustering	Funding	No. of pts	Outcomes
Munstedt 2003 (24)	Germany	Hospital type; ovarian and endometrial	R	Survey of gynecology depts (up to 85% response)	1997-Feb 2001	None	No	NS	1,119 (endometrial) 824 (ovarian)	Rates of lymphadenectomy /omentectomy, intra- and postoperative complications
Fago-Olsen 2011 (26)	Denmark	Hospital type; ovarian	R	Danish Gynecological Cancer Database and Civil Registration System	2005- 2008	To first of 10 Sept 2009 or death	No	NS	2,023	OS, optimal cytoreduction, disease-free survival
Yap 2011 (27)	UK	Comparison with a pre-centralization cohort; primary SCC of the vulva	R-BaA	Review of clinical notes from the database of the Pan Birmingham Gynaecological Cancer Centre	1995-2003	Unclear	No, but treatment took place at only one centre	NS	124	Lymphadenectomy rate, 5-year cause-specific survival, number of surgical procedures/population
Brookfield 2009 (25)	USA	Hospital type and volume; cervical, ovarian, endometrial, vulvar, uterine sarcoma	R	Cases from state-wide database (mortality data passively updated).	1990-2000	None	Yes - correction for clustering in facilities	NS	48,981 cases	OS, 30-day, 90-day, 5-year
Crawford 2011 (28)	UK	Effect of centralization of surgical care and treatment by multidisciplinary	R-BaA	Eastern Region Cancer Registration and	1996-2003	to 31 Aug 2006	No, but patients largely treated at only 2	NS	3406 (9 hospitals)	OS

Study	Location	Comparison of interest	Study design	Data source	Years of diagnosis/operative procedure	Follow-up	Correction for clustering	Funding	No. of pts	Outcomes
		teams; all invasive gyne cancers		Information Centre database; mortality data actively followed up in NHS Strategic tracing Service			hospitals post-centralization			
Rachet 2009 (29)	England and Wales	Trends in 1-year and 3-year survival before and after the implementation of the NHS cancer plan for England	R-BaA	UK National Cancer Registry	1996-2006	Dec. 31, 2007	NA	Funding Office for National Statistics, Cancer Research UK	155,027	1-year and 3-year relative survival

R= retrospective; BaA= Before and After; NS = not stated; NA = not applicable; OS = overall survival; scc = squamous cell carcinoma; NHS = National Health Service; pts = patients.

Outcomes before and after centralization (Table 2)

Crawford (28) assessed the effect of centralization in the Anglia region of England, comparing the time period 1996-1999 with 2000-2003. The area of study comprised four English counties, with care predominantly delivered at two specialized hospitals, based on the *IOG* recommendation that surgical expertise be concentrated in hospitals serving in excess of one million people (28).

The *IOG* guidance was implemented by the year 2000 in this area. The study data are described as high quality, and only the 60% of cases for whom data on stage and grade were available were included in the survival analysis. Survival for patients with gynecologic cancer had improved significantly in the post-centralization study period compared to pre-centralization (HR: 0.71, 95%CI 0.64-0.79, $p < 0.001$). Improvements are attributed by the authors to a central pathology review for high-risk endometrial cancer, state of the art imaging, more extensive specialist surgery resulting in better staging and more tailored adjuvant therapy, using the Risk of Malignancy Index to make appropriate referrals, MDT review for those having non-specialist surgery, and early discussion of cases in the “unit” hospital. Overall, the major differences can be summarized as “access to specialized surgery” and “management within a multidisciplinary team” (28).

Rachet et al. (29) looked at outcomes before and after the implementation of the UK National Health Service cancer plan for England in 2000, nearly coinciding with the 1999 release of the *IOG* guidance. Improvements in relative survival post-implementation were more modest than those detected by Crawford. The disparity in findings may be due to incomplete implementation of the *IOG* guidance in some of the networks included in the study, whereas the *IOG* was swiftly implemented in the Anglia region that was the subject of Crawford’s study (28).

Yap et al. looked at outcomes after centralization of treatment for vulvar cancer and compared them to a previous study of patterns of care and outcomes before centralization in West Midlands, UK (27). Pre-centralization, 15 different surgical procedures had been described (30). After centralization, only four types of surgery were performed, and 84% of patients that required lymph node dissection had this procedure, although heterogeneity of surgical technique remained evident. Implementation of centralization also coincided with improved histology reporting and achievement of adequate excision margins. Although only 52% of case notes had enough information to evaluate 5-year disease-specific survival, survival improved from 51.3% pre-centralization to 73.8% post-centralization ($p = 0.055$).

Overall survival by hospital type or volume (Table 2)

Munstedt et al. hypothesized that centralization of surgery for ovarian and endometrial cancers could be an effective way of achieving uniformly high-quality treatment, which had been found to vary appreciably from relevant national and international guidelines. In the population of patients for whom lymphadenectomy is recommended and feasible, it was more likely to be performed in central hospitals; however, even in these centres, adherence to appropriate guidelines was found to be lacking. A limitation of this study is that it was not possible to determine whether treatment in central hospitals was carried out by specialists (24).

The treatment of ovarian cancer was slowly centralized over a decade in Denmark (26). A significant reduction in mortality for stage IIIC-IV ovarian cancer patients was found for patients treated in tertiary centres compared to others. No data on the involvement of gynecologic oncologists was available for this analysis.

Brookfield et al. (25) included ovarian, cervical, uterine, vulvar and uterine sarcoma cases together in a multivariate model that controlled for clustering of outcomes within facilities. They found no significant differences in overall survival over a 10-year period by

hospital volume or hospital type. Before the correction for clustering was applied, a significant difference for ovarian cancer patients had been found by teaching hospital and hospital volume. Data on treating physician was not available in the database, although the researchers were able to verify that all high-volume facilities had board-certified gynecologists, and many low-volume facilities did not. Also, data on comorbidities was not available, although the authors speculate that the addition of this information would not have altered the results.

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Table 2. Survival and surgical outcomes, centralization of gynecologic oncology services.

Study	FIGO Stage	No. of pts	Comparison	5-year survival %	HR	95% CI	p-value	Statistical analysis	Surgical outcomes (%)	Potential covariates included in adjusted model
Munstedt 2003 (24)	<u>Endometrial</u> IC-II (ASA score <III) (i.e. patients who should receive lymphadenectomy) <u>Ovarian</u> III (ASA score <III) (ie. patients who should receive omentectomy and lymphadenectomy)	1,119 824	HT primary HT secondary HT tertiary HT central HT primary HT secondary HT tertiary HT central	NR	NR	NR	NR	Chi-square	<u>Lymphadenectomy performed:</u> 15.8 28.4 52.6 47.9 p<0.001 0 20 32 38 p=0.046	Analysis limited to patients for whom lymphadenectomy (and omentectomy for ovarian cancer) is recommended and feasible.
Fago-Olsen 2011 (26)	IIIC-IV ovarian	2,023	HT tertiary HT others		0.83*	0.70-0.98	<0.05	Cox proportional hazards model	NR	Age, ASA score, ECOG score, comorbidity score, surgery yes/no, cytoreductive surgery yes/no, stage 3 vs 4, elective vs acute surgery
Yap 2011 (27)	I-IV	124	Pre-central Post-central	51.3% 73.8%**	NR	NR	0.055	Chi-square	<u>Lymphadenectomy performed:</u> 76% 46% (p=0.003)	NA

Study	FIGO Stage	No. of pts	Comparison	5-year survival %	HR	95% CI	p-value	Statistical analysis	Surgical outcomes (%)	Potential covariates included in adjusted model
Brookfield 2009 (25)	All SEER summary stages	48,981 cases	HT teaching HT non-teaching HV high HV inter-low	Combined survival NR	ref 1.08 ref** 0.96	0.99-1.18 0.91-1.03	0.08 0.25	Cox proportional hazards model	NR	type of cancer, HT, HV, age, race, ethnicity, payor, lymph nodes examined, stage, grade, surgical extirpation, chemotherapy treatment lack of radiation therapy, and clustering effects
Crawford 2011 (28)	All TNM stages	3406 (9 main NHS hospitals)	Pre-central Post-central	58.6% 68.6%	0.71	0.64-0.79	<0.001	Cox proportional hazards model	NR	age, stage, grade, year of diagnosis
Rachet 2009 (29)	No data	155,027	Pre-central Post-central	For “cervix, uterus, and ovary, survival trends in England improved between 2001-03 and 2004-06”	NA	NA	NA	Comparison of relative survival using “various analytical approaches” including “hybrid”, “complete”, “cohort”, “conditional” (see full text article for more detail)	NA	NR

* disease-specific survival ** death from a gynecologic malignancy during the 10-year study period

FIGO = International Federation of Obstetricians and Gynecologists; TNM = tumour, node, metastases; SEER = Surveillance, Epidemiology and End Results; pts = patients; OR = odds ratio; CI = confidence interval; HT = hospital type; HV = hospital volume; ref = reference group; NR = not reported; ECOG = Eastern Cooperative Oncology Group.

Ovarian cancer

Background

There were an estimated 1,050 new cases, 700 deaths and an age-standardized mortality rate of 8 per 100,000 for ovarian cancer in Ontario in 2011. Ovarian cancer is the second most-commonly diagnosed type of gynecologic cancer in the province after endometrial cancer (3). Because of nonspecific symptoms, it is often discovered at an advanced stage, leading to a 5-year survival rate of approximately 40% (31).

Treatment should include extensive surgical staging to rule out occult metastatic disease for patients with early-stage disease confined to the ovary (32). For advanced-stage disease, aggressive surgical debulking is appropriate (33), as there is a positive relationship between completeness of cytoreduction and survival (11). Despite evidence showing that high rates of complete cytoreduction are achievable (34), biopsy alone was the definitive procedure for 34.2% of patients in Ontario in 2003-2004. In the same time period, only 8.1% of ovarian cancer patients who received surgery had lymph nodes excised, although guidelines (31,35), including a PEBC guideline, recommend comprehensive surgical staging. Surgery requires a clinician with a high degree of suspicion of the diagnosis, access to intraoperative frozen pathology, subspecialty-trained surgical involvement and appropriate allied health professionals (6). Appropriate treatment also includes platinum-based chemotherapy.

There is some disparity in Ontario regarding the rates of ovarian-cancer-related surgery, ranging from 58% in the North West Local Health Integration Network (LHIN) to 88% in the Erie St. Clair LHIN. Forty percent of women who underwent surgery did so outside of their LHIN of residence (36). Gynecologic oncologists comprised about 7% of physicians performing ovarian cancer surgery in Ontario; however, they performed 49% of surgeries (GYNs performed 39.7% and GS performed 11.6%). In addition, the lymph node excision rate in Ontario is low across all physician specialties (36).

Literature search results

Systematic reviews

Du Bois et al. (5) addressed whether any institutional (type, teaching affiliation, residency status, availability of special oncology services, study participation, volumes), or physician characteristics (discipline, sub-specialization, volumes) are associated with the outcomes of survival, tumour debulking, completeness of staging, and compliance with guidelines regarding selection of chemotherapy. Of 44 studies, all but five were retrospective, with patient data in most cases gathered from population- or hospital-based cancer registries. Three had fewer than 100 patients, while the rest ranged from 114 to more than 12,000. Adjustment for covariates was assessed and reported for each study. Failure to adjust analyses or control for clustering were cited as study weaknesses. Overall, although the systematic review methods were rigorous and comprehensive, the body of evidence included in the review was judged of lower quality due to the risk of bias inherent in the retrospective, non-randomized design of the studies. A meta-analysis was not conducted for these reasons, in addition to the heterogeneity of comparison groups and outcome measures.

In du Bois et al., a positive impact on survival with higher degree of specialization was found, particularly in the poorer prognostic subgroup of patients. The majority of studies also found a significant positive effect of physician discipline and subspecialization on surgical outcomes, including staging and extent of debulking. Aside from participation in clinical studies, institutional characteristics were not related to survival outcome; however, this association was not tested in a multivariate analysis and could be clustered with other factors

such as hospital volume. The relationship between hospital volumes and outcomes measures was inconclusive; however, the authors noted that this could be due to insufficient distinction between high- and low-volume groups in most studies. There was a significant difference found in the single study with the greatest distinction between high and low volume. The review also looked at the impact of institution- and physician-related variables on quality of chemotherapy and found some evidence that these factors affected quality of chemotherapy; however, the majority of these studies did not control for covariates.

Individual studies

Study characteristics and quality assessment (Table 3)

Individual studies published after the final literature search date for the du Bois et al. systematic review (July 2007) were also considered. Seven articles were found that met the inclusion criteria (11,12,20,37-40). Analyses should be adjusted for comorbidities, age, stage, and grade in order to avoid an overestimation of the impact of organizational factors on surgical outcomes and survival (17). Of the single studies, only one adjusted for comorbidity (40), and another adjusted for mortality risk (38). Except for two studies (11,12) that prospectively collected data on consecutive patients using questionnaires, all were retrospective studies (18,32-35) that used patient databases and records. The number of included patients ranged from 275 (11) to almost 32,000 (39). Number of years of data collection included a minimum of one year (11) to a maximum of 15 years (39), with follow-up from zero months (37,38), for studies reporting only short-term or peri-operative outcomes, to five years for one of the prospective studies (11). Funding was provided by governmental/medical organizations for the majority of studies, a foundation in one case (38), and not stated in the other two (37). Outcomes included a variety of measures of survival and quality of surgery. No studies corrected for clustering of outcomes by hospital. Assessment of the overall quality led to a conclusion similar to that of du Bois et al. (17): that the body of evidence as a whole is of lower quality due to variations in endpoints, presentation of results, definitions of independent variables, and study populations.

Table 3. Study characteristics and quality assessment, ovarian cancer.

Study	Location	Comparison of interest	Study design	Data source	Years of diagnosis / operative procedure	Follow-up	Correction for clustering	Funding source	No. of pts	Outcomes
Bristow 2010 (37)	USA	HV	R	National Cancer Database (nearly 80% of incident cancers in the US)	1996-2005	None	No	NS	12,276	OS and likelihood of receiving standard recommended care
Bristow 2009 (38)	Maryland, USA	PV, HV	R	Cross-sectional analysis of hospital discharge data from non-federal acute care hospitals in Maryland collected by the Maryland Health Service Cost Review Commission	Jul 1, 2000-Jun 30, 2008.	None	No	Entertainment Industry Foundation via the Callaway Golf Ovarian Cancer Research Collaborative	1,894	In-hospital mortality, extent of surgery performed, hospital length of stay, hospital cost of care after surgery. Primary clinical endpoint: in-hosp death during index admission
Elit 2008 (40)	Ontario, Canada	PS, HT	R	Data abstracted from patient records and charts. CIHI databases and Ontario Cancer Registry used to identify cases.	1996-1998	To latest available health insurance data	No	National Cancer Institute of Canada	1341	Unnecessary repeated abdominal surgery* and long-term survival
Kumpulainen 2009 (11)	Finland	HV	P	Data questionnaire verified by Finnish Cancer Registry.	1999	5 years or death	No	Finnish Cancer Society, Medical Society, Turku University, Obstetrics and Gynecology Society	275 (5 university hospitals, 16 central hospitals, other smaller city and district hospitals)	5-year DFS and CSS
Marth 2009 (12)	Austria	HV	P	Questionnaire completed for all consecutive patients by gynecologic oncology departments. Overall survival passively collected	1999-2004	Dec. 31, 2006	No	NS	1,948	OS

Study	Location	Comparison of interest	Study design	Data source	Years of diagnosis / operative procedure	Follow-up	Correction for clustering	Funding source	No. of pts	Outcomes
				from Statistics Austria.						
Mercado 2010 (39)	New York, Florida, Washington, California, USA	PS, HV	R	State cancer registries, inpatient hospital databases, AMA physician master file, US census	Date ranges between 1991 and 2004 varied by state, linked to hospital inpatient databases.	at least one year of follow-up	No	Centers for Disease Control, American Cancer Society	31,897	Surgery by specialist type, receipt of an ostomy (proxy for quality of care and life), and time to death
Vernooij 2009 (20)	The Netherlands	PS, HT	R-cohort	Patient records and hospital patient databases abstracted by one of the investigators	1996 to 2003	Date of death up to Feb. 1 2006	No	Netherlands Health Research, Development, Dutch foundation	1077 patients from a random sample of hospitals	Adequate staging, optimal debulking, length of overall survival

CIHI = Canadian Institute for Health Information; R = retrospective; P = prospective; HV = hospital volume; PV = physician volume; HT = hospital type; PS = physician specialty; OS = overall survival; NS = not stated; pts = patients; DFS = disease-free survival; CSS = cancer-specific survival; *second abdominal surgery unrelated to complications, performed within 5 months of the index surgery.

Survival by hospital or physician volumes or specialty (Table 4)

Three studies found a significant association between survival and hospital volumes, each using different definitions of high or low volume. Bristow found a significantly greater risk of in-hospital death for low- and intermediate-volume hospitals versus very high-volume hospitals, with very high being defined as greater than 35 ovarian cancer patients per year (37). This analysis did not control for individual surgeon case volume or specialty. Marth et al. found a significant association between 5-year survival and a high/low volume cut point of 24 cases per year (12). Likewise, Mercado et al. found a decrease in risk of death at a volume level of 10 to 19 cases per year and 20+ cases per year compared to 0 to 4 cases per year (39). In-hospital death was less likely for patients of physicians with a caseload of at least 10 patients per year (38).

Table 4 Survival, by physician or hospital volume and/or specialty, ovarian cancer.

Study	FIGO Stage	No. of pts	Comparison	Unadjusted 5-year survival %	HR	95% CI	p-value	Statistical analysis	Potential covariates included in adjusted model
Bristow 2010 (37)	IIIC/IV EOC	10,641	HV >35/yr HV 21-25/yr HV 9-20/yr HV <9/yr	28.9 28.5 26.1 24.3	ref 1.03 1.08 1.16	0.98-1.09 1.01-1.15 1.09-1.24	0.26 0.03 0.00	Cox proportional hazards model	Treatment, stage, ethnicity, age, payer status, household income, and tumour grade
Bristow 2009 (38)	NA	1,894	PV ≥10/yr PV <10/yr HV≥20/yr HV<20/y	<u>In-hospital death</u> 1.69 4.05 2.21 2.83	<u>In-hospital death</u> OR 0.31 Ref	0.16-0.61	0.001	Multivariate logistic regression	Age, ethnicity, payer status, mortality risk score, hospital type. <i>Not adjusted for:</i> Stage, grade, histological subtype, extent of disease, residual disease
Elit 2008 (40)	I-IV	1341	GYO GYN GS -Centres with GYO -Other regional cancer centre -Remaining centres	NR	ref 1.02*** 1.19	0.81-1.30 0.90-1.58	NR	Cox proportional hazards model	Age, comorbidity, residence location, stage and grade
				NR	ref 0.81	0.56-1.17	NR		
					0.93	0.74-1.16			
Kumpulainen 2009 (11)	I-IV	275	HV as a continuous variable GYO GYN	Overall: CSS=56% OS=53%	0.998**** ref 1.237	0.981-1.016 0.752-2.033	0.857 0.403	Cox proportional hazards model	Age group, FIGO stage, hospital volume, operating physician, residual disease, differentiation and primary chemotherapy
Marth 2009 (12)	I-IV and unstaged	1,948	HV >24/yr HV ≤24/yr	69% 61%	ref 1.38	1.15-1.65	0.001	Cox proportional hazards	Department volume, FIGO stage, lymphadenectomy, age,

Study	FIGO Stage	No. of pts	Comparison	Unadjusted 5-year survival %	HR	95% CI	p-value	Statistical analysis	Potential covariates included in adjusted model
								model; backward elimination	grade, residual disease
Mercado 2010 (39)	IIIC/IV	31, 897	HV 0-4/yr HV 10-19/yr HV 20+/yr GYO/GYN GS Other	NR	ref 0.89 0.79 ref 1.63 1.56	0.86-0.93 0.76-0.83 1.56-1.71 1.52-1.61	<0.0001 <0.0001 <0.0001 <0.0001	Cox proportional hazards model	Age, comorbidity, urban/rural hospital location
Vernooij 2009 (20)	I-IV	1,077 (18)	PV high ^c PV low ^c HT general HT semi-specialized HT specialized HV high HV inter HV low		ref 0.7 ref -- 0.8 ref NS NS	0.5-1.0 -- 0.7-1.0		Cox proportional hazards model	Age, stage

FIGO = International Federation of Obstetricians and Gynecologists, GYO = gynecologic oncologist, GYN = gynecologist, GS = general surgeon, EOC = epithelial ovarian cancer, CSS = cancer specific survival, NR = not reported, NA = not available, pts = patients, HR = hazard ratio, CI = confidence interval, PV = physician volume, HV = hospital volume, HT = hospital type, ref = reference group.
 ***survival time from initial surgery to date of death from any cause. Follow up to latest available health insurance data.
 ****ovarian cancer-specific mortality. NS= non-significant (HR not provided).
^cgynecologist volume.

Surgical outcomes by hospital or physician volumes or specialty (Table 5)

One study showed that cytoreductive surgery was more often performed in higher volume hospitals (≥ 20 cases per year) (38). In a prospective study of patients operated upon in Finland in 1999, a significant association was found between hospital operative volume as a continuous variable and optimal cytoreductive surgery (11).

In stage I-IIA patients, Vernooij et al. found significant associations between adequate staging and degree of specialization of hospital as well as surgeon specialty and volume. For stage III patients, hospital type and surgeon volume were significantly associated with optimal debulking (20).

Elit et al. assessed repeat abdominal surgery unrelated to complications within five months of the index surgery in a population of Ontario patients, and found that the risk of repeat surgery was higher when a general surgeon (i.e., non-specialist) performed the index surgery, although the reason for this could not be explored further due to data limitations (40).

Table 5. Surgical outcomes, physician or hospital volume and/or specialty, ovarian cancer.

Study	FIGO Stage	Pts (hosp)	Comparison	Cytoreductive surgery	95% CI	p-value	Adequate staging	95% CI	Statistical analysis	Potential covariates included in adjusted model
Bristow 2009 (38)	NA	1,894	HV \geq 20/yr HV<20/y	OR for performance of cytoreductive surgery 1.44 ref	1.17-1.78	p=0.001	NR		Multivariate logistic regression	Age, ethnicity, payer status, mortality risk score, hospital type
Elit 2008 (40)	I-IV	1341	GYO GYN GS	RR of repeat surgery: ref 6.54 16.97	-- 2.52-16.93 6.35-45.32	NR	NR		Poisson regression	Age, comorbidity, residence location, stage and grade
Kumpulainen 2009 (11)	I-IV	275	HV continuous	OR for no residual disease 1.203	1.022-1.417	0.027			Logistic regression	NR
Vernooij 2009 (20)	I-IV	1,077 (18)	PV high ^c PV low ^c HT general HT semi-specialized	Stage III OR for optimal debulking: 1.6 2.8 ref --- 1.7	1.1-2.5 1.4-5.7	NR	Stage I and IIa OR for adequate staging: ref 4.6	2.3-9.2	Multivariable logistic regression	Age, stage

Study	FIGO Stage	Pts (hosp)	Comparison	Cytoreductive surgery	95% CI	p-value	Adequate staging	95% CI	Statistical analysis	Potential covariates included in adjusted model
			HT specialized GYN Semi-GYO GYO	ref ns ns	1.1-2.7		3.9 ref 8.5 9.5	2.0-7.6 3.8-19.3 4.7-19.0		
			HV high HV inter HV low	ns ns ref			"Patients treated in HV hospitals were 5 times more often adequately staged than patients in low volume hospitals"			

FIGO = International Federation of Obstetricians and Gynecologists; pts = patients; CI = confidence interval; PV = physician volume; HV = hospital volume; HT = hospital type; ref = reference group; NR = not reported; RR = relative risk; OR = odds ratio; NR = not reported; GYO = gynecologic oncologist; GYN = gynecologist; GS = general surgeon; semi-GYO = semi-specialized gynecologist; ns = not significant; NA = not available; NR = not reported.
^cgynecologist volume.

Summary of findings (Table 6)

In order to compare results across studies, Table 6 presents the basic comparison under study and whether or not a significant difference was found for the systematic review and single studies related to ovarian cancer. Only results that were stratified or properly adjusted for confounding factors are included. Several studies found a significant association between hospital volume or physician type and surgical outcomes. Some studies also found a significant relationship between organizational variables and survival. Physician type was associated with improved surgical and survival outcomes in the only systematic review (17).

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Table 6. Ovarian cancer, summary of findings, including only adjusted or stratified analyses.

	Survival [†]				Surgical outcomes ^{††}			
	Physician Volume	Hospital Volume	Physician Type	Hospital Type	Physician Volume	Hospital Volume	Physician Type	Hospital Type
<u>Systematic review</u>								
du Bois 2009 (5) ^a	X	IC	√ ^b	X	-	IC	√	IC
<u>Primary studies</u>								
Bristow 2010 (37)	-	√	-	-	-	√	-	-
Bristow 2009 (38)	√	-	-	-	-	√	-	-
Elit 2008 (40)	-	-	X	X	-	-	√	-
Kumpalainen 2009 (11)	-	X	X	-	-	√	-	-
Marth 2009 (12)	-	√	-	-	-	-	-	-
Mercado 2010 (39)	-	√	√	-	-	-	-	-
Vernooij 2009 (20)	X	X	X	X	√	√	√	√

√ = significantly improved outcomes with higher volumes or greater specialization.

X = no significant differences in outcomes with higher volumes or greater specialization.

- = no comparison available.

IC = inconclusive.

For comparison groups, hazard ratios and confidence intervals for individual studies, see Results tables.

^a this systematic review included 44 primary studies.

^b the impact of physician type on survival was stronger for advanced stage disease (FIGO III-IV).

[†] including short and/or long-term survival.

^{††} including optimal cytoreduction for advanced stage patients, and/or complete surgical staging for early stage patients.

Chemotherapy

One study looked at number of medical oncologists in a hospital and outcomes of chemotherapy (41), asking whether it should be centralized, in addition to surgery. There was a significant improvement in overall survival for patients in facilities with higher numbers of medical oncologists. The authors conclude that patients should be referred to a specialized centre for both surgery and chemotherapy. This recommendation takes into account that travel distance in the Netherlands is not an impediment.

Another argument for the centralization of chemotherapy is data showing that low/intermediate-volume hospitals were significantly more likely to employ a treatment paradigm other than the recommended initial surgery followed by adjuvant chemotherapy (37).

Kumpalainen et al. confirmed the associations between survival and optimal cytoreduction and platinum-based combination chemotherapy. They concluded that these treatments are more likely to occur in larger units with higher operative volumes (11).

In Ontario, more women had chemotherapy than saw a medical oncologist, which indicates that chemotherapy is likely being managed by gynecologic oncologists (36).

Endometrial cancer

Background

In Ontario in 2011, there were an estimated 1,950 new cases, 320 deaths, and an age-standardized mortality rate of 3 per 100,000 for endometrial cancer (3).

A patterns-of-care study found that total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) is the standard of care in Ontario, with lymphadenectomy useful in defining the need for adjuvant therapy in women with high-risk features such as grade 2 or 3 tumours or deep myometrial invasion (8). Whether or not lymph nodes are assessed depends on whether treatment is provided by a subspecialist: GYNs provided primary surgery for 76.1% of Ontario women, and only 9.4% of these included a lymph node sampling procedure while gynecologic oncologists operated on 21.3% of women and conducted node sampling in approximately half. The rate of lymph node excision in addition to TAHBSO or unilateral salpingo-oophorectomy ranges from 9% to 25.9% in Ontario LHINs, with two outliers: Champlain at 56.4% and North West at 47.6% (36). Overall, the lymphadenectomy rate in Ontario is considered to be low (8).

Literature search results

Study characteristics and quality assessment (Table 7)

Seven fully published articles (8,42-47) and one abstract (48) were found that met the inclusion criteria for studies of organizational factors that contribute to outcomes in endometrial cancer. Six were conducted in the USA (43-46,48), one in Scotland (42), and one in Canada (8). Comparisons involving physician specialty were made in five studies (8,44-46,48), and physician and/or hospital volumes were assessed in the others. All studies were retrospective in design. Data sources were patient records and hospital records or cancer registry databases. Some studies were designed to assess patterns of care and did not attempt to follow up outcomes (8,44). Some studies did not have access to data beyond readmissions within 30-60 days (43,49). Others were able to use registries and databases to follow patients for up to several years (42,45,46,48). Some studies controlled for the major potential confounders age and stage, through the use of multivariate analysis (most often a Cox proportional hazards model) (45,46). In both US studies that used administrative databases, information on the stage of the patients was not available. Statistical methods that correct

for clustering of outcomes in patients who are treated at the same hospital or by the same physician were applied in only one analysis (48); however, two other studies looked only at patients in one or two hospital sites (44,45), thereby eliminating clustering by hospital as a concern. Where funding was stated, it was provided by a family foundation (48), a local health board (46), a provincial agency (8), and a research grant from an academic centre (46). Number of patients varied considerably, ranging from 204 (44) to over 18,000 (46). The most common outcome was overall survival. Other outcomes of interest were short-term survival, local or distant recurrence, surgical staging (as a proxy of overall quality of management), and various measures of perioperative morbidity, some of which were provided separately by stage of endometrial cancer.

Overall, the non-randomized, retrospective design resulted in an overall assessment of the evidence base as of lower quality. In addition, the heterogeneity of the study designs and outcome measures, and additional study limitations in some cases, such as no follow-up after discharge, make it difficult to draw conclusions. Despite the limitations in data quality, some trends were noted, as described below.

Table 7. Study characteristics and quality assessment, endometrial cancer.

Study	Location	Comparison	Study design	Data source	Years of diagnosis	Follow-up	Correction for clustering?	Funding source	No. of pts	Outcomes of interest
Crawford 2002 (42)	Scotland	PV, notation of surgical stage, adjuvant radiotherapy	R	Hospital discharge data and cancer registry	1996 - 1997	2.25-4.25 years	No	Greater Glasgow Health Board	703	OS, notation of surgical stage
Diaz-Montes 2006 (43)	USA	PV HV	R	Hospital discharge data collected by a cost review commission from nonfederal acute care hospitals.	1994- June 2005	30 days of discharge	No	None stated	6,181 patients 894 surgeons 49 hospitals	In-hospital death rate
Wright 2011 (49)	USA	PV HV	R	Perspective (administrative) database (voluntary, collects inpatient data from more than 500 acute-care hospitals in USA)	2003- 2007	Up to readmissions within 60 days	GEE	Milstein Family Fund	6,015	Perioperative morbidity and mortality
Roland 2004 (44)	USA	PS	R-POC	Tumour registry	1998 - 2000	None	No; all care received in a single community system	None stated	204 patients from 3 tertiary care hospitals	Histologic assessment of retroperitoneal lymph nodes, mean number of lymph nodes removed
MacDonald 2005 (45)	USA	PS	R	Patient records and tumour registry databases	1990- 2003	Median follow-up of 3.7 years.	No; two tertiary sites investigated.	None stated	349	OS, DSS, disease-free survival, or any local or distant disease event, local recurrence-free

Study	Location	Comparison	Study design	Data source	Years of diagnosis	Follow-up	Correction for clustering?	Funding source	No. of pts	Outcomes of interest
										survival, and distant metastasis-free survival
Elit 2009 (8)	Ontario	PS	R-POC	OCR linked to other provincial health databases	Apr 2003 -Mar 31, 2004	None	No	Cancer Care Ontario	1,436	Rate of pelvic and/or paraaortic lymphadenectomy
Chan 2011 (46)	USA	PS	R	SEER, Medicare and Medicaid Services data	1991-2002	200 months	No	Stanford Cancer Center John A. Kerner Research Funding in Gyn Oncology	18,338	Overall survival, disease-specific survival
Kwon 2008 (7)	Ontario	HT, HV, PS	R	OCR and CIHI	Cases from 1996-2000	2005	Yes	Cancer Care Ontario, the Mitchell Family, the National Ovarian Cancer Assoc.	3,875	Overall survival
Soisson 2010 (48) (abstract)	USA	PS	R	Operative reports, pathology reports, anesthesia records	NR	NR	No	NR	267	Rate of appropriate surgical procedures, adherence to national guidelines

R= retrospective; R-POC = Retrospective patterns of care; GEE = Generalized Estimating Equations; PS = physician specialty; PV = physician volume; HV = hospital volume; HT = hospital type; OCR = Ontario Cancer Registry; CIHI = Canadian Institute for Health Information; NR = not reported; OS = overall survival; DSS = disease-specific survival; SEER = Surveillance, Epidemiology and End Results.

Hospital or physician volumes, short-term outcomes (Table 8)

Two studies based on administrative data assessed short-term outcomes by physician and/or hospital volume (43,49). Staging information was not available for either of these studies.

In a study that was limited to patients treated by gynecologic oncologists only, low- and high-volume surgeons were defined as ≤ 14.5 patients/year and >30 patients/year, respectively (48). This study detected a significant relationship between surgeon volume and perioperative survival. No relationship between hospital volume and in-hospital mortality, or perioperative complications by low versus high surgeon volume, or hospital volume, was detected.

Diaz-Montes et al. included all surgeons who operated on endometrial cancer patients in their analysis: only 1% of surgeons were categorized as high volume. They found no relationship between surgeon or hospital volumes (both cut-offs of <8 vs. ≥ 8 /year) and in-hospital survival (43).

Table 8. Survival by hospital or physician volume, endometrial cancer.

Study	FIGO Stage	No. of pts	Comparison	Peri-operative death %	OR	95% CI	p-value	Comprehensive lymph node evaluation	Statistical analysis	Potential covariates included in adjusted model
Diaz-Montes 2006 (43)	All stages	6181	PV ≤99/12 yrs	NA	ref	0.26-1.00	≥0.05	NR	Univariate logistic regression	NA
			PV ≥100/12 yrs	NA	0.52					
			HV ≤199/12 yrs	NA	ref	NA	≥0.05			
			HV ≥200/12 yrs	NA	1.09					
Kwon 2008 (7)	All stages	3,875	HV “low” HV “high”		HR: ref 1.20	0.96-1.50	NR	NR	Cox regression model	Age, income, co-morbidity index, grade, stage, surgical staging, adjuvant therapy
Wright 2011 (49)	All stages	6015	PV ≤14.5 ^b /yr	1.1%	ref	0.15-0.93	0.01	69.0%	Multivariable GEE	Case mix and surgeon or hospital volume
			PV 14.6-30 ^b /yr	0.5%	---					
			PV >30 ^b /yr	0.4%	0.38			74.6%		
			HV ≤36/yr	1.0%	ref	0.15-1.33	0.09	70.4%		
			HV 36.1-53/yr	0.5%	---					
			HV >53/yr	0.6%	0.46			73.3%		
								70.2%		

FIGO = International Federation of Obstetricians and Gynecologists; pts = patients; OR = odds ratio; CI = confidence interval; PV = physician volume; HV = hospital volume; ref = reference group; GYO = gynecologic oncologist; GEE = generalized estimating equations; NA = not applicable
^bGYO only.

Staging and survival by physician specialty (Table 9)

Crawford (42) considered the notation of patients' surgical stage as a predictor of mortality (i.e., as proxy of overall quality of management, not of direct surgical benefit). Gynecologic cancer specialists were more likely than others to document the FIGO stage. Documentation was not related to surgeon caseload. Higher-volume hospitals were also more likely to document stage (42).

Roland et al. (44) found that women receiving care from gynecologic oncologists were significantly more likely to be staged for all stages combined and for women with T1 or T2 tumours at risk for extra-uterine disease. Patients of GYNs were 2.6 times more likely to receive adjuvant radiation, usually in the absence of complete staging information (significance level not provided).

In Chan et al. (46), patients cared for by gynecologic oncologists were more likely to undergo staging procedures with lymph node assessment and to receive chemotherapy. Those with stages II to IV disease who underwent care by gynecologic oncologists had significantly improved disease-specific survival after adjustment for age, surgery, stage, grade, and histology. After adjustment for the effect of surgical staging on those with stage III disease, gynecologic oncologist care was no longer associated with an improvement in survival.

MacDonald (45) found no significant differences in survival by physician specialty; however gynecologic oncologists were significantly more likely to perform comprehensive staging.

Soisson (48), in an abstract, concluded that surgical procedures are markedly different when surgery is performed by GYNs compared to gynecologic oncologists. With a gynecologic oncologist, pelvic or para-aortic lymph node staging is much more likely, and the surgery involves a more-comprehensive assessment of the extent of tumour invasion, which would make possible a more-accurate determination of stage.

Table 9: Staging and survival outcomes, by physician specialty, endometrial cancer.

Study	FIGO Stage	No. of pts	Comparison	5-year OS %	HR for survival	95% CI	p-value	Comprehensive lymph node evaluation	p-value	Statistical analysis	Potential covariates included in adjusted model
Roland 2004 (44)	All stages (78.4% FIGO stage I)	204	GYO GYN	NA	NA	NA	NA	83% 26%	<0.05	Fisher's exact test	NA
	T1,T2 at risk for EUD ^a	139	GYO GYN	NA	NA	NA	NA	96% 19%	<0.05		
MacDonald 2005 (45)	IA-IIA	349	GYO GYN	78% 89%	1.3 ref	0.9-1.7	0.13	79% 23%	0.006	Cox proportional hazards model	Age, HIR disease, adjuvant RT
Chan 2011 (46)	I-IV ^b	18,338	GYO Other	NA NA	0.71 ^c ref	0.62-0.82	0.001	NR	NA	Cox proportional hazards model	Age, stage, grade
	III-IV ^b	2,987	GYO Other	41.8 35.4				NR	NA		
Elit 2009 (8)	All stages	1,360	GYO GYN	NA	NA	NA	NA	50% 9.4%	NR	No testing for statistical significance	NA
Kwon 2008 (7)	All stages	3,875	GYO Other	NA	1.23	0.95-1.59	NR	NR	NA	NA	Age, income, co-morbidity index, grade, stage, surgical staging, adjuvant therapy
Soisson 2010 (48) (abstract)	All stages	267	GYO GYN	NA	NA	NA	NA	91% 2%	<0.001	NR	NR

FIGO = International Federation of Obstetricians and Gynecologists; GYO = gynecologic oncologist; GYN = gynecologist; pts = patients; HR = hazard ratio; CI = confidence interval; ref = reference group; HIR = high-intermediate risk of local failure (stage IB, grade III, IC grade II or III or stage IIA); NA = not applicable; NR = not reported.

^aAt risk for EUD: those with myometrial invasion, grade 2 and 3 tumours, or cervical involvement. EUD - extra-uterine disease.

^bAmerican Joint Committee on Cancer codes.

^cdisease-specific survival.

Cervical cancer

Background

Cervical cancer is the third most-common type of gynecologic cancer in Ontario. There were an estimated 500 new cases, 140 deaths, and an age-standardized mortality rate of 2 per 100,000 for cervical cancer in the province in 2011 (3). Early-stage cervical cancer is usually treated surgically, while radiotherapy is used to treat advanced disease (50).

A study of the management of cervical cancer in Ontario showed that 57.1% of cases over the study period underwent surgical procedures. Of these procedures, 26.8% were cone biopsies, 32.1% were simple hysterectomies with or without lymph node excision, and 38.5% were radical hysterectomy with lymph node dissection. Staging information was not available for that analysis, limiting the ability of the study to determine whether women received the appropriate operative procedure (51). Gynecologic oncologists performed 70.3% of radical hysterectomies. The remainder were performed by GYNs or other surgeons. GYNs performed 85.5% of cone biopsies and 66.2% of simple hysterectomies (51).

Only 41% of women received definitive operative care in the LHIN where they lived, indicating that centralization of these surgeries is already occurring to some extent within the province (52).

Literature search results

Study characteristics and quality assessment (Table 10)

Four retrospective studies (47,53-55) were found that explored the impact of hospital and/or physician volumes on the longer term outcome of overall survival, and shorter term operative outcomes. Data sources included cancer registries (53,54), survey data (55) and an administrative database (51). Two studies that assessed shorter term outcomes adjusted their analyses for clustering of outcomes (47,55); however, the administrative database used for the Wright et al. analyses lacked detailed tumour characteristics (51). Analyses did not specify patient disease stage; however, Wright and Yasunaga limited their studies to patients who underwent a radical abdominal hysterectomy, which may be a proxy for cancer stage, as earlier stage patients typically undergo surgery (50). Studies of the relationship between provider specialty and outcomes were not found in the literature.

Table 10. Study characteristics and quality indicators, cervical cancer.

Study	Location	Comparison of interest	Study design	Data source	Years of diagnosis/operative procedure	Follow-up	Correction for clustering?	Funding source	No. of pts	Outcomes
Ioka 2005 (53)	Osaka, Japan	HV	R	Osaka Cancer Registry database	1990-1997	to 5 years after first diagnosis	No	None stated	1937 (94 hospitals)	OS
Downing 2007 (54)	UK	PV*	R	Northern and Yorkshire Cancer Registry and Information Services	1995-2000	December 2005	No	Cancer Research UK	1500	OS
Yasunaga 2009 (55)	Japan	HV, PV	R	Hospital surveys completed by gynecologists using patient records	Oct 2006 - Feb 2007	No follow-up	Yes (GEE model)	Ministry of Health, Labour and Welfare, Japan	407 (84 hospitals)	Operating times, postoperative complications
Wright 2011 (47)	USA	HV, PV	R	Voluntary administrative database	2003-2007	Up to readmissions within 60 days	Yes (GEE model)	None stated	1536 (>500 hospitals)	Operative and perioperative complications

R = retrospective; GEE = general estimating equations; OS = overall survival; pts = patients.

*98% gynecologists

Overall survival by hospital or physician volume (Table 11)

Two studies reported 5-year overall survival for cervical cancer by hospital or physician volume (54). In one study, there was a significant increase in mortality in very low volume hospitals versus high-volume hospitals, after controlling for covariates (53). In the study that assessed the relationship between OS and physician volume, no significant differences were found (54).

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Table 11. Survival outcomes by volume, cervical cancer.

Study	FIGO Stage	No. of pts	Comparison	5-year survival %	HR	95% CI	p-value	Statistical analysis	Potential covariates included in adjusted model
Ioka 2005 (53)	All stages	1937	HV 33/yr	75.7	ref			Cox proportional hazards model	age, sub-site and extent of disease, surgery and hospital type
			HV 26/yr	71.6	1.2	1.0-1.5			
			HV 8/yr	59.7	1.2	1.0-1.5			
			HV <1/yr	45.0	2.1	1.6-2.6	NR		
Downing 2007 (54)	All stages (>50% stage 1)	1500	PV ≥12/yr	75.3	0.81	0.64-1.01	NR	Cox proportional hazards model	Age, stage, Carstairs quintile
			PV 4-11/yr	64.1	0.85	0.68-1.05			
			PV <4/yr ^b	50.0	ref				

FIGO = International Federation of Obstetricians and Gynecologists; pts = patients; HV = hospital volume; PV = physician volume; NR = not reported; ref = reference group; yr = year.

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Short-term survival by hospital or physician volume (Table 12)

In Wright's analysis, adjusted for case mix and hospital volume, high-volume surgeons had significantly fewer medical complications and shorter lengths of stay than did low-volume surgeons. Surgeon volume was not related to operative injuries, perioperative surgical complications, ICU use, or readmission. After adjustment for case mix and surgeon volume, hospital volume had no independent effect on any outcomes of interest (47).

Yasunaga et al. also explored the relationship between radical hysterectomy and provider volumes and outcomes, and found a significant reduction in urinary disorders but not defecation disorders or lymphedema with increased surgeon volume. Operating time was also significantly shorter with higher volume surgeons. No significant differences were found for operating time or postoperative complications by hospital volume (55).

Table 12. Peri-operative outcomes, by volume, cervical cancer.

Study	FIGO Stage	No. of pts	Comparison	OR	95% CI	p-value	Statistical analysis	Potential covariates included in adjusted model
Yasunaga 2009 (55)	IA1 to IV undergoing radical hysterectomy	407 (84 hospital)	<u>Operative time</u> HV <20 HV ≥20 PV <200 ^b /lt PV ≥200/lt <u>Urinary disorders</u> HV <20 HV ≥20 PV <200 ^b /lt PV ≥200/lt <u>Defecation disorders</u> HV <20 HV ≥20 PV <200 ^b /lt PV ≥200/lt <u>Lymphedema</u> HV <20 HV ≥20 PV <200 ^b /lt PV ≥200/lt	ref 1.16 ref 0.37 ref 0.71 ref 0.45 ref 0.63 ref 0.74 Ref 2.08 Ref 1.27	 0.52-2.42 0.16-0.86 0.37-1.35 0.21-0.96 0.22-1.81 0.21-2.24 0.55-7.87 0.59-2.73	0.70 0.02 0.29 0.04 0.40 0.45 0.28 0.54	Proportional odds model fitted with GEE for operative time, logistic regression fitted with GEE for postoperative outcomes	Hospital or surgeon volume (depending on the outcome of interest), age, stage, diabetes, abdominal surgery, lymph node dissection, radiotherapy
Wright 2011 (47)	All stages undergoing radical hysterectomy (IB-IIA)	1536 (>500 hospitals)	<u>Medical complications^c</u> HV <4.5/yr HV >7.0/yr PV <2.26/yr PV >3.75/yr <u>Length of stay</u> HV <4.5/yr HV >7.0/yr PV <2.26/yr PV >3.75/yr	ref 1.50 ref 0.55 ref 0.87 ref 0.49	 0.86-2.59 0.34-0.88 0.44-1.73 0.25-0.98	NR NR NR NR	Multivariate analysis using GEE equations	Case mix, and surgeon or hospital volume (depending on the outcome of interest)

FIGO = International Federation of Obstetricians and Gynecologists; GEE = generalized estimating equations; NR = not reported; pts = patients; OR = odds ratio; CI = confidence interval; PV = physician volume; HV = hospital volume; ref = reference group, average volumes.

^bGynecologist volume.lt = lifetime; yr = year.

^cno significant findings for other outcomes assessed: operative injury, perioperative complications, transfusion, intensive care use, readmission.

Vulvar cancer

Background

Vulvar cancer is relatively rare: there were 148 cases in Ontario in 2003/04; however, incidence is reportedly increasing (56). There are currently no guidelines for the management of vulvar cancer in the province. Treatment usually involves wide local excision of the primary lesion with a groin node dissection (GND) for patients with greater than stage 1A disease (i.e., ≥ 1 -mm depth of invasion) (56,57). A guideline on the role of sentinel node biopsy in vulvar cancer is being developed by the PEBC. Until it has been completed, full groin node dissection remains the standard treatment. Pelvic node dissection is generally not considered useful (57).

Failure to perform GND may be associated with its being a significant source of morbidity, and the knowledge that many stage I and stage II patients will be proven node negative (57). Despite this, GND is important because failure to detect groin node metastases and treat them with radiation therapy is associated with lower rates of survival (56), and failure to perform lymphadenectomy has been identified as an independent adverse factor for 5-year survival (30). An exploratory study of patient care in Ontario found that only 62% of vulvar cancer surgeries included a GND. This rate is considered low, although the authors speculate that it may be an artifact of the data (56).

Another study of patterns of care in Ontario found that gynecologic oncologists performed 75.7% of vulvar cancer operations. Surgery consisted of radical vulvectomy with GND in 62.6% of patients. GYNs performed 22.8% of operations and 41% of these included a GND (52).

Literature search results

Study characteristics and quality assessment (Table 13)

Three studies that addressed organization factors in vulvar cancer were identified (27,30,57). One was retrospective and used data from a cancer intelligence unit from the years 1980-1982 and 1986-1988 (57), while the other was a combined retrospective and prospective study using forms completed by physicians in the years 1997-2002 (30). Both took place in England, had over 400 patients, and looked at the impact of surgeon or hospital volumes on surgical outcomes in vulvar cancer. A third study, Yap et al. (27), is described under the heading *Centralization*, above.

Table 13. Study characteristics and quality assessment, vulvar cancer.

Study	Location	Comparison of interest	Study design	Data source	Years of diagnosis/operative procedure	Follow-up	Correction for clustering?	Funding source	No. of pts	Outcomes
Rhodes 1998 (30)	West Midlands, England	HV	R	West Midlands cancer intelligence unit	1980-1982 and 1986-1988	Active follow-up to confirm 5-year survival	NA	NS	411	Rate of lymphadenectomy, cause-specific death rate
Falconer 2007 (57)	Southwest England	PV	R/P	forms completed by clinicians	1997-2002	NA	NA	NS	436	Adherence to standards derived from the NHS <i>Improving Outcomes in Gynecologic Cancers</i> guidance document

HV = hospital volumes; PV = physician volumes; R/P = Retrospective/prospective; pts = patients; NA = not applicable; NS = not stated; NHS = National Health Service (United Kingdom).

Survival and surgical outcomes (Table 14)

Falconer found a significantly higher achievement of adequate margins for high-activity surgeons, although this may have been the result of case mix (57). In Rhodes (30), treatment in a specialist centre (defined as ≥ 20 patients over six years) was not independently significant on multivariate analysis.

Yap et al. (27) compared practice post-centralization to that reported pre-centralization. After centralization, 84% of patients that required lymph node dissection received it, and four different types of surgery were performed, compared to 15 before centralization.

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Table 14. Survival and surgical outcomes, vulvar cancer.

Study	FIGO Stage	No. of pts	Comparison	5-yr survival %	HR	95%CI	p-value	Statistical analysis	Surgical management	Potential covariates included in adjusted model
Rhodes 1998 (30)	SCC, any stage	411	HV <20/six yrs HV ≥20/six yrs (ie specialist unit)	45.0 ^a 55.7	NR	NR	Not significant	Cox proportional hazards model, chi-square	Rate of lymphadenectomy 48% 44% p=0.408 (chi-square)	Age, stage, differentiation, excision complete?, lymph node excision
Falconer 2007 (57)	All stages (NR in up to 20% of patients) SCC or VVC	436	PV high PV med PV low	NA	NA	NA	NA	Chi-square	Achievement of adequate margins* 49% 39% 28% (p<0.01)	NA

FIGO = International Federation of Obstetricians and Gynecologists; VVC=verrucous vulval cancer; SCC = squamous cell cancer; pts = patients; HR = hazard ratio; CI = confidence interval; PV = physician volume; HV = hospital volume; ref = reference group; NA = not applicable; NR = not reported.

^acause-specific survival rate.

*2-cm healthy tissue excision margin to ensure a histological margin in excess of 8 mm.

Multidisciplinary teams

Background

According to the PEBC standards for multidisciplinary cancer conferences (MCC), the primary function of the weekly MCC is to ensure that a multidisciplinary team of specialists works together to generate appropriate treatment recommendations for each cancer patient prospectively (2). At this time, the model of the MDT is the standard of care for all cancer types (1).

The working group for this project endorses the 2006 PEBC MCC standards (2), and multidisciplinary management of gynecologic cancers. Thus, the literature review for this project focussed on considerations related to structure and organization that would be specific to gynecologic cancer disease sites. Please refer to the 2006 standards documents for general recommendations regarding MCCs (2).

Results (Table 15)

Treatment by a multidisciplinary team was recommended as the ideal method for managing gynecologic cancers in the NHS' *IOG* (21), and in a framework proposal for an ovarian cancer surgery program in Europe.

Five retrospective quantitative (58-62) and two qualitative studies (63,64) were identified that assessed the performance of multidisciplinary teams in gynecologic oncology, and more specifically, the MCC. Although these studies were of lower quality because of their retrospective or qualitative nature, they provided some information on outcomes of interest, including rates of discrepancies in pathology and diagnosis before and after the MCC discussion, and the rate of acceptance of recommendations made in the MCC. Also of interest is the description of several working gynecologic oncology MDTs, including membership, frequency of meetings, and number of patients seen in each meeting.

The core members of the teams in these studies were gynecologic oncologists, medical oncologists, radiation oncologists, pathologists, radiologists, nurse specialists, and the team coordinator. Occasional members included specialists in paediatrics, anaesthesia, gastroenterology, urology, social work, palliative care, genetic services and trainees. A single study that did not report outcomes data recommended that for vulvar cancer specifically, experts in psychosocial rehabilitation should be part of the MDT (59).

Most MCCs met weekly and discussed either all patients with a gynecologic cancer diagnosis or a selection of cases, such as rarer or more complex cases. In one instance, selection of cases presented at the MCC was at the discretion of the attending physician, leading more often to the review of the most difficult or controversial cases (60).

Santoso et al. (58) demonstrated that the MCC improved care in patients with gynecologic malignancies. In this study, minor discrepancies before and after discussion were found in 1.9% of cases, which did not affect patient care but were still important in discussing patient care. Major diagnostic discrepancies, which were defined as discrepancies that resulted in changes in patient care, were the result for 5% of patients. Examples of major changes were to tumour sites, stages and prognostic indicators (58). Cohen noted a major discrepancy rate of 1.4% and 4.5% after radiologic and histopathologic review, respectively (61). Discrepancy in this case was defined as a change in tumour site, histological type, stage or grade. A very large major discrepancy rate of 22% was found in one study that was conducted in India (62), while another in the USA found a rate of 19.8% (60).

The option of an online gynecologic oncology MDT was evaluated and found to be feasible by Chekerov et al. (65). Seventy-eight percent of the recommendations generated in the conference were accepted, while 20% were partially acceptable, which the authors consider to be a high rate of acceptance, perhaps due to the presentation of all relevant

guidelines and studies with detailed references during the conference, leading to the transparent formulation of individual recommendations for treatment. Similarly, Crawford notes that in the PORTEC study, the reduction in the use of adjuvant radiotherapy for early low-risk cases reflected the use of evidence-based protocols by a multidisciplinary team (28). Further study of additional meetings of the online tumour board showed that contributors found it to be an optimal way to exchange information between disciplines and care sectors. The option of the online conference also stimulated 50% of survey respondents to seek more second opinions (65).

A study that primarily assessed the impact of staging in endometrial cancer found that attendance at a multidisciplinary clinic was a significant prognostic factor in a model that did not include 'FIGO stage documented' and 'adjuvant radiotherapy used' (42).

Table 15. Study characteristics and measures of effectiveness, multidisciplinary teams.

Study	Location	Study type	MDT members	Cases discussed	Years of data collection	No. of pts	Frequency	Minor discrepancies (%)	Major discrepancies	Cases discussed per session	Acceptance of recommendations
Chekerov 2008 (65)	Germany	R	Per session, a median of 17 participants online; regular participants: surgery, radiotherapy, pathology and oncology specialists, external GYOs and MOs. Other specialties as needed: pediatrics, anaesthesiology, gastroenterology, urology	Complex cases which require an interdisciplinary approach. Criteria: all gyne cancers in adjuvant or recurrent disease stage, recently operated or otherwise pretreated patients, and patients with difficult comorbid constellations.	Dec 2004-Aug 2006	144	Twice monthly	NR	NR	Average=4(range 2-7)	78% fully 20% partially 2% refused
Cohen 2009 (61)	New Zealand	R	gynecologic pathologist, GYO, MO, RO, radiologists, trainees in gynecology and oncology, oncology nurses	All referrals to dept of gynecologic oncology, pre and post-op pts	Aug 2005-Aug 2006	509	Twice weekly	1.4% after histopathologic review and 1.8% after radiologic review	4.5% after histopathologic review and 1.4% after radiologic review	NR	NR
Santoso 2004 (58)	USA	R	GYOs, pathologists, ROs, GYO fellows, OBGYN residents, medical students, oncology nurses, social worker, cancer registrar, occasional guests	All gyne cancer; preinvasive disease recently operated on; 'interesting' recurrent cancers	1998-Jan 1 2001	459	Weekly for one hour	1.9	5%	3.7 (SD 1.68)	NR
Ganesan 2008 (62)	India	R	Consultants and residents from	Mismatches between		91	Weekly for one hour	30%	22%	NR	NR

Study	Location	Study type	MDT members	Cases discussed	Years of data collection	No. of pts	Frequency	Minor discrepancies (%)	Major discrepancies	Cases discussed per session	Acceptance of recommendations
			pathology and medical oncology departments	clinician impressions and histopathology ; unusual/interesting cases; inadequate pathological or clinical information for deciding on management or prognosis							
Greer 2010 (60)	USA	R	GYO, MOs, ROs, pathologists, and radiologists	Reasons for presentation: review of available outside hospital pathology specimens or radiographic images, confirmation of rare pathological diagnoses, discussion of difficult cases, and tx options in recurrent malignancies.	2004-2006,	526 pathology review	Weekly	6.8%	19.8%	6	88.5%
Kidger 2009 (63)	UK	Q	Surgical oncologists, MOs, pathologists, radiologists, nurses, team	Unclear; according to UK DoH, all women with a possible	Meeting observations over 10 weeks plus participant	NR	Weekly for up to 90 minutes	NR	NR	~300 tx decisions /year	NR

Study	Location	Study type	MDT members	Cases discussed	Years of data collection	No. of pts	Frequency	Minor discrepancies (%)	Major discrepancies	Cases discussed per session	Acceptance of recommendations
			coordinator (~25 regular members and additional visiting observers)	diagnosis of gynecologic cancer should be discussed	interviews						
Lanceley 2008 (64)	UK	Q	Large team (upwards of 30); general nurses, site-specific surgeons, palliative care physicians, clinical and MOs, cellular pathologists, radiologists, radiographer, social worker, specialist nurses, "audience" of visiting research fellows and clinicians	Cases forwarded to the MD coordinator for radiologic, pathologic review or discussion; according to UK DoH, all women with a possible diagnosis of gynecologic cancer should be discussed	4-month period of observation plus participant interviews	NR	Weekly	NR	NR	Number not stated, but meetings described as "highly pressurized" and the agenda "crowded"	NR

MDT = multidisciplinary team; pts = patients; SD = standard deviation; DoH = Department of Health (United Kingdom); R = retrospective; Q = qualitative; NR = not reported; MO = medical oncologist; RO = radiation oncologist; GYO = gynecologic oncologist; OBGYN = obstetrician/gynecologist; post-op = post-operative; tx = treatment.

Qualitative findings

Two qualitative studies identified some of the limitations of MCCs (63,64) in gynecologic cancer. Kidger et al. (63) found that meetings were postponed if radiologic information was not available, and that the team could not make decisions if the pathologist was absent. Other types of information did not play as large a role in the discussion. Comorbidities were only discussed sometimes, because it is difficult to quantify comorbidities without seeing the patient in person. Clear-cut decisions were not always made, although some members may have had the perception that a decision was made. Time constraints were an issue. Meetings tended to be disease centred, and incorporation of patient-related factors was not systematic. A checklist was suggested as a way of ensuring that these factors were discussed.

Lanceley et al. (64) looked at factors influencing decision making in a large team with upwards of thirty members. The Department of Health in the UK has mandated that all cases be discussed at multidisciplinary meetings, and this has increased time pressures. This paper describes women as emerging as the “semi-predictable embodiment of medical science” and the dominance in discussion of the biomedical mode. It was difficult for nonmedical team members to contribute with different views of the patients. The MDT in this case was found by the authors to be incompatible with a person-focused agenda.

Pathology

The PEBC is currently developing a guideline on secondary review of pathologic specimens in gynecologic oncology; therefore, any articles found on secondary review were excluded from our evidence base. This review included articles that assessed the rate of discrepancy in initial diagnoses and intraoperative consultation between non-specialist pathologists and gynecologist pathologists.

The *IOG* guidance from the UK (21) states that biopsy specimens and pathology reports should be sent to the (specialized) Cancer Centre when women are referred there from the (community) Cancer Unit, as diagnosis, staging and prognostic evaluation is highly dependent on pathology (21). With a European perspective on surgical program building in advanced ovarian cancer, Verleye et al. conclude that a specialized pathologic team, with senior pathologists experienced in gynecologic oncology, improves the quality and completeness of the diagnosis and the pathology reporting (33).

Five single studies assessed subspecialist gynecologic pathologists. In one hospital in Ontario, intraoperative consultation (IOC) (i.e., analysis of frozen sections) for gynecologic surgery by GYNs is provided by surgical pathologists, while subspecialized gynecologic pathologists provide this support for gynecologic oncologists. In this setting, there was a significantly increased rate of major discrepancies ($p=0.0266$) between IOC and final pathology for surgeon pathologists compared to subspecialist pathologists. The authors conclude that IOC should be rendered by gynecologic pathologists whenever feasible, or that they at least be available to provide consultation (66). Another study that assessed the use of frozen section in ovarian cancer found that non-specialist pathologists were significantly more likely than gynecologic oncologist pathologists to “misdiagnose” a tumour ($p=0.005$). This study found that accurate diagnosis of borderline ovarian tumours in IOC depended mainly on the level of experience of the pathologist (67). Similarly, Bige et al. looked at the accuracy of frozen section in ovarian cancer with the aim of identifying the role of the gynecologic pathologist, based on level of experience. Sensitivity and specificity were higher in the subspecialist group (p -value not reported) and more malignant tumours diagnosed by frozen section were found to be discordant with the final diagnosis in the non-gynecologic oncologist pathologist group (68). Another assessment of IOC that compared the diagnostic error rate in a specialist gynecologic pathology unit and a general pathology laboratory found that errors

due to the quality of technical preparations and pathologist misinterpretation were more common in the general pathology laboratory; however, because several pathologists worked in both laboratories it was not possible to conclude that this discrepancy was due to experience or expertise (69).

Pathologic grade is an important prognostic indicator and can be an important factor in the selection of appropriate therapy. A review by Verleye et al. (70) of 479 pathology reports from 40 institutions in 11 countries participating in a clinical trial showed that degree of differentiation (grade) was missing in 22.0% of reports for both arms of the study combined. Although the level of experience of individual pathologists was not available in this study, they recommend specialization of pathologists, which would require centralization in order to ensure sufficient case loads.

Supportive care delivery within a gynecologic cancer MDT

Steele and Fitch (71) conducted a cross-sectional descriptive study to look at the supportive care needs of women with gynecologic cancer and to determine whether women wanted assistance meeting those needs. Eight of the top 10 most frequently reported needs were non-physical: e.g., expressions of fear and uncertainty. Identifying the presence of a need did not necessarily mean that the woman wanted help with it. In a mixed-methods study, Maughan and Clarke (72) note that within an MDT, nurses are in a key position to be able to address the complex and often unmet needs of patients in the psychological, social and sexual realms. Allen (73) outlined the role of the clinical nurse specialist in vulvar cancer, concluding that this member of the MDT is in a key position to address the complex and often sensitive issues faced by women with gynecologic cancer, and especially vulvar cancer. Booth et al.'s study also stresses the importance of the clinical nurse specialist in helping patients with their information needs (74).

DISCUSSION

The Gynecologic Oncology Organizational Guideline Working Group and Expert Panel systematically reviewed the evidence for organizational factors that affect patient surgical and survival outcomes in gynecologic oncology. Not surprisingly, as in previous reviews of organizational factors, the evidence was limited in quality, and largely comprised of non-randomized, retrospective studies with inconsistent definition of comparison groups and outcomes and failure to control for clustering of outcomes, among other limitations. Thus, as other reviews have noted in the past, it has been difficult to draw strong conclusions from the available literature on this topic. Because of this, the guideline developers relied heavily on their consensus-based opinion when formulating recommendations.

One higher quality systematic review was found that assessed the relationship between organizational factors and outcomes in ovarian cancer. It concluded that there is a link between treatment by gynecologic oncologists and improved outcomes, especially for surgical staging (5). Another methodologically strong review with strict inclusion criteria published after our final search date agreed that although the evidence was of lower quality, there was a consistent association between survival and treatment in specialized centres, especially for ovarian cancer (50). Likewise, this review, also comprised largely of retrospective observational studies, found some evidence to recommend treatment in specialized centres for most patients with gynecologic cancer.

As each gynecologic cancer disease site has different incidence rates, mortality rates and treatment options, it was also important for the working group to consider the evidence separately for each one. As stated, there was more evidence available for ovarian cancer, and fewer articles related to the less commonly diagnosed cervical and vulvar cancers. Therefore,

the recommendations for ovarian cancer patients were made with more consideration for the evidence base, while those for cervical and vulvar cancer were more consensus based, with the knowledge that the rarity of these latter conditions, and the complexity of their treatment justified consolidation among experienced subspecialists in higher volume centres.

In summary, the working group concluded that all cases of invasive ovarian, vulvar, and cervical cancer should be referred to the coordinator of a multidisciplinary cancer conference at a designated specialized centre (a gynecologic oncology centre), and that surgical treatment for these cases take place only at these centres and be performed by a gynecologic oncologist. This recommendation was based on the consensus that gynecologic oncology centres will be best equipped to provide the resources that are needed to support the work of gynecologic oncologists, including proximity to other members of the multidisciplinary team, and more specialized pathology expertise, capacity to support multidisciplinary cancer conferences, facilitation of accrual to clinical trials, and the necessary human and physical resources.

It is recognized that these recommendations will likely not have an overall positive impact on wait times, which have been identified as a problem in Ontario. However, several of the recommendations should help to minimize the exacerbation of the wait-times problem due to the project patient-population increase, through better flow of patients, and more collaboration treatment. The implementation of these recommendations will necessitate a shift because, according to preliminary data from CCO, currently 59% and 66% of surgeries for cervical and ovarian cancer, respectively, are being conducted at hospitals that have a gynecologic oncologist (36). Recruitment of more gynecologic oncologists may be necessary to handle this increase in cases.

Endometrial cancer treatment recommendations are more complex. Endometrial cancer is a surgically staged disease (22), and the rate of full staging, including a lymph node sampling procedure during surgery, is significantly higher when surgery is performed by a gynecologic oncologist (36). As sufficient human or operating room resources are not available in Ontario to stage all patients diagnosed grade 1 preoperatively, it was agreed that surgery may be performed by gynecologic oncologists at specialized centres or gynecologists with an interest in oncology at an affiliated centre that does not have all the features of specialized care but that does have an established and maintained partnership with a specific gynecologic oncology centre. Patients with a higher risk of recurrence (grade 2 or 3) endometrial cancer should undergo surgery at gynecologic oncology centres.

All patients, regardless of treatment location, should have access to multidisciplinary care. While multidisciplinary teams have been accepted as the optimal working model for the treatment of cancer, several barriers to good practice and functioning have been identified in this review, which include lack of administrative support, incomplete attendance, and lack of time available to review all patients (75). In a review of the NHS cancer plan, Sikora states that the MDT discussion of every patient, which is now enshrined in the NHS culture, is very time consuming (76). Thus, this guideline states that while each new case should be listed for potential discussion, other options, such as a documented discussion between physicians from more than one discipline, are acceptable. Zorbas notes, in an abstract, that multidisciplinary care is difficult in Australia due to its geography and significant differences in population and resource availability (77). One solution to the issue of geography in Ontario may be the online conference described by Chekerov et al. (65).

Surgery is often the primary treatment for patients, but this review and consensus process also looked at delivery of chemotherapy and radiation, and other services such as palliative care. The consensus was that, provided a strong linkage was established and maintained with a gynecologic oncology centre, these other treatment could be delivered at affiliated centres in order to allow patients to receive ongoing treatments closer to home.

Often where care is not centralized, multidisciplinary teams from specialized hospitals closely collaborate with other hospitals, and many gynecologists have a special interest in gynecologic oncology although no formal training (20). These features of the gynecologic oncology-centre–affiliated-centre partnership will be important to ensure that the recommendations have an impact on patient outcomes.

The working group expects that the limitation of treatment provision to gynecologic oncology centres and affiliated centres will result in more consistent care across the province, better adherence to established guidelines, greater access to multidisciplinary teams and subspecialists and better adherence to established guidelines. As reorganization occurs, it will also be important to ensure that centres are following established guidelines and disease management pathways in order to realize the full potential for improvements in patient-related outcomes.

CONCLUSIONS

The results of this systematic review indicate that most gynecologic cancer patients would benefit from more specialized care. This can best be achieved in Ontario by designating gynecologic oncology centres, where most surgery and other care takes place, and other centres that are affiliated with gynecologic oncology centres, where low-grade endometrial surgery may take place as well as some other service delivery. Underpinning these recommendations is the need for access to multidisciplinary teams, and a strong partnership between the two levels of centres. If implemented, it is hoped that these changes will lead to improved outcomes for gynecologic cancer patients in Ontario.

Future Research

As mentioned, the recommendations are underpinned by a limited evidence base, and it is not foreseeable that higher quality evidence, i.e., prospective randomized studies, will ever be conducted due to issues of feasibility. Forthcoming before-and-after studies, as more jurisdictions implement centralized or regionalized care for gynecologic oncology patients, will help to inform best practices for the organization of care for gynecologic cancer.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. This section will be completed prior to guideline publication.

ACKNOWLEDGEMENTS

The Gynecologic Oncology Organizational Guideline Working Group would like to thank the following participants in the guideline development process:

1. Hans Messersmith, Assistant Director
2. Sheila McNair, Assistant Director
3. Bruce Histed, Copy Editor
4. Harkanwal Randhawa, Student Assistant, for conducting an audit of the extracted data.
5. Internal Peer Reviewers Nadia Coakley and Bryan Rumble.
6. Wei Cao, Project Coordinator, Surgical Oncology Program, Cancer Care Ontario.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

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Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Appendix 1. Members of the Gynecologic Oncology Organizational Guideline Development Group: Working Group and Expert Panel.

Working Group

- **Dr. Michael Fung-Kee-Fung** (chair), Gynecologic Oncologist, Ottawa General Hospital, Ottawa, Ontario
- **Dr. James Biagi**, Medical Oncologist, Cancer Centre of South-eastern Ontario, Queen's University, Kingston, Ontario
- **Wei Cao**, Project Coordinator, Surgical Oncology Program, Cancer Care Ontario, Toronto, Ontario
- **Dr. Terry Colgan**, Gynecologic Pathologist, University Health Network, Toronto, Ontario
- **Dr. David D'Souza**, Radiation Oncologist, London Health Sciences Centre, London, Ontario
- **Dr. Laurie Elit**, Gynecologic Oncologist, Juravinski Cancer Centre, Hamilton, Ontario
- **Amber Hunter**, Manager, Surgical Oncology Program, Cancer Care Ontario, Toronto, Ontario
- **Dr. Jonathan Irish**, Provincial Head, Surgical Oncology Program, Cancer Care Ontario
- **Erin Kennedy**, Research Coordinator, PEBC, Cancer Care Ontario/McMaster University, Hamilton, Ontario
- **Dr. Robin McLeod**, Surgeon, Mount Sinai Hospital and Lead, Quality Improvement & Knowledge Transfer, Surgical Oncology Program, Cancer Care Ontario, Toronto, Ontario
- **Dr. Barry Rosen**, Gynecologic Oncologist, University Health Network (Princess Margaret Hospital), Toronto, Ontario

Expert Panel

- **Dr. Al Covens**, Gynecology Oncologist, Sunnybrook Health Sciences Centre, Toronto, Ontario
- **Lindsey Crawford**, Regional Vice President, North Simcoe Muskoka Local Health Integration Network
- **Dr. Denny DePetrillo**, Gynecology Oncologist, Credit Valley Hospital, Mississauga, Ontario
- **Dr. Dimitrios Divaris**, Chief of Pathology, Grand River Hospital, Kitchener-Waterloo, Ontario
- **Dr. Julie Ann Francis**, Gynecology Oncologist, Kingston General Hospital, Kingston, Ontario
- **Esther Green**, Registered Nurse, Provincial Head of Nursing and Psychosocial Oncology, Cancer Care Ontario
- **Dr. Leonard Kaizer**, Medical Oncologist, Credit Valley Hospital, Mississauga, Ontario
- **Dr. Felice Lackman**, Gynecologic Oncologist, Markham Stouffville Hospital, Markham, Ontario
- **Dr. Audrey Li**, Radiation Oncologist, Lakeridge Health, Oshawa, Ontario
- **Dr. Alice Lytwyn**, Pathologist, Juravinski Hospital, Hamilton, Ontario
- **Dr. Michel Prefontaine**, Gynecology Oncologist, London Health Sciences Centre, London, Ontario
- **Dr. Andrew Robinson**, Medical Oncologist, Health Sciences North, Sudbury, Ontario
- **Dr. Carol Wade**, Gynecologist, Credit Valley Hospital, Mississauga, Ontario

Targeted Peer Reviewers

- **Dr. Robin Crawford**, Cambridge Lea Hospital, Impington, UK
- **Dr. Diane Miller**, University of British Columbia, Vancouver, British Columbia
- **Dr. Michael Quinn**, The University of Melbourne, Victoria, Australia

IN REVIEW

Appendix 2. Search strategy.

1. ((endometr* or uter* or cervi* or ovar* or vulva* or gynae* or gyne*) adj (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).ti,ab.
2. Organizational Policy/ or Efficiency, Organizational/ or Models, Organizational/
3. *health facilities/
4. centralization.mp. or Centralized Hospital Services/
5. (patterns adj5 care).ti.
6. clinical competence.mp. or Clinical Competence/
7. palliative care.mp. or Palliative Care/
8. patient care.mp. or Patient Care/
9. cancer care facilities.mp. or Cancer Care Facilities/
10. (training or competency or proficiency).ti.
11. Surgical Procedures, Operative/ or surgical volumes.mp.
12. volume*.ti.
13. (centrali?ation or speciali?ation or speciali?\$).ti.
14. regional*.ti.
15. (subspecialty or specialty).ti.
16. multidisciplinary.ti.
17. multidisciplinary team management.mp. or Patient Care Team/
18. 1 and (2 or 3 or 4 or 6 or 8 or 9 or 10)
19. 1 and 5
20. 1 and 7
21. 1 and (11 or 12)
22. 1 and (13 or 14 or 15)
23. 1 and (16 or 17)
24. 18 or 19 or 20 or 21 or 22 or 23
25. limit 24 to (english language and yr="1995 -Current")
26. 25 not screening.ti.

Initial citations: 955 in MEDLINE; search conducted December 12, 2011 .

Domain 1: Scope and Purpose (Score: 3/3)

1. The overall objective(s) of the guideline is (are) specifically described. Yes.
2. The health question(s) covered by the guideline is (are) specifically described. Yes.
3. The populations (patients, public, etc.) to whom the guideline is meant to apply is specifically described. Yes.

Domain 2: Stakeholder Involvement (Score: 2/2)

4. The views and preferences of the target population (patients, public, etc.) have been sought. Yes.
5. The target users of the guideline are clearly defined. Yes.

Domain 3: Rigour of Development (Score: 4/8)

7. Systematic methods were used to search for evidence. Yes.
8. The criteria for selecting the evidence are clearly described. No.
9. The strengths and limitations of the body of evidence are clearly described. No.
10. The methods for formulating the recommendations are clearly described. Yes.
11. The health benefits, side effects and risks have been considered in formulating the recommendations. Yes.
12. There is an explicit link between the recommendations and the supporting evidence. No.
13. The guideline has been externally reviewed by experts prior to its publication. Yes.
14. A procedure for updating the guideline is provided. No.

Domain 4: Clarity of Presentation (Score: 3/3)

15. The recommendations are specific and unambiguous. Yes.
16. The different options for management of the condition or health issue are clearly presented. Yes.
17. Key recommendations are easily identifiable. Yes.

Domain 5: Applicability (Score: 3/4)

18. The guideline describes facilitators and barriers to its application. Yes.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice. Yes.
20. The potential resource implications of applying the recommendations have been considered. Yes (in a separate analysis).
21. The guideline presents monitoring and/or auditing criteria. No.

Domain 6: Editorial Independence (Score: 0/2)

22. The views of the funding body have not influenced the content of the guideline. No.
23. Competing interests of guideline development group members have been recorded and addressed. No.

Appendix 4 - AMSTAR Scores of Systematic Reviews

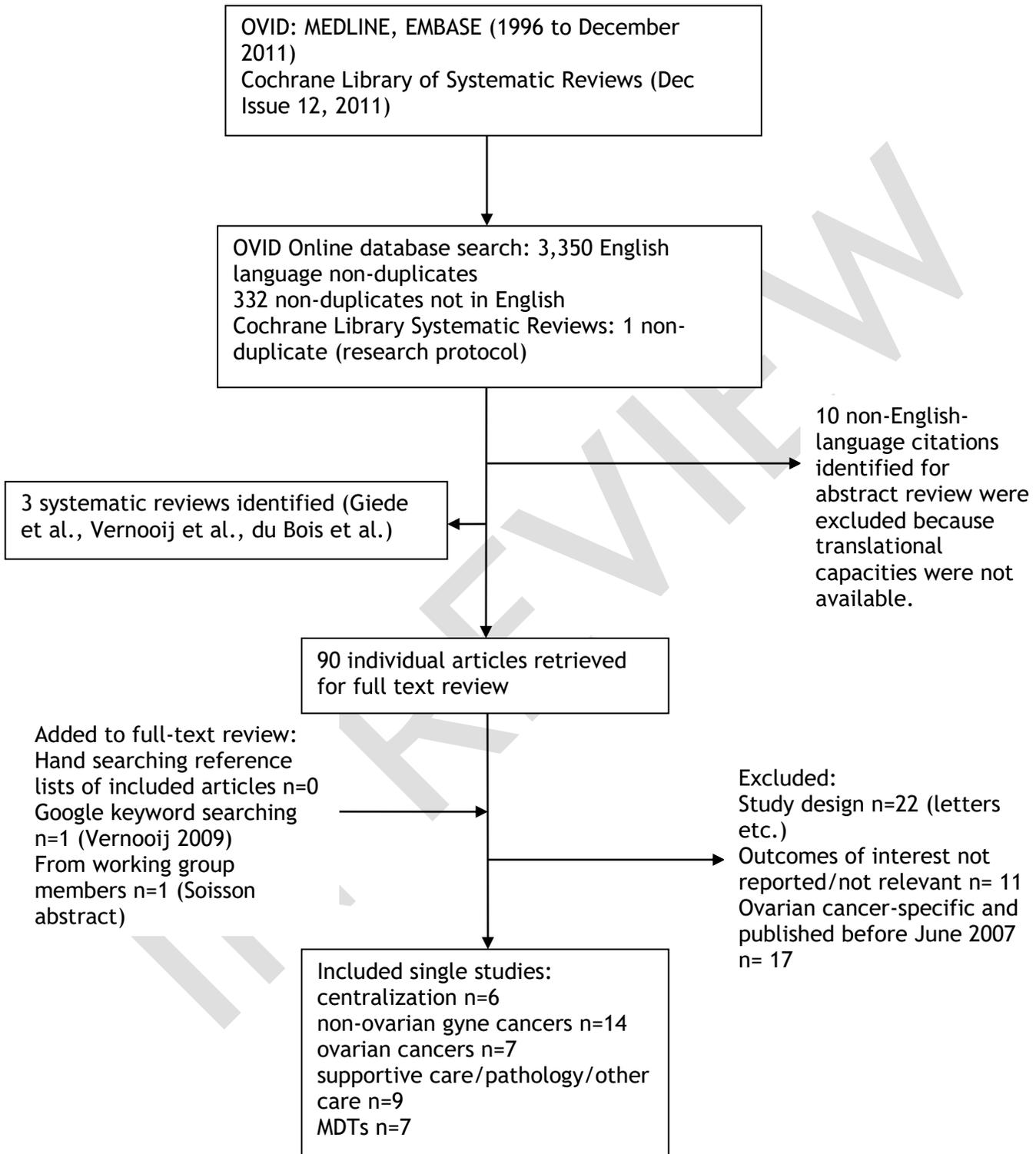
Response options:

- Yes
- No
- Can't answer
- Not applicable

	Giede (2005) (23)	Vernooij (2007) (20)	Du Bois (2009) (17)
1. Was an 'a priori' design provided?	Yes	Yes	Yes
2. Was there duplicate study selection and data extraction?	Not mentioned	Not mentioned	Yes
3. Was a comprehensive literature search performed?	Yes - Cochrane library, Medline, EMBASE, HealthStar, cross-referencing	No - did not include searching beyond electronic databases. (PubMed plus related articles and CDSR, DARE, NHS-EED, HTA-Database, CENTRAL, CCT, clinical trials.gov)	Medline plus searching reference lists and contacting experts
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Can't answer	No	No
5. Was a list of studies (included and excluded) provided?	Included yes, excluded no	Included yes, excluded studies described	Included yes
6. Were the characteristics of the included studies provided?	No	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes	No	Adjustment for covariates assessed and noted in the results

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes
9. Were the methods used to combine the findings of studies appropriate?	Not combined as authors felt that the studies were too heterogeneous for a meta-analysis	Too much heterogeneity	Too much heterogeneity
10. Was the likelihood of publication bias assessed?	No	Yes, informally	No
11. Was the conflict of interest stated?	No	No	Yes

Appendix 5. Literature search flow diagram.



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

**Organizational Guideline for Gynecologic Oncology Services in Ontario:
EBS Development Methods and External Review Process**

*M. Fung-Kee-Fung, E.B. Kennedy, J. Biagi, T. Colgan, D. D'Souza, L. Elit, A. Hunter, J. Irish,
R. McLeod, B. Rosen and members of the
Gynecologic Oncology Organizational Guideline Expert Panel*

Report Date: June 6, 2013

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations.* Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process.* Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Gynecologic Oncology Organizational Guideline Working Group of the CCO PEBC. The series is a convenient and up-to-date source of the best-available evidence on optimal chemotherapy for recurrent ovarian cancer developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Expert Panel (EP) Review and Approval

The draft guideline was presented to the EP (Appendix 1) in August 2012 and discussed at an in-person meeting with the EP and the Working Group on September 7, 2012. The draft for discussion included a specific-volume recommendation for the number of cases for a facility to qualify as an affiliated centre. The Expert Panel objected to a volume recommendation due to the low quality of the evidence-base, stating that an arbitrary volume recommendation was not warranted. In response, the working group removed the volume recommendation for affiliated centres.

Another significant point of discussion was the pathology-related recommendations, which the pathologist on the Expert Panel felt had insufficient specificity and detail. In response, CCO's Surgical Oncology Program convened a teleconference with several Ontario pathologists working in the area of gynecologic oncology. The outcome of this consultation was the agreement that constraints in the system in Ontario necessitated the formulation of various options for pathology review, as reflected in the recommendations. As well, the group noted that this topic will be informed by the results of a separate gynaecologic-oncology pathology secondary-review project that the PEBC is currently undertaking.

Other changes to clarify roles and responsibilities of the centres and/or the relationship between gynecologic oncology centres and affiliates included:

- Statement that gynecologic oncology centres must provide radiation, systemic treatment and perform surgery.
- Statement that affiliated centres can provide any or all of radiation, systemic treatment and perform surgery.
- Statement that an affiliated centre needs to have a partnership with a gynecologic oncology centre.

After these and other more minor modifications were made, the draft document was recirculated to the Expert Panel and a teleconference was convened on October 17, 2012. The changes were discussed, and the Expert Panel approved the document (approval was also obtained via email from three EP members who could not attend the teleconference).

Report Approval Panel Review and Approval

After EP approval, and prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise. Key issues raised by the Report Approval Panel included the following:

1. This should be called a consensus statement rather than a guideline.
2. The guideline did not provide adequate background information to inform the reader regarding why this guideline is necessary. The guideline assumes problems in Ontario that are not substantiated by data.
3. The research questions are confusing; what is the main question?
4. More accurate presentation of the evidence:
 - There is a tendency to report on the number of studies that support arguments but not give the full denominator (X of Y studies supported).
 - Also make sure the comparison is always known to the reader.
 - State that the evidence is often conflicting.
 - Evidence is used that is not applicable to the Ontario context.
 - The survival data from Ontario by Elit et al. shows no difference in survival by surgeon specialty.
 - A more thorough discussion of the strengths and weakness of the selected evidence should be provided throughout this document.
5. Ambiguity about the respective roles of GYOs and medical oncologists in the delivery of systemic therapy.
6. Recommendations on multidisciplinary teams including staff and training requirements may not be needed, this is not researched in a systematic manner, rather, previous statements, guidelines are accepted. May be best to include this somewhere in discussion, or in final recommendations - but not as chief question of this guideline.
7. Justify why ovarian masses with RMI less than 200 are not included.
8. The authors provide limited data on quality of care in Ontario among GYOs and GYNs - while there are improvements in staging, etc. - there are still major gaps with provision of care by GYO...
9. There is lack of clarity about the extent to which the recommendations are derived directly from the evidence-base versus consensus of the working group. Are there other reasons for centralization - ? poor accrual to clinical trials, ? introduction of resource-intense advances in care, e.g., HIPEC, ? dismal prognosis of advanced-stage disease. As well, need for psycho-social-sexual counselling and support is something likely most affiliated centres can't offer.
10. Currently, guideline tone and interpretation of evidence base is suggestive of inferior care in 'affiliated centres.' Current tone/interpretation not justified by evidence and may result in disengagement of relevant stakeholders from a process that only begins with the publication of this guideline...the authors recommend that low-risk uterine CA can be done in affiliated centres, but should these cancers as well be properly staged - thus the recommendation does not make sense unless there is support to ensure proper staging happens for all patients??
11. It may be easier to ensure that all GYNs and GYOs are aware of the type of patient that can be treated in an AC. This document to this reviewer does not appreciate the high-quality training received by GYNs. It may be better to supplement and support GYNs to the benefit of all patients, rather than expend great energy moving nearly all

- gyne onc surgery to RCCs. This may be a huge waste of GYN expertise with little advantage for patients, and implications for patient travel, including for follow-up.
12. This should be better justified, are all gyo's currently providing this, may wish to delete this from document if lack of data, or if there are data, outlining which cases should be done using laparoscopic robotic approaches.
 13. I do not understand the rationale for a volume recommendation for GYO's at the specialized centres and not the GYNs at the non-specialized centres - the rationale is not compelling as stated. Requires more transparency.
 14. This section on affiliated centres is not informed by evidence at all. If anything, if one accepts the previous arguments, then one could argue that low-grade endometrial surgery should not be done at such centres.
 15. [Striving to have surgery at affiliated centres performed by a minimum number of gynecologists is a] paternalistic model that may irritate surgeons at [affiliated centres (ACs)].
 16. This statement suggests discussion between an AC surgeon and a nurse specialist or local pathologist would be adequate?? If MCCs are the accepted standard, they should not be watered down for certain patients.
 17. The statement that the lymph node excision rate in Ontario is low across all physician specialties is very important - and implies centralization will not lead to improved care unless other mechanisms are also used. Underscores importance of engaging all stakeholders in a process of quality improvement...concerns with quality of GYO care.
 18. Subspecialty pathology is another key factor that may encourage centralization - this is downplayed in this document due to a perceived focus on volume-outcome GYN versus GYO relationship. The evidence from these latter comparisons is unimpressive. Could the authors suggest creative ways to support gynaecologists in ACs with their work - on for example a wider array of uterine cancer or even ovarian cancer - through facilitated path review, or MDC review.
 19. This transition from poor-quality evidence to 'a link between gyo tx/high-volume tx and improved outcomes' is premature. Even if a link were consistently shown, other evidence (pancreas, thoracic, evidence of suboptimal care by GYOs) should encourage a re-working of the reasons for centralization, or the actual operationalization of greater regionalization in the province for gyne cancer.
 20. Drop the Appendix with the detailed human resource requirements and make more succinct, i.e., they must meet the specialist training required to practice in the province. Non-oncology specialists should have an interest in oncology. Non-gyne specialists should have an interest in gyne.

Actions/Modifications/Response

1. The PEBC is constrained in naming its documents, thus we continue to call this a guideline; however, we have inserted text in several places to make it clear to the reader that the recommendations are consensus-based.
2. Added a Rationale for a Guideline to Section 1 and background information on the current organization and quality gaps in the Section 2 Introduction.

3. Changed questions to present the systematic review questions first, then indicated that these questions would be used to address the consensus-based implementation recommendations.
4. Key evidence parts of Section 1 were expanded to include the total number of studies on each topic and the proportion that support or were in opposition to the recommendations. Comparisons were specified wherever applicable, and several statements were added to make it clear that the evidence was often conflicting. We added statements to indicate that the evidence may not be applicable to the Ontario context.
 - The survey by Elit also showed that repeat surgery was less likely with GYOs. That is why we considered this study to be an important piece of evidence. Our response to #1 also helps to put the Elit study into context with the other evidence.
 - A more thorough discussion of the strengths and weaknesses was included in the Key Evidence parts of Section 1 and reiterated in the Discussion part of Section 2.
5. This question was outside of the scope of this guideline; however, this topic was discussed in working group meetings. In particular, a member of the working group pointed out that a study had recently been released showing that there is no difference in survival of gynecologic oncology patients who are treated by GYOs compared to those treated by MOs (3).
6. We added text to indicate that we were not intending to systematically review the evidence on multidisciplinary teams, as we were willing to accept previous conclusions that MDTs are the standard of care. However, there were some points related to MDTs that were systematically reviewed, including the composition of the multidisciplinary team. We tried to clarify which aspects of the MDT section were based on endorsements of previous guidance and which were based on our own systematic review.
7. We added a statement saying that patients with an RMI of less than 200 are less likely to have invasive disease, and we are limiting the target patient population to invasive cases.
8. A qualifying statement was added to the recommendations for GYO care and for GYO care in GOCs to acknowledge that GYO care has historically been sub-optimal in the province, and that strategies for better adherence to guidelines and identifying and filling gaps in guidance are necessary.
9. There are other reasons for centralization. We have modified the recommendation to include the following justification: “As the evidence for treatment at designated centres was mixed and may have limited applicability to the Ontario context, the recommendation for treatment of most invasive gynecologic cancers by GYOs at designated GOCs is the opinion of the working group, based on the consensus that GOCs will be best equipped to provide the resources that are needed to support the work of GYOs, including proximity to other members of the multidisciplinary team, and more specialized pathology expertise, capacity to support multidisciplinary cancer

conferences, facilitation of accrual to clinical trials, and the necessary human and physical resources outlined in the recommendations below.”

10. We attempted to modify the tone so that inferior care at affiliated centres was not implied. Full staging of grade 1 endometrial cancer is a controversial topic in gynecologic oncology, and as there is no clinical practice guidance for this in Ontario, the consensus of the group was that full staging is not necessary. This may be interpreted by some as inferior care; however, it is the opinion of the working group that the travel, operating room time and human resources would not be worth the staging of all of these patients when their risk of metastases is low. We recommend that appropriate pathology review be available to these patients in order to ensure that as many as possible undergo surgery in the right environment.
11. The working group consensus was for treatment of most gynecologic oncology cases by GYOs in GOCs. We had attempted to recruit several gynecologists for the Expert Panel, but could only successfully find one individual who wished to participate. It is unfortunate that the Expert Panel for this project only included one gynecologist; however, her opinion was that centralizing care in the manner that we were proposing was not objectionable, and indeed, would free gynecologists’ time to attend to other cases. A subsequent review phase will solicit feedback on the guideline from relevant professionals [“Professional Consultation (PC)”], including gynecologists from across Ontario. We will look carefully at their feedback on the proposed centralization of services and we will modify the guideline if there is a majority opinion that increasing support for gynecologists is a better plan of action than centralization.
12. We specifically chose to include minimally invasive surgery as a requirement for GOCs, based on the working group’s opinion that this should be offered at all centres.
13. The volume recommendation for GOCs was removed based on RAP reviewer feedback.
14. The working group added the following justification for treatment at affiliated centres, which includes the statement that the recommendation is not evidence based, but rather based on the consensus of the working group: “As there was no evidence found in the literature search to support the establishment of treatment at affiliated centres, these recommendations are the consensus of the working group, which agreed that, provided a strong linkage was established and maintained with a GOC, radiation and systemic therapy could be delivered at affiliated centres, in order to allow patients to receive ongoing treatments closer to home.”
15. We will assess the PC feedback from practitioners across the province to determine whether this statement is irritating.
16. We clarified that, in addition to a discussion between two specialties, appropriate pathology review is required for these patients.
17. See item #8 above.
18. Pathology review was extensively discussed as it was noted by the Expert Panel as a weakness in our guideline. There is another project currently underway at the PEBC on pathology secondary review in gynecologic oncology. We are hoping that the results from that review help to inform what is needed for complete gyne pathology review in Ontario. We are recommending that gynecologists who operate on low-grade endometrial cancer patients participate in MCCs; however, the consensus of the

working group is that all other invasive cancers undergo surgery by GYO's at GOCs. The rationale for this has been more explicitly spelled out in the Justification sections for these two recommendations.

19. The working group agrees that the evidence for centralization is of lower quality. The justification for centralization, based on consensus, was improved. See item #9 above.
20. This change was made; the Appendix was removed.

External Review by Ontario Clinicians and Other Experts

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.

Following approval of the document at Internal Review, the Gynecologic Oncology Organizational Guideline Expert Panel circulated the draft document with recommendations modified as noted under Internal Review, above, to external review participants for review and feedback.

Methods

Targeted Peer Review: During the guideline development process, seven targeted peer reviewers from Ontario considered to be clinical and/or methodological experts on the topic were identified by Gynecologic Oncology Organizational Guideline Working Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed, and the draft report and a questionnaire were sent via email for their 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 out on February 11, 2013. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Gynecologic Oncology Organizational Guideline Working Group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All gynecologists with interests in: gynecology oncology, pathology, systemic therapy, radiation oncology, and those that are surgical leads, or imaging leads, or regional vice presidents in the PEBC database were contacted by email to inform them of the survey. Participants were from Ontario. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on February 12, 2013. The consultation period ended on March 12, 2013. The Gynecologic Oncology Organizational Guideline Working Group reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Reviewer Ratings (N=3)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	1	0	2
2. Rate the guideline presentation.	0	1	0	1	1
3. Rate the guideline recommendations.	0	0	1	2	0
4. Rate the completeness of reporting.	0	0	0	1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	1	1	1
6. Rate the overall quality of the guideline report.	0	0	1	2	0
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	1	0	1	1
8. I would recommend this guideline for use in practice.	0	0	1	1	1

9. What are the barriers or enablers to the implementation of this guideline report?

The reviewers were concerned with community and physician buy-in, that patients would have to travel long distances, and that there were too few gynecologic oncologists in Ontario.

Table 2. Summary of written comments by targeted peer reviewers and modifications/actions taken.

<i>Summary of Written Comments</i>	<i>Modifications/Actions/Comments</i>
1. You need to address the reasons for low node dissections etc. In some situations it may be appropriate. You need further study to see what are the drivers are. Just making it a benchmark without inquiring into the “barriers” to lymph node dissection may be a barrier in and of itself.	Pg 7 - The working group included this statement as an example of when adherence to recommended clinical practice guidelines can be sub-optimal for gynecologic oncologists at teaching centres. In order to not distract the reader from the main point, the working group decided to remove “including a low rate of performance of ... data in Ontario” in first bullet under Qualifying Statement.
2. In the human resources section, the cancer centre needs access to plastic surgeons.	Pg 11 - The working group decided to add plastic surgery to the other on-site specialist list.
3. Given 80% of cases are uterine and ovary I feel that 150 new cases annually is on the low side. I would suggest 200 cases per 2 specialists.	Pg 14 - Since the recommendation of 150 surgical cases was determined through expert consensus, the working group decided not to change it.
4. There is a mismatch; a centre with 150 cases with radiotherapy will need a much greater surgical centre feeding in.	Pg 14 - Radiation oncologists at GOCs often see patients who are referred from other centres not just from gynecologic oncologists within the GOC.
5. There could be or should be centralization to a	Pg 11 - The working group decided to add

greater level with respect to fertility sparing procedures for cervical cancer and for other cancers. Increasingly, we should be joining up the approach for a holistic management of the young patient offering oocyte vitrification and an expert reproductive medicine consult. Given the specialization around brachytherapy it seems strange to have this service spread over the affiliated centres	access to experts in reproductive medicine.
6. Another indication for centralization is the recruitment into studies and trials and the good collection of data. The comment is that there has been poor data collection, poor staging with delays and small volumes. Surely this document needs to drive the change since at the moment it reads rather reactive. We do not have sufficient personnel nor do we want to upset people so we will not change.	Pg 12 - The working group recognizes this and have recommended access to clinical trials at GOCs. The organizational guideline provides recommendations for optimal care. A plan will be developed to address the implementation of these recommendations.
7. There is little detail about the radiotherapy. I would suggest an aspiration to usage of image guided (probably MRI) brachytherapy which carries better outcomes and less morbidity.	The working group agrees with this and has recommended access to MRI for GOCs.
8. There is no reason why patients with grade 1 endometrial cancer should not get the benefit of multidisciplinary care.	Multidisciplinary/collaborative discussion has been recommended for all patients treated at affiliated centres.

Professional Consultation: Forty-two responses were received. Key results of the feedback survey are summarized in Table 3.

Table 3. Responses to four items on the professional consultation survey.

General Questions: Overall Guideline Assessment	Number (%)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	1 (2%)	8 (19%)	22 (52%)	11 (26%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	1 (2%)	12 (29%)	14 (33%)	15 (36%)
3. I would recommend this guideline for use in practice.	0	4 (10%)	5 (12%)	13 (31%)	20 (48%)

4. What are the barriers or enablers to the implementation of this guideline report?
The reviewers were concerned if there would be adequate funding and resources available so that patients would have appropriate access to care and patients would be seen in a reasonable amount of time. The reviewers were concerned with the lack of evidence to support the recommendations. They also hoped that the recommendations would be disseminated and accepted by the target audience and that appropriate education of physicians would occur.

Table 4. Summary of Written Comments by professional consultants and Modifications/Actions Taken.

<i>Summary of Written Comments</i>	<i>Modifications/Actions/Comments</i>
1. I believe that in the future, the expert panel should include not only a regional vice president but also a representative from a hospital designated as a regional centre. These hospitals must implement the guideline but there is little information on how to operationalize such a guideline.	The panel included representation across the regions, disciplines, and academic as well as community hospitals.
2. The document reads as overly gynecologic oncology focused, and not reflective of the multidisciplinary nature of care nor of the research questions. Either the questions should be narrowed or scope of report broadened.	Pg 4 - The working group believes the first question was specific for gynecologic oncologists but the other questions were more general and addressed radiation oncology, systemic treatment requirement as well as other human and physical resource issues and, therefore, need not be changed.
3. For page 4, under patient population, I would suggest defining in further detail the complete/partial molar pregnancy category, since this conflicts with recommendations on page 6 regarding low risk GTN & chemotherapy. It might also help to clarify what is meant by low/moderate/high risk GTN for clarity in the document.	Pg 4 - Under Patient Population, complete and partial molar pregnancy” was removed and replaced with “Low-risk GTN that resolves spontaneously”. Pg 6 - Gynecologic oncologists: removed last two bullets and created a separate recommendation: “Patients who have Intermediate- to high- gestational trophoblastic neoplasia (GTN), and low-risk GTN in need of chemotherapy need to be assessed and treated by gynecologic oncologists”
4. For page 6, only ovarian cancers are included. I am wondering about where borderline epithelial tumour fit in.	Pg 6 - The working group believed no change was needed because borderline epithelial tumours are included in the range of epithelial cell cancer.
5. I have some concerns about recommendations for brachytherapy resource allocations. It is an expensive and resource-intensive service that requires a highly skilled team from therapy, nursing, physics and radiation oncology.	Pg 11 - The specific supporting personnel involved in offering radiation therapy are necessary, but the working group decided not to make an exhaustive list.
6. One of the difficulties of this report is an attempt to use evidence, when in fact there is none. Where did the number 10 for the number of minimum cervix cases to be treated come from? That would mean less than 1 patient a month. This report suggests that from a radiation oncology or systemic therapy perspective any radiation oncologist can treat gynecologic cancers but that is not the case for surgery.	Pg 14 - The brachytherapy volume was derived from another CCO guideline (4).
7. There is an overwhelming emphasis on gynaecologic oncologists being "onsite" in order to designate centres as level 1. This is not feasible for many centres, and there is no evidence that care is better. Care is improved if surgery is performed by a gynaecologic oncologist, so centres that want to be	Pg 15 - The purpose of designating centres is to ensure the best quality of care, and this requires onsite multidisciplinary team care.

<p>designated level 1 must have an affiliated gynaecologic oncologist reviewing all of the cases and performing the necessary surgeries, but there is no evidence having a gynecologic oncologist onsite is necessary or even advantageous.</p>	
<p>8. Final grade and stage is surgically determined therefore an approach that bases all of our decisions on RMI or endometrial biopsy results is fraught with a 15-30% risk of leading to the "wrong" pathway, where a basic gynaecologist who never now sees more advanced cancer is not equipped to deal with the findings and vice versa, the gynecologic oncologists are no longer treating grade 1 or negative RMI's while those patients are waiting longer for appropriate referral and treatment.</p>	<p>Pg 15- The issue of endometrial biopsy was discussed by the working group, and this concern is addressed in the recommendation for pathology services that will verify the stage and grade of cancer.</p>
<p>9. It may be more complex and more resource intensive for an institution to look after grade 1 endometrial cancer which occurs often in morbidly obese patients, as compared to the more advanced grades in otherwise healthy patients. It would oversimplify to suggest that gynecologic oncologists are skilled at grade 2/3 endometrial cancer yet grade 1 can/should be taken up by general obstetricians/gynecologists.</p>	<p>There are specific surgical cases that should be treated at a GOC only. The recommendations restrict treatment of advanced endometrial cancers at GOCs but grade 1 endometrial cancer can be treated by gynecologic oncologists or gynecologists at a GOC.</p>
<p>10. Gynecologic oncology cases may present alongside other malignancies or with other medical issues where a patient is best treated in a hospital not presently designated as a gynecologic oncology site. Local expertise is essential for ensuring patient-focused care at least in large community or academic centres.</p>	<p>The working group agree with this and have recommended a partnership network between GOCs and affiliated centres for easy patient referral and communication.</p>
<p>11. Figure 1: In the block diagram for "Gynecology Oncology Centre", it may be useful to indicate that the brachytherapy services must be available at all the primary gynecology oncology centres.</p>	<p>Pg 18 - The working group believes the diagram should be kept as it is. The guideline does not provide specific procedure types for surgery, or systemic therapy in the diagram, therefore detail is not required for radiation oncology.</p>

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Gynecologic Oncology Organizational Guideline Expert Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Gynecologic Oncology Organizational Guideline Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Seven authors declared they had no conflicts. Three authors did declare conflicts. Dr. L. Elit reported being paid a salary as a gynecologic oncologist by the Ministry of Health. Dr. T. Colgan reported receiving employment income and having managerial responsibility as a Section Head for Cytopathology and Gynaecological Pathology at Mount Sinai Hospital in Toronto, Ontario. Dr. Colgan's professional income might change by more than \$10,000 per year, depending on the outcome of this guideline. Dr. Colgan also reported receiving more

than \$5000 in a single year as a consultant pathologist with LifeLabs. Dr. Colgan is a member of the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Dr. J. Irish reported receiving more than \$5000 in a single year as the Provincial Head of the Surgical Oncology Program at CCO and reported owning the JC Irish Medicine Professional Corporation.

For the Expert Panel, ten members declared they had no conflicts of interest, and three declared conflicts. Dr. A. Covens reported being a principal investigator for clinical trials involving the objects of study as well as having multiple publications. Dr. P. DePetrillo reported receiving employment income from Credit Valley Hospital and receiving more than \$5000 in a single year from consulting fees as well as owning a relevant business. Dr. A. Lytwyn reported receiving research support from Merck Frost for the investigation of HPV types in vulvar cancer.

For the External Reviewers, two members declared they had no conflicts of interest and one member declared conflicts. Dr. R. Crawford reported having a relevant business entity, a private medical business called Craw4d Ltd. Dr. Crawford also reported receiving grants from the Target Ovarian Cancer Charity and provided advice or guidance for while serving on the quality standards board relating to the CG 122 NICE guideline on ovarian cancer.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.

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