Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 21-3-7- EDUCATION AND INFORMATION 2013

The Role of IMRT in Gynecologic Cancers

D.P. D'Souza, R.B. Rumble, A. Fyles, B. Yaremko, P. Warde,
and members of the IMRT Indications Expert Panel

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

Report Date: October 29, 2010

An assessment conducted in November 2013 put Evidence-based Series (EBS) 21-3-7 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

EBS 21-3-7 is comprised of 3 sections
and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Cancer Screening page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/clin-program/radther/

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

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

Journal Citation (Vancouver Style): D'Souza DP, Rumble RB, Fyles A, Yaremko B, Warde P; Members of the IMRT Indications Expert Panel. Intensity-modulated radiotherapy in the treatment of gynaecological cancers. Clin Oncol. 2012;24:499-507. doi:10.1016/j.clon.2012.05.005.

Guideline Citation (Vancouver Style): D'Souza DP, Rumble RB, Fyles A, Yaremko B, Warde P; Members of the IMRT Indications Expert Panel. The role of IMRT in gynecologic cancer. Toronto (ON): Cancer Care Ontario; 2010 Oct 29 [Education and Information Nov 2013. Program in Evidence-based Care Evidence-based Series No.: 21-3-7 Education and Information 2013.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 21-3-7: Section 1

The Role of IMRT in Gynecologic Cancer: Guideline Recommendations

D.P. D'Souza, R.B. Rumble, A. Fyles, B. Yaremko, P. Warde, and members of the IMRT Indications Expert Panel

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

Report Date: October 29, 2010

QUESTIONS

1. When external-beam radiotherapy (EBRT) is given as adjuvant postoperative treatment with or without chemotherapy, is there a benefit associated with intensity-modulated radiation therapy (IMRT) compared with three-dimensional conformal radiation therapy (3DCRT)?
2. When EBRT is selected as the primary modality with or without chemotherapy, is there a benefit associated with IMRT compared with 3DCRT?
3. When an additional dose is required to boost residual disease, what is the role of IMRT compared with 3DCRT or brachytherapy?

Outcomes of interest included locoregional recurrence rates, disease-free recurrence rates, overall survival, acute adverse effects, and late adverse effects.

TARGET POPULATION

The target population is comprised of all adult patients with gynecologic cancers for whom treatment with radiation is being considered.

INTENDED USERS

This guideline is targeted for radiation oncologists, physicists, dosimetrists, patients, and others involved in the treatment of gynecologic cancers where treatment with IMRT is being considered. Administrators may find the report of value when considering the benefits of IMRT over 3DCRT or brachytherapy for gynecologic cancers.

BACKGROUND

IMRT is a newer method of delivering radiation to target structures that differs from traditional methods of radiation delivery. The basis of IMRT is the use of intensity-modulated

beams that can provide two or more intensity levels for any single beam direction and any single source position (1). Through this mechanism, IMRT treatment plans are able to generate concave dose distributions and dose gradients with narrower margins than those allowed using traditional methods (1,2). This fact makes IMRT especially suitable for treating complex treatment volumes and avoiding close proximity organs at risk (OAR) that may be dose limiting (1). As a consequence, IMRT theoretically may provide benefits in terms of increased tumour control through escalated dose and reduced normal tissue complications through OAR sparing. It must be noted that as total radiation dose delivered via IMRT would be the same as the total radiation dose given via any other method of radiation therapy, no difference in disease-related outcomes would be expected. The main benefit expected with IMRT is a reduction in adverse event rates, especially those associated with radiation damage to nearby OAR.

Given the potential dosimetric advantages of IMRT and the commercial availability of IMRT-enabled treatment planning systems and linear accelerators, IMRT has been introduced clinically for a number of disease sites, including head and neck cancer and prostate cancer. This evidence-based series reviews the published experience with IMRT in the treatment of gynecologic cancers to quantify the potential benefits of this new technology and make recommendations for radiation treatment programs considering adopting this technique.

RECOMMENDATIONS AND KEY EVIDENCE

If acute and chronic toxicities are the main outcomes of interest, IMRT should be considered over 3DCRT for women undergoing radiotherapy for gynecological cancer.
Evidence All four cohort studies (3-6) showed improvements in either acute or chronic toxicities. However three (4-6) out of the four studies showed only small improvements. Either the toxicities reported were low (grade 2 or less) or the magnitude of difference between groups was quite small. The largest study (5) showed significant improvements in grade 3 toxicity rates for serious complications such as rectovaginal and vesiculovaginal fistula.
If disease-related outcomes are the main outcomes of interest, there is insufficient evidence to recommend IMRT over 3DCRT for women undergoing radiotherapy for gynecologic cancers.
Evidence All four cohort studies (3-6) gave a similar dose of radiation between comparison groups; therefore, an improvement in disease-related outcomes would not be expected. Two of the included studies (4,5) reported on disease-related outcomes, with one (5) of them detecting a statistically significant difference in favour of treatment with IMRT.

Qualifying Statement:

This Evidence-based Series (EBS) reports largely on the reduction of acute and chronic radiation toxicity achieved through the use of IMRT, with all of the studies being single-institution reports with short follow-up times. Three of the four studies (3,4,6) were relatively small, and various modalities of treatments were administered; adjuvant or neoadjuvant RT in the study by Mundt et al (6), neoadjuvant CRT in the study by Beriwal et al (3), adjuvant CRT in the study reported by Chen et al (4), and RT alone in the study reported by Kidd et al (5). Additional prospective studies are needed to demonstrate the portability and use of IMRT in a multi-institutional setting and provide important data on toxicity and disease recurrence rates. None of the included studies (3-6) suggested that either of these outcomes were compromised as a result of IMRT; therefore, IMRT could be considered a viable treatment option as determined by the Precautionary Principle (7), which states that it is ethical to recommend a treatment with little known harm over one with greater expected

harm prior to scientific proof of the difference in harm being established. There are many issues to consider in the planning and delivery of gynecologic IMRT, and long-term outcome data is lacking. Clinicians should be aware of these uncertainties and be judicious in the use of gynecologic IMRT with the primary goal of reducing toxicity. Participation in clinical research should be encouraged and will hopefully offer more evidence that supports the use of gynecologic IMRT. At this time, there is limited data to support the use of IMRT in the treatment of gynecologic cancers in order to reduce the toxicity of treatment.

FUTURE RESEARCH

Future research should focus on implementing gynecologic IMRT in a multi-institutional setting and report relevant outcomes. If it can be shown to safely reduce toxicity without compromising disease-related outcomes, there is the potential to look at dose escalation to deliver higher doses to areas of disease.

RELATED GUIDELINES

- Whitton A, Warde P, Sharpe M, Oliver TK, Bak K, Leszczynski K, et al. Organisational standards for the delivery of intensity-modulated radiation therapy in Ontario. Clin Oncol. 2009;21(3):192-203.

Funding

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

Contact Information

For further information about this series, please contact:

Dr. David P. D'Souza, Assistant Professor
Department of Oncology, University of Western Ontario
Phone:519-685-8650 Fax:519-685-8627 Email: david.dsouza@lhsc.on.ca
or
Dr. Padraig Warde, Provincial Head
Radiation Treatment Program, Cancer Care Ontario
Phone: 416-971-9800 ext. 3734 Fax: 416-971-6888 Email: padraig.warde@rmp.uhn.on.ca

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

REFERENCES

1. Veldeman L, Madani I, Hulstaert F, De Meerleer G, Mareel M, De Neve W, et al. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. Lancet Oncol. 2008;9(4):367-75.
2. Galvin JM, Ezzell G, Eisbrauch A, Yu C, Butler B, Xiao Y, et al. Implementing IMRT in clinical practice: a joint document of the American Society for Therapeutic Radiology and Oncology and the American Association of Physicists in Medicine. Int J Radiat Oncol Biol Phys. 2004;58(5):1616-34.
3. Beriwal S, Heron DE, Kim H, King G, Shogan J, Bahri S, et al. Intensity-modulated radiotherapy for the treatment of vulvar carcinoma: a comparative dosimetric study with early clinical outcome. Int J Radiat Oncol Biol Phys. 2006;64(5):1395-400.
4. Chen MF, Tseng CJ, Tseng CC, Kuo YC, Yu CY, Chen WC, et al. Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. Int J Radiat Oncol Biol Phys. 2007;67(5):1438-44.
5. Kidd EA, Siegel BA, Dehdashti F, Rader JS, Mutic S, Mutch DG, et al. Clinical Outcomes of Definitive Intensity-Modulated Radiation Therapy with Fluorodeoxyglucose-Positron Emission Tomography Simulation in Patients with Locally Advanced Cervical Cancer. Int J Radiat Oncol Biol Phys. 2009;In Press, Corrected Proof.
6. Mundt AJ, Lujan AE, Rotmensch J, Waggoner SE, Yamada SD, Fleming G, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2002;52(5):1330-7.
7. Andorno R. The Precautionary Principle: A new legal standard for a technological age. J Int Biotechnol Law. 2004;1(1):8.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 21-3-7: Section 2

The Role of IMRT in Gynecologic Cancer: Evidentiary Base

D.P. D'Souza, R.B. Rumble, A. Fyles, B. Yaremko, P. Warde, and members of the IMRT Indications Expert Panel

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

Report Date: October 29, 2010

QUESTIONS

1. When external-beam radiotherapy (EBRT) is given as adjuvant postoperative treatment with or without chemotherapy, is there a benefit associated with intensity-modulated radiation therapy (IMRT) compared with three-dimensional conformal radiation therapy (3DCRT)?
2. When EBRT is selected as the primary modality with or without chemotherapy, is there a benefit associated with IMRT compared with 3DCRT?
3. When an additional dose is required to boost residual disease, what is the role of IMRT compared with 3DCRT or brachytherapy?

Outcomes of interest included locoregional recurrence rates, disease-free recurrence rates, overall survival, acute adverse effects, and late adverse effects.

BACKGROUND

IMRT is a newer method of delivering radiation to target structures that differs from traditional methods of radiation delivery. The basis of IMRT is the use of intensity-modulated beams that can provide two or more intensity levels for any single beam direction and any single source position (1). Through this mechanism, IMRT treatment plans are able to generate concave dose distributions and dose gradients with narrower margins than those allowed using traditional methods (1,2). This fact makes IMRT especially suitable for treating complex treatment volumes and avoiding close proximity organs at risk (OAR) that may be dose limiting (1). As a consequence, IMRT theoretically may provide benefits in terms of increased tumour control through escalated dose and reduced normal tissue complications through oar sparing. It must be noted that as total radiation dose delivered via IMRT would be the same as the total radiation dose given via any other method of radiation therapy, no difference in disease-related outcomes would be expected. The main benefit expected with

IMRT is a reduction in adverse event rates, especially those associated with radiation damage to nearby OAR.

Given the potential dosimetric advantages of IMRT and the commercial availability of IMRT-enabled treatment planning systems and linear accelerators, IMRT has been introduced clinically for a number of disease sites, including head and neck cancer and prostate cancer. This evidence-based series reviews the published experience with IMRT in the treatment of gynecologic cancers to quantify the potential benefits of this new technology and make recommendations for radiation treatment programs considering adopting this technique.

INTRODUCTION

Radiotherapy is a standard treatment used as part of the multimodality treatment of gynecological cancers. It is frequently employed in the role of primary and adjuvant therapy for cancers of the endometrium, cervix, vulva, and vagina (3-7). There are two modalities of radiotherapy commonly used, EBRT, and brachytherapy.

Historically, RT planning was guided by fluoroscopic or x-ray imaging that provided two-dimensional data to determine areas to be treated by using bony landmarks. Limited soft tissue delineation was sometimes possible, for example, by instilling contrast into the bowel and bladder.

With the introduction of advanced planning software and more powerful computers, the process of planning and delivering radiation changed. Information obtained from magnetic resonance imaging (MRI) and computed tomography (CT) scanning could be incorporated into the planning. This includes three-dimensional (3D) identification of visible tumour and OAR that needed to be included or avoided. Therefore, a better quantitative assessment of what tissues and/or structures were being radiated was obtained. However, despite these advancements in planning, therapy remained similar, with standard radiation delivery providing a homogeneous photon flux across treatment fields.

The advent of IMRT permitted treatments with varying intensity across fields, allowing for dosimetry that can be optimally tailored to fit a patient's anatomy and resulting in improved avoidance of critical structures, while maintaining adequate tumour volume coverage. IMRT also allows for differential dose wedging along the axis of a beam, and a particular advantage is its ability to sculpt concavities within the high-dose volume. This dosimetric advantage of IMRT over traditional radiation techniques has resulted in clinical improvements in toxicity in several disease sites, including cancers of the head and neck (8) and of the prostate (9).

Not unexpectedly, IMRT demands a level of complexity and infrastructure not previously required in radiation oncology. More time is demanded of the oncologist to provide contours of target volumes and multiple OAR for toxicity. The need for computing power and time are greater as a result of an increased number of treatment beams, each consisting of multiple segments. Planners balance the dose constraints of various OAR of normal tissue toxicity with the minimal dose requirements for volumes at risk for disease. Multiple iterations are often required before an optimal plan is achieved. Radiation delivery is also more complex, requiring specialized software to automate the process, in an attempt to reduce treatment time and the risk of delivery error. In addition, as the precision of radiation delivery increases, so does the need for accurate daily patient positioning (10). This increased complexity has significant resource implications for radiation departments, demands that have been identified in a previous Cancer Care Ontario (CCO) document (11).

The overall benefit of IMRT in delivering RT to gynecologic sites must be balanced against this increased demand on resources. Given the ongoing CCO commitment to improving cancer care for the citizens of Ontario, the conclusion was that a clearer understanding of these benefits could be obtained through a summary of the available

literature. The findings are presented in the following report, a quality initiative of the CCO Program in Evidence-based Care (PEBC) and Radiation Treatment Program (RTP).

METHODS

The evidence-based series (EBS) guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (12). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one member of the IMRT Indications Expert Panel and one methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on the role of IMRT in gynecologic cancers. The body of evidence in this review is primarily comprised of published reports of comparative studies between IMRT and 3DCRT or brachytherapy. That evidence forms the basis of the recommendations developed by the IMRT Indications Expert Panel and will be published when completed. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC and RTP are supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC and any associated Programs is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE and Embase databases were searched for evidence on gynecologic cancers and IMRT on November 11, 2009. In both databases, keywords for "Ovarian neoplasms/cancers", "Uterine cervical neoplasms/cancers", "Genital neoplasms/cancer female", "gynecological neoplasms/cancers", and "vulvar neoplasms/cancer" were combined with keywords for "intensity-modulated radiotherapy," and the following terms were excluded: "proton therapy", "biological markers", "gene therapy", "children", "childhood cancer", "paediatric cancer", "quality assurance", "treatment plan comparison", "aperture optimization", independent dose calculation", "EPID dosimetry", and "set up errors". Results were limited to those published in English from the year 2000 to the current date in 2009.

A search for clinical practice guidelines (CPG), systematic reviews (SR), and health technology assessments (HTA) was also performed. A search of the National Guidelines Clearinghouse (located at: http://www.guideline.gov) was performed on March 9, 2009. Additionally, a search of the MEDLINE and Embase databases was performed on March 25, 2009 using keywords for IMRT in combination with terms for all disease sites and limited to review articles published after 2000. Finally, the Scottish Collegiate Guidelines Network (SIGN) (located at: http://www.sign.ac.uk), the National Institute for Health & Clinical Evidence (NICE) (located at: http://www.nice.org.uk), and the Agency for Healthcare Research & Quality (AHRQ) (located at: http://www.ahrq.gov) were searched on March 25, 2009 using keywords for "IMRT", and "radiation" in combination with disease-site specific terms. Abstracts from the 2000 through 2009 conference proceedings from the American Society for Radiation Oncology (ASTRO) were also searched for relevant evidence.

Study Selection Criteria

Inclusion Criteria

All of the following publication types must include comparative data on IMRT versus 3DCRT or brachytherapy in the treatment of gynecologic cancers, and report on at least one of the following outcomes of interest: locoregional recurrence rates, disease-free recurrence rates, overall survival, acute adverse effects, or late adverse effects.

- Clinical practice guidelines, systematic reviews, health technology assessments
- Randomized phase II or phase III trials

- Dose escalation studies, toxicity reports, quality of life (QoL) reports, case-series, and retrospective studies

In addition, the studies must be:

- Published in English
- Published in the year 2000 to current date

Exclusion Criteria

- Published in a language other than English
- Does not provide comparative data
- Reports on fewer than 50 patients
- Published prior to 2000

Synthesizing the Evidence

No statistical analyses were planned in this systematic review; however, analysis would be considered if data allow.

RESULTS

Literature Search Results

The MEDLINE and Embase searches returned 74 and 29 potential articles, respectively. After removing ineligible articles based on a title and abstract review, four (13-16) were ordered for full-text review. All were retained, and these four articles comprise the body of evidence in this systematic review.

Study Design

Three of the articles obtained were retrospective cohort studies (13-15) and one was a prospective cohort study (16). Table 1 details the years on study, the specific disease site, the total number of included patients, and the funding source where reported.

Table 1. Study design of included evidence.

Author, year published	Years on study	Disease site	Total included N	Sponsorship
Retrospective cohort studies				
Mundt et al, 2002 (15)	2000-2004	Gynecologic cancers (60% cervical)	75	Illinois Department of Public Health
Beriwal et al, 2006 (13)	2002-	Vulvar carcinoma	24	NR
Chen et al, 2007 (14)	2002-2006	Post-hysterectomy cervical cancer	68	NR
Prospective cohort studies				
Kidd et al, 2009 (16)	1997-2008	Locally advanced cervical cancer	452	NR

Table 2 describes the study details, including the comparison that was made, the radiation dose administered in each group, the number of patients in each group, the disease stages included in the study population, the overall median follow-up, and what outcomes were reported. In the study reported by Mundt et al (15), 70% of all patients received surgery in addition to RT, and of those patients, 60% received surgery prior to RT. In this same study, 42.5% of all patients received CT in addition to RT and/or surgery (15). In the study reported by Beriwal et al (13), 46.7% of all patients received preoperative CRT, and the remaining 53.3% received postoperative RT. In the study reported by Chen et al (14), all patients received adjuvant CRT with brachytherapy following a hysterectomy. In the study reported

by Kidd et al (16), all patients received definitive RT for the primary treatment of locally advanced cervical cancer.

Table 2. Details of included studies.

Author, year published	Comparison	Dose	Total N	Disease stage	Median follow-up (months)	Outcomes reported
Retrospective cohort studies						
Mundt et al, 2002 (15)	IMRT 4F EBRT	45 Gy/1.8f 45 Gy/1.8f	40 35	T1-4	NR	Acute AE
Beriwal et al, 2006 (13)	IMRT 3DCRT	Preop CRT: 46.4 Gy* (42.8-46.4) Postop: 50.4 Gy* (50.4-64) NR	15 9	T2-4A	12	Dosimetric
Chen et al, 2007 (14)	IMRT 4F EBRT	50.4 Gy/1.8f + 6 Gy brachytherapy+cisplatin 50.4 Gy/1.8f + 6 Gy brachytherapy+cisplatin	33 35	T1-2	14 (6-25) 35.6 (12-52)	TRO, acute AE, late AE
Prospective cohort studies						
Kidd et al, 2009 (16)	IMRT Non-IMRT	50.4 Gy/1.8f to pelvic lymph nodes + 20 Gy to cervix ~50 Gy to pelvic lymph nodes + ~20 Gy to the central pelvis	135 317	T1b1-IVa	Mean 22 (5-47) Mean 72 (29-117)	TRO, AE

Note: IMRT, intensity-modulated radiotherapy; 4F EBRT, four-field external beam radiotherapy (BoxRT); Gy, Gray; f, fraction; T, tumour; NR, not reported; AE, adverse effect; CRT, chemoradiotherapy; 3DCRT, three-dimensional conformal radiotherapy; TRO, treatment-related outcomes.
* Median dose

Table 3 outlines the technical details of the IMRT regimen, including the planning system used, the type of IMRT administered (e.g., step & shoot, sliding window, volumetric arc), the field arrangement (e.g., 5 field, 7 field), the planned target volume, the planned target volume expansion (mm), and the image guidance method used (e.g., none, implanted fiducial markers, EPID, daily ultrasound, in-room CT).

Table 3. IMRT details of included studies.

Author, year published	Planning system	Type of IMRT	Field arrangement	Planned target volume	Planned target volume expansion (mm)	Image guidance
Retrospective cohort studies						
Mundt et al, 2002 (15)	Corvus	Step & shoot	7 or 9 field, 6MV, co-planar	NR	NR	CT
Beriwal et al, 2006 (13)	Eclipse	NR	Median 7 field (5-8), 6MV	NR	NR	CT
Chen et al, 2007 (14)	Eclipse	NR	6-7 field, 10MV,	NR	NR	CT

			coplanar			
Prospective cohort studies						
Kidd et al, 2009 (16)	Eclipse	Step-wedge	NR	NR	NR	PET/CT

Note: NR, not reported.

Study Quality

The four studies were assessed for quality according to criteria such as the balance between the treatment groups, identification of prognostic factors, and reporting of differences between baseline prognostic factors. Other variances in study design that could affect the reliability of the study findings were also reported.

Two (14,15) of the studies were on similar numbers of patients in each treatment, but the studies by Beriwal et al (13) and Kidd et al (16) included a disproportionate number of patients in each group (Beriwal: 15, IMRT: 9, 3DCRT; Kidd: 135, IMRT: 317, non-IMRT). The studies reported by Mundt et al (15) and Chen et al (14) also reported on baseline prognostic factors, with no significant differences being reported. For these two papers (14,15), as no differences between groups were reported, no changes were made to the groups to correct for imbalances. As Beriwal et al (13) did not report any data on baseline prognostic factors, it is unknown whether the patient groups were dissimilar. The study by Kidd et al (16) did note that both the IMRT and the non-IMRT groups had similar stage distributions, histology, and rates of lymph node involvement.

Outcomes: Dosimetric

The paper by Beriwal et al (13) reported on dosimetric outcomes in a treatment plan comparison between IMRT and 3DCRT. In this comparison, treatment with IMRT was associated with a reduction in the amount of radiation administered to several nearby OAR. Three main OAR for radiation treatment in gynecologic cancers are the small bowel, the bladder, and the rectum. Significant mean volume reductions were detected in all three OAR (small bowel: -27%, p=0.03; bladder: -41%, p=0.01; rectum: -26%, p=0.004).

Outcomes: Disease-related

The retrospective cohort study by Chen et al (14) and the prospective cohort study by Kidd et al (16) reported on disease-related outcomes, and no significant differences were detected in locoregional recurrence or recurrence-free survival rates, but a significant benefit was detected in favour of IMRT compared with non-IMRT regimens for overall survival in the study by Kidd et al (16) (IMRT: 67.4% v. non-IMRT: 49.2%; p<0.0001). Disease-related outcomes appear in Table 4.

Table 4. Disease-related outcomes.

Author, year published	Comparison	Locoregional recurrence rates	Overall Recurrence-free survival	Overall survival
Retrospective cohort study				
Chen et al, 2007 (14)	IMRT 4F EBRT	6% 8.6% p=0.96	NR NR	100% 100% p>0.05
Prospective cohort studies				
Kidd et al, 2009 (16)	IMRT Non-IMRT	8.1% 10.4% p>0.05	28.8% 43.8% p>0.05	67.4% 49.2% **p<0.0001**

Note: IMRT, intensity-modulated radiotherapy; 4F EBRT, four-field external beam radiotherapy; NR, not reported.

Outcomes: Acute adverse effects

Two of the papers obtained reported on acute adverse effects, Mundt et al (15) (total study n=75 patients) and Chen et al (14) (total study n=68 patients). Statistically significant differences were detected in acute gastrointestinal (GI) effects by Mundt et al (15) (Grade 2: 60%, IMRT versus [vs.] 90%, 4F EBRT; p=0.002), and by Chen et al (14) (Grade 1-2: 36%, IMRT vs. 80%, 4F EBRT; p=0.00012). The Chen et al study also reported on acute genitourinary (GU) effects, and a statistically significant benefit in favour of treatment with IMRT was detected (Grade 1-2: 30%, IMRT v. 60%, 4F EBRT; p=0.022). No grade 3 GI or GU effects were detected for either study, but Grade 3 hematologic effects (p=nonsignificant) were reported in the study by Chen et al (14). Acute adverse effect outcomes appear in table 5.

Table 5. Acute adverse effects.

Author, year published	Comparison	GI effects %			GU effects %			Hematologic	
Retrospective cohort study									
Mundt et al, 2002 (15)	IMRT 4F EBRT	Grade 2 (no Gr. 3) 60 90 **p=0.002**			Grade 2 (no Gr. 3) 10 20 p>0.05			NR	
Chen et al, 2007 (14)	IMRT 4F EBRT	Grade 1	2	3	Grade 1	2	3	Grade 2	Grade 3
		12	24	0	18	12	0	27	6
		23	57	0	34	26	0	31	9
		p=0.00012			**p=0.022**			p>0.05	

Note: IMRT, intensity-modulated radiotherapy; 4F EBRT, four-field radiotherapy; NR, not reported.

Outcomes: Late adverse effects

Only the study by Chen et al (14) reported on late adverse effects. In this study, a statistically significant difference was detected in late GI effects (p=0.002) but not in late GU effects. Late hematologic effects were also reported. Late adverse effect outcomes appear in Table 6.

Table 6. Late adverse effects.

Author, year published	Comparison	GI effects %				GU effects %			
Chen et al, 2007 (14)	IMRT 4F EBRT	Gr. 0	1	2	3	Gr. 0	1	2	3
		0	2	0	0	0	2	1	0
		0	4	6	2	0	5	2	1
		p=0.002				p>0.05			

Note: IMRT, intensity-modulated radiotherapy; 4F EBRT, four-field external beam radiotherapy; Gr., grade; p, probability.

Outcomes: adverse effects

The study by Kidd et al (16) reported on the total Grade 3 or higher adverse effects (both acute and late), with a statistically significant benefit being detected in favour of treatment with IMRT (IMRT: 6% vs. non-IMRT: 17%; p=0.0017).

ONGOING TRIALS

The U.S. National Institutes of Health online directory of clinical trials (located at http://www.clinicaltrial.gov) was searched on October 5, 2009 for listings of relevant trials. The details of the single relevant trial appear in Table 7.

Table 7. Ongoing studies.

A Pilot Study of Conformal Intensity Modulated Radiation Therapy (IMRT) for Gynecological Cancer Patients Not Suitable for Intracavitary Brachytherapy Boost (GY03.2) Phase: Phase I/II Type: Interventional Status: Active, recruiting Age: 18+ Sponsor: University Health Network (Toronto), Princess Margaret Hospital (Toronto) Protocol ID: UHN REB 03-0298-C, NCT00188578 Description: The standard treatment for gynecological cancer is radiation in two phases; whole pelvic radiation and then an internal radiation boost via brachytherapy to treat any remaining tumour. The purpose of this study is to test an alternative radiation boost treatment with IMRT.

DISCUSSION

The search of MEDLINE and EMBASE databases yielded just four studies that met our study criteria for providing an appropriate comparison between IMRT and 3DCRT or brachytherapy. This result underlies the fact that such technology has not been reported with long-term outcomes. Our search included all gynecologic cancers relevant to radiation oncology practice, but the majority of patients in these studies had cervix cancer. Many of the factors that were considered for cervix cancer IMRT would be similar for other gynecologic cancers. While there are many studies reporting dosimetric parameters associated with gynecologic IMRT, they lack the information on important patient outcomes that was sought in this systematic review. Similarly, there are some pilot studies reporting initial results with gynecologic IMRT but lacking an appropriate comparison group.

With IMRT, clinicians hope to enhance the therapeutic ratio; to improve the disease control to toxicity ratio. The largest study in this review, by Kidd et al (16), showed an improvement in cause-specific and overall survival between IMRT and 3DCRT. The role of IMRT was to reduce the dose to normal tissues rather than deliver higher doses to areas of disease. Although there was a relatively short follow-up in the IMRT group compared to the non-IMRT group (mean 22 vs. 72 months), IMRT appears to be at least as good as 3DCRT. Appropriate statistical comparisons were made between both groups. All patients had a pre-staging PET scan and a three month post-treatment PET scan; therefore, stage migration would not be a factor. An additional PET scan was fused with CT at the time of treatment planning in the IMRT group, providing further guidance on the tumour volumes that were to be included and better sparing of normal tissues. The remaining studies either did not report disease outcomes or did not find a difference and were likely underpowered to detect a modest difference between the groups. In the two studies reporting acute toxicity, acute GI toxicity was significantly reduced by IMRT in the study by Mundt et al (15). However, no differences were seen in GU toxicity, and in the study by Chen et al (14), no differences resulted when including hematologic toxicity. Of perhaps greater importance are the long-term toxicities of treatment. The study by Kidd et al (16) did report an associated benefit favouring IMRT compared with non-IMRT radiation treatment on GI and GU grade 3 or higher adverse effects. In particular, the incidence of rectovaginal and vesicovaginal fistulas was substantially less in the IMRT group. Chen et al (14) reported a reduction in late GI toxicity with two patients compared to none having Grade 3 toxicity. The difference found between the studies may relate to the total dose of radiation given. In the primary treatment of cervical cancer, the radiation dose (both external beam and brachytherapy) is higher than in the postoperative setting and so the benefit of sparing normal tissues with IMRT would likely be greater. The other two studies did not report late toxicity.

This review highlights the fact that the use of IMRT for gynecologic cancers is still in its early stages. There are no reported randomized controlled trials to guide clinical practice. The largest study (16) is also the most recently published in this review. The reduction in Grade 3 and higher long-term toxicity of the magnitude seen (from 17% to 6%) is not only of statistical significance but is also clinically relevant. For this reason, IMRT may be considered a viable treatment option as determined by the Precautionary Principle (17), which states that it is ethical to recommend a treatment with little known harm over one with greater known harm prior to scientific proof of the difference in harm being established. There remain many unknown aspects to the planning, delivery, and subsequent effects of gynecologic IMRT. While 3D imaging may allow the identification of target volumes, to some extent, accurate delineation is not always possible. For example, CT imaging often does not show a tumour in the cervix or identify any parametrial involvement. MRI provides better soft tissue definition but has its limitations in identifying tumour volumes (18). Many clinicians also find there is a learning curve in accurately contouring MRI-based volumes. Inaccuracies in contouring come with a heavy price. Derived plans report coverage to a planning target volume (PTV), e.g., 95% coverage of the PTV. Actually delivering this dose to the disease site is dependent on the accurate delineation of a PTV. The typical radiation fields used to treat cervix cancer cover a fairly large volume, whereas IMRT treats very specific target volumes, but it is still not entirely clear what can be safely avoided without compromising disease control. While it is possible to reduce the chances of missing any disease site by widening the margins, this reduces the benefit of IMRT over 3DCRT. Another consideration is accounting for the fourth dimension in the delivery of RT over time. Over a course of radiation, there is organ motion with respiration, changes in organ shape, and position and volume changes in tumour. In a study by Lim et al (19), patients who underwent weekly MRIs during cervix cancer RT showed significant differences in planned and delivered doses of radiation due to some of these factors (19). While IMRT ensures an adequate dose and a conformal distribution to a volume such as the PTV, that too may come at a price. There is more dose heterogeneity, which can create hot spots in adjacent normal tissues that might result in adverse late effects. By using an increased number of beams, from four to six or more, the volume of normal tissue receiving some radiation is significantly increased, which is reflected in a higher integral dose. A higher incidence of radiation-induced malignancies is predicted by some models (20). There are additional issues to consider in implementing gynecologic IMRT that are summarized in a review article by Randall et al (21).

Our systematic review criteria did not find any articles comparing 3DCRT techniques to IMRT for boosting specific sites of disease like the parametria or para-aortic nodes. As these clinical scenarios are less common and may pose unique anatomic challenges, it is unlikely we will see any high-quality studies addressing this issue. When clinicians see a potential benefit to IMRT for these cases, they should also be aware of the challenges of using this technology.

There is an obvious need for better quality data on the use of gynecologic IMRT. Many of the single-arm or dosimetric studies acknowledge the need for high-quality prospective data. Perhaps the first step is to establish an agreed-upon methodology for contouring pelvic anatomy for IMRT. Small et al (22) have proposed consensus guidelines for contouring postoperative cervical and endometrial cases (22). These guidelines were incorporated in a study completed by the Radiation Therapy Oncology Group (RTOG) looking at the transportability of gynecologic IMRT in a multi-institutional setting and relevant clinical outcomes. Preliminary results have been reported in abstract form showing a good compliance with protocol specifications (23,24). There is also a randomized controlled trial reported in abstract form, comparing IMRT with conventional radiation therapy in stage IIB cervix cancer (25). Reduced toxicities were noted, but these findings will require further follow-up for late effects and locoregional control rates.

CONCLUSIONS

This evidence-based systematic review found only a few studies that utilize gynecologic IMRT or that report on comparative clinical outcomes between 3DCRT and IMRT. The largest reported study to date (16) shows a substantial reduction in significant chronic toxicity rates from IMRT over 3DCRT. The other studies showed modest improvements in some domains of acute and chronic toxicity. Additional evidence is needed to establish whether there is a consistent improvement seen with the use of IMRT. IMRT was not used to deliver higher doses of radiation, and therefore, improvements in outcomes related to disease recurrence and overall survival were not expected. There are many issues to consider in the planning and delivery of gynecologic IMRT, and long-term outcome data is lacking. At this time, although there are data to support the use of IMRT in the treatment of gynecologic cancers in order to reduce the toxicity of treatment, clinicians should be aware of the uncertainties involved and be judicious in the use of gynecologic IMRT with the primary goal of reducing toxicity. Participation in clinical research should be encouraged and will hopefully offer more evidence to support the use of gynecologic IMRT.

CONFLICT OF INTEREST

None declared.

JOURNAL REFERENCE

The following article has been published in *Clinical* ***Oncology*** **(**Crown Copyright © 2012 Published by Elsevier Ltd on behalf of The Royal College of Radiologists; http://www.journals.elsevier.com/clinical-oncology/):

- D'Souza DP, Rumble RB, Fyles A, Yaremko B, Warde P; Members of the IMRT Indications Expert Panel. Intensity-modulated radiotherapy in the treatment of gynaecological cancers. Clin Oncol. 2012;24:499-507. doi:10.1016/j.clon.2012.05.005.

ACKNOWLEDGEMENTS

The IMRT Indications Expert Panel would like to thank Dr. David D'Souza and Mr. R. Bryan Rumble for taking the lead in drafting this systematic review.

Funding

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

Contact Information
For further information about this series, please contact:

Dr. David P. D'Souza, Assistant Professor
Department of Oncology, University of Western Ontario
Phone:519-685-8650 Fax:519-685-8627 Email: david.dsouza@lhsc.on.ca
or
Dr. Padraig Warde, Provincial Head
Radiation Treatment Program, Cancer Care Ontario
Phone: 416-971-9800 ext. 3734 Fax: 416-971-6888 Email: padraig.warde@rmp.uhn.on.ca

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

REFERENCES

1. Veldeman L, Madani I, Hulstaert F, De Meerleer G, Mareel M, De Neve W, et al. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. Lancet Oncol. 2008;9(4):367-75.
2. Galvin JM, Ezzell G, Eisbrauch A, Yu C, Butler B, Xiao Y, et al. Implementing IMRT in clinical practice: a joint document of the American Society for Therapeutic Radiology and Oncology and the American Association of Physicists in Medicine. Int J Radiat Oncol Biol Phys. 2004;58(5):1616-34.
3. Kong A, Powell M, Blake P. The role of postoperative radiotherapy in carcinoma of the endometrium. Clin Oncol. 2008;20(6):457-62.
4. Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H, Kunos C, et al. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. Obstet Gynecol. 2009;114(3):537-46.
5. Lukka H, Hirte H, Fyles A, Thomas G, Elit L, Johnston M, et al. Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer--a meta-analysis. Clin Oncol. 2002;14(3):203-12.
6. Rotman M, Sedlis A, Piedmonte MR, Bundy B, Lentz SS, Muderspach LI, et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. Int J Radiat Oncol Biol Phys. 2006;65(1):169-76.
7. Sinha B, Stehman F, Schilder J, Clark L, Cardenes H, Sinha B, et al. Indiana University experience in the management of vaginal cancer. Int J Gynecol Cancer. 2009;19(4):686-93.
8. Kam MK, Leung SF, Zee B, Chau RM, Suen JJ, Mo F, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol. 2007;25(31):4873-9.
9. Zelefsky MJ, Fuks Z, Happersett L, Lee HJ, Ling CC, Burman CM, et al. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiother Oncol. 2000;55(3):241-9.
10. Hartford AC, Palisca MG, Eichler TJ, Beyer DC, Devineni VR, Ibbott GS, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for intensity-modulated radiation therapy (IMRT). Int J Radiat Oncol Biol Phys. 2009;73(1):9-14.
11. Whitton A, Warde P, Sharpe M, Oliver TK, Bak K, Leszczynski K, et al. Organisational Standards for the Delivery of Intensity-modulated Radiation Therapy in Ontario. Clin Oncol. 2009;21(3):192-203.
12. Browman G, Levine M, Mohide E, Hayward R, Pritchard K, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13(2):502-12.
13. Beriwal S, Heron DE, Kim H, King G, Shogan J, Bahri S, et al. Intensity-modulated radiotherapy for the treatment of vulvar carcinoma: a comparative dosimetric study with early clinical outcome. Int J Radiat Oncol Biol Phys. 2006;64(5):1395-400.
14. Chen MF, Tseng CJ, Tseng CC, Kuo YC, Yu CY, Chen WC, et al. Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. Int J Radiat Oncol Biol Phys. 2007;67(5):1438-44.
15. Mundt AJ, Lujan AE, Rotmensch J, Waggoner SE, Yamada SD, Fleming G, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2002;52(5):1330-7.

16. Kidd EA, Siegel BA, Dehdashti F, Rader JS, Mutic S, Mutch DG, et al. Clinical Outcomes of Definitive Intensity-Modulated Radiation Therapy with Fluorodeoxyglucose-Positron Emission Tomography Simulation in Patients with Locally Advanced Cervical Cancer. Int J Radiat Oncol Biol Phys. 2009;In Press, Corrected Proof.
17. Andorno R. The Precautionary Principle: A new legal standard for a technological age. J Int Biotechnol Law. 2004;1(1):8.
18. Hancke K, Heilmann V, Straka P, Kreienberg R, Kurzeder C, Hancke K, et al. Pretreatment staging of cervical cancer: is imaging better than palpation?: Role of CT and MRI in preoperative staging of cervical cancer: single institution results for 255 patients. Ann Surg Oncol. 2008;15(10):2856-61.
19. Lim K, Kelly V, Stewart J, Xie J, Cho YB, Moseley J, et al. Pelvic radiotherapy for cancer of the cervix: is what you plan actually what you deliver? Int J Radiat Oncol Biol Phys. 2009;74(1):304-12.
20. Stathakis S, Roland T, Papanikolaou N, Li J, Ma C, Stathakis S, et al. A prediction study on radiation-induced second malignancies for IMRT treatment delivery. Technol Cancer Res Treat. 2009;8(2):141-8.
21. Randall ME, Ibbott GS, Randall ME, Ibbott GS. Intensity-modulated radiation therapy for gynecologic cancers: pitfalls, hazards, and cautions to be considered. Sem Radiat Oncol. 2006;16(3):138-43.
22. Small Jr W, Mell LK, Anderson P, Creutzberg C, De Los Santos J, Gaffney D, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys. 2008;71(2):428-34.
23. Jhingran A, Winter K, Portelance L, Miller BE, Salehpour M, Gaur R, et al. A Phase II study of intensity modulated radiation therapy (IMRT) to the pelvic for post-operative patients with endometrial carcinoma (RTOG 0418). Int J Radiat Oncol Biol Phys. 2008;72(1, Supplement 1):S16-S7.
24. Portelance L, Winter K, Jhingran A, Miller BE, Salehpour MR, D'Souza DP, et al. Post-operative pelvic intensity modulated radiation therapy (IMRT) with chemotherapy for patients with cervical carcinoma/RTOG 0418 phase II study. Int J Radiat Oncol Biol Phys. 2009;75(3, Supplement 1):S640-S1.
25. Shrivastava SJ, Mahantshetty U, Jamema S, Kinhikar R, Engineer R, Deshpande D, et al. A Phase II randomized trial comparing intensity modulated radiation therapy (IMRT) with conventional radiation therapy in stage IIB carcinoma cervix: an audit (TMH/158/2004/-NCT00193804). Int J Radiat Oncol Biol Phys. 2009;75(3, Supplement 1):S84-S5.

Appendix 1. Members of the IMRT Indications Expert Panel & Gynecologic Cancer Working Group.

Steering Panel

Dr. Padraig Warde Provincial Head, Radiation Treatment Program, Cancer Care Ontario
Mr. Eric Gutierrez Program Manager, Radiation Treatment Program, Cancer Care Ontario
Ms. Kate Bak Project Coordinator, Radiation Treatment Program, Cancer Care Ontario
Mr. Bryan Rumble Research Coordinator, Program in Evidence-based Care, Cancer Care Ontario

Expert Panel

Dr. Anthony Whitton Radiation Treatment Program, Cancer Care Ontario
Ms. Sarah Etheridge Radiation Therapy Representative, Peel Regional Cancer Program
Ms. Lisa Favell Capital Project Representative, Cancer Care Ontario
Ms. Katrina Fleming Radiation Therapy Representative, Grand River Regional Cancer Centre
Ms. Esther Green Chief Nursing Officer and Director of Health Human Resource Planning, Cancer Care Ontario
Dr. Konrad Leszczynski Physics Representative, Northeastern Ontario Regional Cancer Centre
Dr. Michael Sharpe Physics Representative, Princess Margaret Hospital

Working Group

Dr. David P. D'Souza Radiation Oncologist, London Health Sciences Centre Assistant Professor, Department of Oncology, University of Western Ontario
Dr. Anthony Fyles Radiation Oncologist, Princess Margaret Hospital Professor, Department of Radiation Oncology, University of Toronto
Dr. Brian Yaremko Radiation Oncologist, London Health Sciences Centre Assistant Professor, Department of Oncology, University of Western Ontario

Appendix 2. Literature Search Strategies.

Database: Ovid MEDLINE(R) <1996 to July Week 1 2009>

---

1 exp Ovarian Neoplasms/ or exp Uterine Cervical Neoplasms/ or exp Genital Neoplasms, Female/ or gynecological cancer.mp. or exp Vulvar Neoplasms/ (62064)
2 exp Radiotherapy, Intensity-Modulated/ or imrt.mp. (2709)
3 exp Protons/ or proton therapy.mp. (11707)
4 biological marker.mp. or exp Biological Markers/ (318581)
5 gene therapy.mp. or exp Gene Therapy/ (33692)
6 children.mp. or exp Child/ (545765)
7 pediatric cancer.mp. (682)
8 childhood cancer.mp. (2011)
9 exp Quality Assurance, Health Care/ or quality assurance.mp. (140638)
10 treatment plan comparison.mp. (5)
11 aperture optimization.mp. (30)
12 independent dose calculation.mp. (13)
13 EPID dosimetry.mp. (14)
14 set up errors.mp. (88)
15 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (1019202)
16 1 and 2 (87)
17 1 and 15 (10506)
18 16 not 17 (77)
19 limit 18 to (english language and humans and yr="2000 - 2009") (74)
20 from 19 keep 1-74 (74)

Database: EMBASE <1996 to 2009 Week 28>

---

1 gynecological cancer.mp. or exp Gynecologic Cancer/ (4030)
2 imrt.mp. or exp Intensity Modulated Radiation Therapy/ (3527)
3 proton therapy.mp. or exp Proton Therapy/ (729)
4 biological marker.mp. or exp Biological Marker/ (33562)
5 gene therapy.mp. or exp Gene Therapy/ (35409)
6 Child/ or child.mp. or children.mp. (471840)
7 exp Childhood Cancer/ or pediatric cancer.mp. (10161)
8 quality assurance.mp. or exp Quality Control/ (113336)
9 treatment plan comparison.mp. (5)
10 aperture optimization.mp. (31)
11 independent dose calculation.mp. (12)
12 EPID dosimetry.mp. (15)
13 set up errors.mp. (89)
14 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (647159)
15 1 and 2 (35)
16 1 and 14 (282)
17 15 not 16 (30)
18 limit 17 to (human and english language and yr="2000 - 2009") (29)
19 from 18 keep 1-29 (29)

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 21-3-7: Section 3

The Role of IMRT in Gynecologic Cancer: EBS Development Methods and External Review Process

D. D'Souza, R.B. Rumble, P. Warde and members of the IMRT Indications Expert Panel

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

Report Date: October 29, 2010

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) and Guideline Development Groups (GDGs), 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 evidence-based series 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 IMRT Indications Expert Panel of the CCO PEBC and RTP. The series is a convenient and up-to-date source of the best available evidence on the role of IMRT in central nervous system cancer, developed through a review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

IMRT Expert Panel Conference

On December 3, 2009 the IMRT gynecological cancers guideline was presented to members of the IMRT Expert Panel (n=25), and feedback was obtained on the quality and comprehensiveness of the evidence and the recommendations. Results are as follows:

Are you responsible for the care of patients for whom this draft report is relevant?					
Response	Yes	No	Unsure	TOTALS	Missing
N	9	17	0	26	0
%	34.6	65.4	0	100	0

Rate the overall quality of the guideline report.							
Response	1.Lowest	2.	3.	4.	5.Highest	TOTALS	Missing
N	0	0	2	22	2	26	0
%	0	0	7.7	84.6	7.7	100	0

I would make use of this guideline in my professional decisions.							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
N	0	0	2	18	3	23	3
%	0	0	8.7	78.3	13	100	11.5

I would recommend this guideline for use in practice.							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
N	0	0	2	21	3	26	0
%	0	0	7.7	80.8	11.5	100	0

RECOMMENDATIONS

1. If acute and chronic toxicities are the main outcomes of interest, IMRT may be considered over 3DCRT for women undergoing radiotherapy for gynecological cancer.

Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
N	0	0	3	20	3	26	0
%	0	0	11.5	76.9	11.5	99.9	0
Do you agree with this Recommendation?							
Response	Yes	No	Unsure	TOTALS	Missing		
N	24	1	0	24	1		
%	96	4	0	100	3.8		

2. If treatment-related outcomes are the main outcomes of interest, there is insufficient evidence to recommend IMRT over 3DCRT for women undergoing radiotherapy for gynecologic cancers.							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
N	0	0	3	18	4	25	1
%	0	0	12	72	16	100	3.8
Do you agree with this Recommendation?							
Response	Yes	No	Unsure	TOTALS	Missing		
N	23	1	0	24	2		
%	95.8	4.2	0	100	7.6		

Additionally, the following feedback was also obtained (summarized to only include main points that were addressed in subsequent drafts):

What are the barriers to the implementation of this guideline report?
• Largest study also incorporated PET for planning and availability of PET may influence benefit of IMRT. • Equipment and other resources including HR. • IMRT needs to be contextualized within the clinical milieu that also includes brachytherapy.
Comments Recommendation One:
• Recommendation should be stronger than "may be considered", consider “is recommended”. • Reorganize qualifying statements in order of importance.
Comments Recommendation Two:
• Should use stronger language, e.g. IMRT is the recommended treatment.
Other Comments:
No other comments were obtained.

Report Approval Panel

Following the presentation of this EBS draft report for Expert Panel review, the report was submitted to the PEBC Report Approval Panel (RAP) for review on March 8, 2010. The RAP is comprised of two members, including an oncologist, with expertise in clinical and methodological issues.

Key issues raised by the Report Approval Panel included:

- Add the outcomes of interest to the clinical question in both Sections One and Two
- For both of the Recommendations, add in whether IMRT is being recommended alone or in addition to surgery and/or chemotherapy.
- In the Evidence sections below each of the recommendations, explicitly state the study designs of the included evidence.

In response to the RAP review feedback, the following was added to the guideline:

- The outcomes of interest were added to the clinical question in both Sections 1 and 2.

- Information on whether the IMRT was given alone or along with surgery and/or chemotherapy in the included studies was added to the Qualifying Statements. The wording of the Recommendations was not changed.
- The study designs of the included evidence are now explicitly stated in the Evidence sections below each of the recommendations.

No RAP resubmission was requested, and the guideline was approved on April 5, 2010.

External Review: Professional Consultation

On September 20, 2010, the RAP-approved document was distributed to clinicians practicing within the Province of Ontario, as part of a Profession Consultation review process. A total of 126 clinicians were invited to participate, and a total of seven submitted responses (5.5% response rate). Results are as follows:

1. Rate the overall quality of the guideline report							
Response	1. Lowest	2.	3.	4.	5. Highest	TOTALS	Missing
N	0	0	2	4	1	7	0
%	0	0	29	57	14	100	0
2. I would make use of this guideline in my professional decisions							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
N	0	0	1	4	2	7	0
%	0	0	14	57	29	100	0
3. I would recommend this guideline for use in practice							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
N	0	0	1	5	1	7	0
%	0	0	14	71	14	100	0

4. What are the barriers or enablers to the implementation of this guideline report?
   Barriers:
   - Availability of IMRT in this setting.
   - The difficulties with finding concordance between different treatment planning systems.

   Enablers:
   None submitted.

5. Additional comments.
   None submitted.

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

Disclaimer

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information

For further information about this series, please contact:

Dr. David P. D'Souza, Assistant Professor
Department of Oncology, University of Western Ontario
Phone:519-685-8650 Fax:519-685-8627 Email: david.dsouza@lhsc.on.ca
or
Dr. Padraig Warde, Provincial Head
Radiation Treatment Program, Cancer Care Ontario
Phone: 416-971-9800 ext. 3734 Fax: 416-971-6888 Email: padraig.warde@rmp.uhn.on.ca

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

REFERENCES

1. Browman G, Levine M, Mohide E, Hayward R, Pritchard K, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13(2):502-12.
2. Browman G, Newman T, Mohide E, Graham I, Levine M, Pritchard K, et al. Progress of clinical oncology guidelines development using the Practice Guidelines Development Cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.