Diagnostic Imaging in the Assessment of Metastatic and Recurrent Ovarian Cancer

A Cancer Care Ontario Recommendations Report

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I. PURPOSE

This recommendations report was developed to provide some initial guidance to Ontario health care providers and planners on the use of cross-sectional diagnostic imaging technology for patients with metastatic or recurrent ovarian cancer. While diagnostic imaging has an important role in helping clinicians differentiate between benign and malignant disease, and diagnostic imaging using ultrasound (US) remains the modality of choice for this initial staging, the definitive staging of ovarian cancer occurs surgically. The main question with respect to the use of diagnostic imaging in ovarian cancer is delineating between benign and malignant disease, and this question will be addressed in a future report by the Gynecology Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. In this report, recommendations are made covering the use of diagnostic imaging in ovarian cancer for additional staging (e.g. to assist prioritizing surgery, extent of planned surgery, etc.), recurrence, and peritoneal metastases only. Topics of interest included the use of imaging equipment to stage disease, assess tumour response to treatment, and detect recurrence following treatment and during follow-up. The recommendations report can serve as a foundation piece and tool from which further discourse around a larger provincial quality agenda and implementation for diagnostic imaging services for cancer can evolve.

II. INTRODUCTION

For ovarian cancer, definitive staging is performed surgically. Diagnostic imaging has an important role to play in additional staging, detecting recurrence, and in detecting metastases. Imaging is also used to assess the response of cancer to therapy. Follow-up imaging in this patient population is a contentious issue as there is little evidence available and there is a lack of consensus among clinicians, therefore, and any decision regarding follow-up imaging must be done on a case by case basis.

There are concerns with the current state of diagnostic imaging delivery for cancer. There is a perception among Canadians that waiting times for many medical services are excessive and may be causing harm to patients. Such concerns of excessive waits apply to diagnostic imaging, particularly cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). Of importance, radiologists have identified cross-sectional imaging for cancer as the major determinant of CT and MRI use in the province. As well, some have suggested that many imaging studies ordered during active

treatment among patients with cancer are done so for uncertain reasons, and that results will often have no impact on clinical care. Moreover, significant expansion in the number of CT and MRI machines has not meaningfully influenced wait-times for these investigations. For these reasons, Cancer Care Ontario (CCO) established a Diagnostic Imaging Project to develop guidance documents for Ontario health care providers and planners on the use of cross-sectional imaging technologies in cancer.

The recommendations in this document will deal with diagnostic imaging for patients with ovarian cancer and are intended to promote evidence-based practice, provide guidance to clinicians about which imaging techniques are most appropriate to use in the workup and management of their patients, provide information that is useful to those charged with planning for the number of imaging machines needed for patients with cancer in Ontario, and to be used to monitor the use of imaging modalities in patients with cancer.

III. METHODS

In 2003, CCO established a small working panel, the Diagnostic Imaging Panel, consisting of medical, radiation and surgical oncologists, diagnostic radiologists and methodologists, to review guidelines published during the last five years on the use of cross-sectional imaging in oncology. After examining documents from nineteen guideline developers, the panel concluded that the available guidelines did not focus on the particular issues of interest here. Therefore, the panel decided to review the primary research and develop recommendations for Ontario on the use of CT, MRI and ultrasound (US) for any additional staging, assessment of tumour response during active treatment, and follow-up for patients with six types of cancer: lymphoma, breast cancer, colorectal cancer, prostate cancer, lung cancer and ovarian cancer. [1]

A systematic review of the literature identified few randomized studies to provide guidance on the use of cross-sectional imaging in the management of patients with cancer; therefore, it was decided to also include cohort studies and case series reports in the evidence review and incorporate expert opinion in the development of the recommendations. The initial selection and summary of relevant evidence was completed by methodologists at the Program in Evidence-Based Care in consultation with the clinical experts from the Diagnostic Imaging Panel (see Section IV).

[1] The use of positron emission tomography (PET) is being considered in different projects in Ontario, including guidelines under development and clinical trials. Until this work is completed, readers are referred to the systematic review completed by the Institute for Clinical Evaluative Sciences (ICES) (http://www.ices.on.ca/file/Pet_jan20041.pdf).

The reviews served as the evidentiary foundation to inform the deliberation of clinical experts. Formal and informal consultations with radiologists was facilitated by Dr. Anne Keller, diagnostic imaging representative of the CCO Clinical Council, and undertaken with members who participated in the provincial MRI and CT Wait Times Strategy Expert Panel and the CCO Diagnostic Imaging Panel. In addition, consultations with oncologists were undertaken, mainly through the relevant disease site groups of CCO's Program in Evidence-Based Care. Through these consultations emerged the recommendations, which are presented in the format developed by the Canadian Association of Radiologists (1) (see Section VI).

IV. EVIDENCE REVIEW

A. Evidence Review

Literature Search and Evidence Appraisal Strategies

English language evidence published between 1980 and 2004 was searched through MEDLINE, EMBASE, and the Cochrane Databases of Systematic Reviews and Abstracts of Reviews of Effects. Clinical practice guidelines, meta-analyses, systematic reviews, and trials reporting on sensitivity and specificity were sought. Search strategies were modified for each database and disease site (see Appendix A).

B. Eligibility Criteria

Inclusion

Studies were included if they satisfied all of the following criteria:

- included patients with confirmed ovarian cancer
- evaluated CT, MRI or ultrasonography,
- described an objective diagnostic standard,
- reported data for disease recurrence, quality of life, survival, frequency of true- and false-positive tests for extent of disease, or sensitivity, specificity, positive predictive value or negative predictive value to detect distant metastases [2],
- were randomized trials, comparative cohort studies, case series (prospective or retrospective) with more than 12 consecutive patients, meta-analyses (published in English after 1998) of data from randomized trials, comparative cohort studies or case series, or evidence-based clinical practice guidelines.

[2] Where necessary, true positive, false-positive, sensitivity, specificity, positive predictive value and negative predictive value rates were calculated from data provided in primary reports, using the Predictive Value Calculator available on the web at http://www.azzopardi.freeserve.co.uk/easycalc/Additions/predict.htm.

Exclusion

Letters, editorials, and meeting abstracts were not included.

Study Quality Assessment

The study quality of the included trials was assessed using the QUADAS instrument as described by Whiting et al (3), using the unweighted methods described in a later paper (4). The QUADAS instrument scores diagnostic test reports on a scale from 0-14 on criteria that assesses items such as patient spectrum, reference standard, disease progression bias, verification bias, review bias, etc. The QUADAS instrument is scored on the 14 criteria with either a positive (noted with a "+") indicating that the criteria was met, a negative (noted with a "-") indicating that the criteria was not met, or an unsure (noted with a "?"). A limitation of quality assessment using a tool such as QUADAS is that while the intention is to measure the quality of the test performed, it is the quality of the reporting of the test that is actually being measured. It is also difficult to quantify in a meaningful way what the true difference in quality is between studies with similar scores.

C. Literature Search Results and Appraisal

A total of ten papers met the inclusion criteria and were obtained for review (5-14). Of these obtained papers, five (5,7-10) described the results of a single diagnostic test against the gold standard of histopathology, and one compared a single diagnostic test against surgical findings (6). Three papers (11-13) described the results of two or more diagnostic tests against the gold standard of histopathology. The final paper was a consensus opinion paper from the International Ovarian Tumor Analysis (IOTA) group (14). For the studies that compared one diagnostic test against the standard, two tests used CT (5,6), three tests used US (7-9), and one test used MRI (10). For the tests that compared more than one diagnostic test against the standard, all three included both CT and MRI (11-13), one (11) also used CA125, a non-imaging test, and another used US (13). Two of the trials reported a non-industry source of funding (7,11), the remaining studies did not disclose funding sources. See Table 1 for data from all included studies.

QUADAS scores obtained ranged from lows of 10 (6,7) to several that scored highs of 14 (9-11), with a median value of 12. Generally, the quality of the reporting of obtained studies was high. A table detailing the results of the assessment using the QUADAS instrument appears in Appendix 1.

D. Outcomes

Single Imaging tests

For the six studies examining a single mode of diagnostic imaging against the standard, the two studies using CT tests reported sensitivity results ranging from 38% (6) to 80% (5), the three studies using US tests (7-9) reported sensitivity results ranging from 25% to 100%, and the single study using MRI (10) reported sensitivity results ranging from 64% to 87%. The US tests reported the greatest variation in sensitivity results, likely a result of the varying modalities of US tests performed. Only a study using CT (5) reported a positive predictive value of 100%. For this set of trials, comparisons of efficacy between the different imaging modalities is challenging as all were used for different diagnostic purposes.

Multiple imaging tests

For the three studies comparing two or more diagnostic imaging modalities against the standard (11-13), the studies using CT reported sensitivity results ranging from 40% (13) to 100% (12), the studies using MRI reported sensitivity results ranging from 38% (13) to 97% (12), and the studies using US reported sensitivity results ranging from 32% (staging lymph nodes) (13) to 69% (staging peritoneum) (13). Considering all the evidence, the studies using CT showed the greatest sensitivity followed by MRI (CT high of 100% (12) versus an MRI high 97% (12)), and then US, however, when within study comparisons are made, MRI generally showed greater sensitivity then CT (11,12,13). Only a single trial using CT reported a sensitivity score of 100% (12). As before, comparisons of efficacy between the different imaging modalities is challenging as all were used for different diagnostic purposes.

Use of diagnostic imaging in the staging of ovarian cancer

One trial (12) provided data on the use of diagnostic imaging in the additional staging of ovarian cancer. In this trial, MRI showed a higher sensitivity over CT in distinguishing between Stage III and Stage IV disease (91% versus 87%).

Use of diagnostic imaging in assessing disease recurrence

Two trials (5,11) provided data on the use of diagnostic imaging in detecting disease recurrence. The trial by La Fianza (5) used CT alone and obtained a sensitivity of 80%. The trial by Prayer et al (11) compared CT versus MRI and the MRI test showed a higher sensitivity (67% versus 78%).

Use of diagnostic imaging in detecting metastases

Two trials (5,6) provided data on the use of diagnostic imaging in detecting metastases. The trial by La Fianza et al (5) reported a sensitivity of 64% for CT alone, and the trial by Gryspeerdt et al (6) reported sensitivities of 38% for CT alone versus 77% for CT with an injected contrast material.

Table 1. Study results.

Study	Patients	N	Gold standard/ Duration of follow-up	Imaging test	Acc (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Case Series with a Single Imaging Test									
Detecting lymph node metastases									
La Fianza, 1992 (5)	confirmed ovarian cancer	58	Histo-pathology, 12-month follow-up	**CT**	-	64	100	100	82
Detecting lymph node recurrence metastases									
La Fianza, 1992 (5)	Clinical suspicion of recurrent ovarian cancer	41	Histo-pathology, 12-month follow-up	**CT**	-	80	100	100	84
Detecting peritoneal metastases									
Gry-speerdt, 1998 (6)	Suspected primary or recurrent ovarian cancer (4 benign)	25	Surgical findings	**CT**	-	38	83	-	-
				CT with intra-peritoneal perfusion of contrast material	-	77	66	-	-
Distinguish between benign and malignant tumours									
Valentin, 1999 (7)	Pelvic mass of adnexal origin: 149 benign (86%) 24 malignant	173	Histo-pathology	**US**					
				• Grey-scale	-	88	96	78	98
				• Grey-scale + Doppler	-	83	97	80	97
				• Lerner score	-	92	64	30	98
				• Time-averaged max velocity	-	100	49	28	100
				• Peak systolic velocity	-	79	64	31	94
				• Ultrasound morphology	-	96	37	20	98
				• Resistance index	-	25	94	46	86
				• Pulsatility index	-	88	32	21	93
Kurjak, 2000 (8)	Ovarian mass: 109 benign (91%) 11 malignant	120	Histo-pathology	**US**					
				• 2D TVCD	-	91	97	77	99
				• 3D power Doppler	-	100	99	92	100
Kurjak, 2000 (9)	Ovarian mass: 81 benign (90%) 9 malignant	90	Histo-pathology	**US**					
				• Transvaginal	-	67	84	55	96
				• Transvaginal colour Doppler	-	89	95	67	99
				• 2D US + Doppler score	-	89	98	80	99
				• 3D transvaginal	-	78	98	78	98
				• 3D power Doppler	-	89	98	80	99
				• 3D US + Doppler score	-	100	99	90	100

Determining peritoneal spread									
Ricke, 2003 (10)	Advanced or recurrent ovarian carcinoma	57	Histo-pathology	**MRI** to determine peritoneal spread: • Upper abdomen • Bowel • Lower pelvis • Abdominal wall • Lymph nodes • Diffuse peritoneal carcinomatosis	 - - - - - -	 71 80 81 87 64 78	 87 65 81 44 75 70	 89 84 83 63 86 70	 67 58 78 75 47 78
Case series with more than > 2 imaging tests									
Detecting recurrent ovarian cancer									
Prayer, 1993 (11)	Evaluated 6 months after primary therapy for ovarian cancer (stage IB-IV)	24	surgery, biopsy, autopsy	**CT** **MRI** vs. palpation + CA125	- -	67 78	93 93	86 88	83 88
Determining resectability									
Forstner, 1995 (12)	confirmed ovarian cancer	43 50	Histo-pathology	**CT** **MRI**	- -	100 97	50 91	93 97	100 91
Detecting stage III/IV disease									
Forstner, 1995 (12)	Confirmed ovarian cancer	43 50	Histo-pathology	**CT** **MRI**	- -	87 91	83 73	93 89	71 79
Staging peritoneum, lymph nodes, hepatic parenchyma									
Tempany, 2000 (13)	Advanced ovarian cancer	118	Histo-pathology	Staging peritoneum: **US** **CT** **MRI** Staging lymph nodes: **US** **CT** **MRI** Staging hepatic parenchyma: **US** **CT** **MRI**	 86 96 96 68 57 76 85 77 94	 69 92 95 32 43 38 57 40 40	 93 82 80 93 89 84 98 96 96	 - - - - - - - - -	 - - - - - - - - -

Note: CT, chemotherapy; US, ultrasound; 2D, two dimensional; TVCD, transvaginal colour Doppler; 3D, three-dimensional; MRI, magnetic resonance imaging; CA125, cancer antigen-125.

Consensus Opinion paper by the International Ovarian Tumour Analysis (IOTA) Group

In 2000, Timmerman et al (14) published consensus-based recommendations from the International Ovarian Tumour Analysis (IOTA) group on the terms, definitions and measurements used to describe the sonographic features of adnexal tumours. The authors of this report recommend that this paper be referred to in an effort to standardize the terminology used in this disease site.

PEBC Evidence-Based Series

On April 29, 2004, the PEBC made available for this report a draft version of an ongoing Evidence-based Series (#4-15) on the management of suspicious ovarian masses (15). In the recommendations section of that report, some guidance is given with respect to the role diagnostic imaging can play in the management of this disease, and the entire summary of the report is reproduced below in Figure 1.

Figure 1. Summary from PEBC Gynecology Disease Site Group Draft (#4-15).

Questions

1. What is the most appropriate preoperative management for a woman who presents with a suspicious ovarian mass? Outcomes of interest include sensitivity and specificity of interventions.
2. What is the most appropriate intraoperative management for a woman who presents with a suspicious ovarian mass? Outcomes of interest include recurrence, survival and complication rates.

Target Population

This evidence summary applies to women of all ages presenting with a suspicious ovarian mass, either symptomatic or asymptomatic. This evidence summary does not apply to women presenting with obvious advanced ovarian cancer—these women should be referred to gynecologic oncologists for treatment.

Draft Opinions of the Gynecology Cancer Disease Site Group

The lack of sufficient high quality evidence precludes definitive recommendations from being made. Instead, the Gynecology Cancer Disease Site Group (DSG) offers the following opinions based on the evidence reviewed:

- The DSG acknowledges that despite definitions and criteria, it is unrealistic to expect that 100% of ovarian cancers will be identified as suspicious preoperatively.
- The exact criteria that defines an ovarian mass as suspicious is left to the individual physician and ultrasonographer. Criteria may include any of the following: ovarian masses that have mural nodules, solid elements, complex cysts, size >5cm, multiple thick septae, low resistance flow, ascites, and elevated CA 125 (post menopausal women). Discussion with a gynecologic oncologist is encouraged.
- All patients with suspicious ovarian masses should be discussed with a gynecologic oncologist before surgery, if not referred to a gynecologic oncologist.
- Caution should be used in interpreting CA 125 values, as they are of limited use in premenopausal women, and elevated in only 50% of early stage ovarian cancers.
- Computed tomography scan may be of use in looking for extra-ovarian or extra-pelvic abnormalities, such as omental caking, peritoneal implants, adenopathy, etc.
- Laparoscopy is not a contraindicated procedure providing appropriate surgery/staging can/will be done (either via laparoscopy or laparotomy). In certain scenarios, it may be an acceptable method of confirming the diagnosis, however, discussion with a gynecologic oncologist is recommended.
- There are certain scenarios where preservation of fertility is appropriate, and removal of both ovaries and the uterus is unnecessary. These include germ cell tumours and well differentiated surgically stage I ovarian cancers. Discussion with a gynecologic oncologist is encouraged.

V. EXPERT CONSULTATION

The draft report, with recommendations developed by a small panel of experts in oncology and radiology, was distributed with a 4-item survey in March 2006 for review as part of an external consultation process to a broader group of Ontario radiologists and oncologists. The external consultation included the 15 members of the provincial Gynecology Cancer Disease Site Group and 23 other Ontario health care providers. Among the eight respondents (21%), which included two Gynecology Cancer Disease Site Group members, two radiologists,

two obstetricians, and two other clinicians, seven completed the report survey, and two of these respondents provided written comments. An additional respondent provided written feedback only. Results appear below in Table 2.

Table 2. External review results (N=8)

Survey question	Percentage reporting agree/strongly agree
The methods used in the report development are appropriate	87.5%
Agree with the draft recommendations as stated	87.5%
Recommendations should be approved as guidelines for practice	75%
Would follow the recommendations of the report	87.5%

Summary of Written Comments

Radiology Perspective

One respondent queried why ultrasound was not recommended, although this same respondent agreed that to recommend ultrasound based on the evidence reviewed in this report would be inappropriate.

Obstetrics/Gynecology Perspective

One respondent advocated that suspicious masses should be referred to a general gynecologist or a gynecological oncologist to ensure proper diagnostic imaging is arranged.

Gynecological Cancer DSG Member Perspective

None of the Gynecological Cancer DSG members that responded provided any written feedback.

Other Clinicians

One clinician commented that it was not clear from the document what the definitive staging modality is for ovarian cancer, but it is stated explicitly in the Purpose section that the gold standard remains surgery.

This same clinician challenged the importance of the quality assessment using the QUADAS tool, as no analysis using its data was performed.

Report Approval Panel Feedback

The feedback from the Report Approval Panel (RAP) was an acknowledgement that that included recommendations are principally based on consensus and that the methods involved in the consensus process is unclear. Also, the role of any diagnostic testing in follow-up is not

provided. Adding some information on follow-up would help to make the document more helpful in assisting non-experts, promoting uniformity among experts, and for assisting those responsible for determination of resource needs.

The authors added information concerning follow-up into the document to address this concern.

VI. RECOMMENDATIONS

These recommendations were developed by radiology and oncology experts in Ontario and are informed by research evidence and clinical expertise.

Recommendations

Clinical/ Diagnostic Problem	Investigation	Recommendation (Grade)	Comment	Band[A]
Local Staging	CT	Indicated (primary)	Best modality to stage abdomen and pelvis concurrently	III
	MRI	Indicated (supplementary)	Use when: 1. CT contra-indicated. 2. Adnexal lesion detected by US or CT needs additional characterization. 3. Extent of local invasiveness needs better delineation.	0
	US	Not indicated	While many adnexal lesions are initially detected by US, staging is limited by limited field of view and bowel gas	0
Recurrence	CT	Indicated (primary)	See peritoneal metastases (recurrence usually in peritoneal cavity and retroperitoneum)	IV
	MRI	Indicated (supplementary)	See peritoneal metastases	0
	US	Not indicated	See peritoneal metastases	0
Peritoneal Metastases	CT	Indicated (primary)	See suggested protocol	IV
	MRI	Indicated (supplementary)	Use when: 1. CT contra-indicated (e.g. contrast allergy) 2. highest sensitivity needed (CA 125 positive but CT negative)	0
	US	Not indicated	Sensitivity limited by bowel gas Limited reproducibility	0
Follow-up	Decisions regarding follow-up imaging must be done on a patient by patient basis			

Note: CT, chemotherapy; MRI, magnetic resonance imaging; US, ultrasound.
[A] For Band Classification see Table 3 below.

Table 3. Band classification of the typical effective doses of ionizing radiation from common imaging procedures.

Band	Typical effective dose (mSv)	Examples
0	0	US, MRI
I	less than 1	CXR, XR limb, XR pelvis
II	1-5	IVU, XR lumbar spine, NM (e.g. skeletal scintigram), CT head and neck
III	5-10	CT chest or abdomen, NM (e.g. cardiac)
IV	more than 10	Extensive CT studies, some NM studies (e.g. some PET)

Note: Taken from p.12 of the Canadian Association of Radiologists. Diagnostic Imaging referral guidelines. 2005. Available by order from the Canadian Association or Radiologists at: http://www.car.ca/ethics/guidelines/index.html.

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Appendix 1. QUADAS Scores.

Study details	QUADAS results														
	Spectrum composition	Selection criteria	Reference standard	Disease progression bias	Partial verification bias	Differential verification bias	Incorporation bias	Test execution details	Reference execution details	Test review bias	Diagnostic review bias	Clinical review bias	Uninterpretable results	Withdrawals	TOTAL SCORE
La Fianza A et al, 1992 (5)	+	+	+	+	+	+	+	+	+	?	?	+	+	?	11
Gryspeerdt S et al, 1998 (6)	+	+	-	+	+	+	+	+	+	-	-	-	+	+	10
Valentin L et al, 1999 (7)	+	+	+	+	+	+	?	+	+	?	?	?	+	+	10
Kurjak A et al, 2000 (8)	+	?	+	+	+	+	+	+	+	+	+	+	+	?	12
Kurjak A et al, 2000 (9)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14
Ricke J et al, 2003 (10)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14
Prayer L et al, 1993 (11)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14
Forstner R et al, 1995 (12)	+	+	+	+	+	+	+	+	+	+	?	?	+	+	12
Tempany CMC et al, 2000 (13)	+	+	+	+	+	+	+	+	+	+	+	?	+	+	13

Note: +, Yes; ?, Unsure.

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