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Evidence-Based Series 21-3-2

The Role of IMRT in Breast Cancer

I. Dayes, R.B. Rumble, J. Bowen, P. Dixon, 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 27, 2010

An assessment conducted in November 2013 put Evidence-based Series (EBS) 21-3-2 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 21-3-2 is comprised of 3 sections
and is available on the CCO website (http://www.cancercare.on.ca)
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Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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Evidence-Based Series 21-3-2: Section 1

The Role of IMRT in Breast Cancer: Guideline Recommendations

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QUESTIONS

When external beam is given as adjuvant postoperative treatment, what is the role of intensity-modulated radiation therapy (IMRT) compared to standard tangent radiation therapy (RT), three-dimensional conformal RT (3DCRT), brachytherapy (including MammoSite), or mastectomy?

TARGET POPULATION

The target population is comprised of all female patients with breast cancer for whom treatment with radiation is being considered. Whether the findings reported below are relevant to male patients with breast cancer is unknown.

INTENDED USERS

This guideline is targeted for radiation oncologists, physicists, and dosimetrists. Administrators may find the report of value when considering the benefits of IMRT over standard tangent RT for breast cancer.

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 breast cancer 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 toxic effects are the main outcomes of interest, then IMRT is the recommended treatment option over tangential RT (TanRT) to patients undergoing adjuvant radiotherapy following breast-conserving surgery.
Evidence All six studies (3-8) included in this review, including one randomized controlled trial (RCT) (8), reported a significant reduction in toxic acute skin effects.

If treatment-related outcomes are the main outcomes of interest, there is no evidence to support or refute a recommendation of IMRT over TanRT to patients undergoing adjuvant RT following breast-conserving surgery.
Evidence: The evidence examined in this review did not detect a statistically significant difference between IMRT and TanRT for the treatment-related outcomes of freedom from contralateral breast cancer recurrence, clinical recurrence-free survival, or disease-specific survival.

Key Evidence

A total of six papers were included in this evidence review, one RCT (8) involving 331 patients, three retrospective cohort studies (4-6) involving 1216 patients altogether, one historically controlled trial (3) involving 133 patients, and a prospective cohort study (7) involving 332 patients.

Qualifying Statement

The following guideline reports mainly on the reduction of acute radiation toxicity achieved through the use of IMRT, largely due to short follow-up times and the comparative rarity of serious late effects. Longer follow-up of prospective studies will provide important data on late toxicity and disease recurrence rates, although none of the included studies suggested that either of these outcomes were compromised as a result of IMRT.

FUTURE RESEARCH

Future research should focus on studies with longer follow-up that provide data on late toxicity and disease recurrence rates.

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.
- Evidence-based Series #21-1: Organizational standards for the delivery of intensity modulated radiation therapy (IMRT) in Ontario (available from http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=44428).

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

The Role of IMRT in Breast Cancer: Evidentiary Base

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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

breast cancer to quantify the potential benefits of this new technology and make recommendations for radiation treatment programs considering adopting this technique.

INTRODUCTION

Postoperative RT has been a mainstay of breast-conserving therapy following lumpectomy for decades, supported by a large body of evidence for its improvement of local control (3). Despite a considerable reduction in local recurrence rates, individual trials of adjuvant RT did not show a reduction of mortality rates, in part due to long-term, particularly cardiac, toxicity (3,4), which is also a concern following post-mastectomy RT (5-7).

Historically, breast irradiation used fluoroscopic techniques that required two-dimensional planning and had potential cardiac complications. With the advent of more powerful computers and computed tomography (CT) scanning, improved three-dimensional (3D) planning techniques evolved that may have decreased cardiac morbidity (8,9). However, despite improvements in planning, therapy techniques remained unchanged, 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 toxicity reduction in several disease sites, including cancers of the head and neck (10) and of the prostate (11).

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 organs at risk 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 organs at risk 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 risk of delivery error. In addition, as the precision of radiation delivery increases, so does the need for accurate daily patient positioning (12). This increased complexity has significant resource implications for radiation departments, demands that have been identified in a previous Cancer Care Ontario (CCO) document (13).

The overall benefit of IMRT in delivering adjuvant breast RT must be balanced against this increased demand on resources. Given CCO's ongoing 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 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 (14). 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 (Appendix 1) 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 breast cancer. The body of evidence in this review is

primarily comprised of published reports of comparative studies between IMRT and other methods of radiation delivery. 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 breast cancer and IMRT on March 18, 2009. In both databases, keywords for "breast cancer" were combined with keywords for "intensity-modulated radiotherapy," and the following terms were excluded: "proton therapy", "biological markers", "gene therapy", "children", "childhood cancer", "pediatric 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. The literature search strategies used for the MEDLINE and Embase databases appear in Appendix 2. 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.

Study Selection Criteria

Inclusion Criteria

All the following publication types must include comparative data on IMRT (inverse planned) versus 3DCRT or tangent RT or brachytherapy (including MammoSite), or mastectomy in the adjuvant setting following surgery for the treatment of breast cancer:

- CPG, practice guidelines (PG), SR, HTA
- Randomized phase II or phase III trials
- Dose-escalation studies, toxicity reports, quality of life (QoL) reports, case series, and retrospective studies

and must:

- Report on 50 or more patients
- Be published in English
- Be 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 for or conducted in this systematic review.

RESULTS

Literature Search Results

The MEDLINE and Embase search returned 125 and 173 potential articles, respectively. After removing ineligible articles, based on a title and abstract review, 13 articles in total were ordered for full-text review, six based on the MEDLINE results, and seven based on the Embase results. One guideline from the National Institute for Health & Clinical Evidence was also ordered for full-text review, as well as two American Society for Therapeutic Radiology and Oncology (ASTRO) Conference proceedings abstracts.

Of the one guideline, 13 fully published papers, and two ASTRO Conference proceedings abstracts that were ordered for full-text review, only five of the 13 fully-published papers were retained (15-20), including one ASTRO abstract (15). This ASTRO abstract was replaced by the fully-published paper when it became available in May 2009 (21). These six papers comprise the body of evidence in this systematic review. The single guideline ordered was excluded. Appendix 3 contains a table of excluded evidence, including the single guideline, one abstract, and eight articles and the reasons for exclusion.

Study Design

The six articles retained included three retrospective cohort studies (17,18,21), one historically controlled trial (16), one prospective cohort study (19), and one RCT (20). Table 1 details the years on study, 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	Total included N	Sponsorship
Retrospective cohort study			
Freedman et al, 2009 (21)	2001-2006	804	NR
Harsolia et al, 2007 (17)	1999-2001 1999	172	Alfred Berkowitz Foundation, William Beaumont Hospital Foundation
McDonald et al, 2008 (18)	1999-2003	240	NR
Historically controlled trial			
Freedman et al, 2006 (16)	2003-2004 1985-2000	133	NR
Prospective cohort study			
Morganti et al, 2009 (19)	NR	332	NR
Randomized controlled trial			
Pignol et al, 2008 (20)	2003-2005	331	CIHR Grant MCT-63156

Note: NR, not reported; RCT, randomized controlled trial, CIHR, Canadian Institutes of Health Research.

Table 2 describes 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.

Table 2. Details of included studies.

Author, year published	Comparison	Dose	Total N	Disease Stage	Median follow-up (months)	Outcomes reported
Retrospective cohort study						
Freedman et al, 2009 (21)	IMRT TanRT	46-50 Gy/2f+14-20 Gy 46-50 Gy/+10-18 Gy	399 405	T0-2	NR	AE
Harsolia et al, 2007 (17)	IMRT TanRT	45 Gy/1.8f+16 Gy/2f 45 Gy/1.8f+16 Gy/2f	93 79	T0-2B	56.4	AE
McDonald et al, 2008 (18)	IMRT TanRT	50 Gy [37-68 Gy] 50 Gy [44-50.4 Gy]	121 124	T0-3	75.6 90	TRO AE
Historically controlled trial						
Freedman et al, 2006 (16)	IMRT TanRT	60 Gy/2f [60-66] 64 Gy/2f [50-64]	73 60	T0-2	NR	AE
Prospective cohort study						
Morganti et al, 2009 (19)	MARA1-IMRT MARA2-IMRT TanRT	40 Gy/2.5f+4 Gy/0.25f 50 Gy/2f+10 Gy/0.40/f 50.4 Gy/1.8f+10 Gy/2.5f	99 102 131	pT1-3 pT1-4	24 24 42	TRO AE
Randomized controlled trial						
Pignol et al, 2008 (20)	IMRT TanRT (WC)	50 Gy/2f 50 Gy/2f	170 161	Early stage breast cancer	NR	AE

Note: IMRT, intensity modulated radiotherapy; TanRT, tangential radiotherapy; Gy, Gray; f, fraction; T, tumour; NR, not reported; AE, adverse effects; TRO, treatment-related outcomes; p, pathologic.

Table 3 outlines the technical aspects 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 (e.g., whole breast), the planned target volume margin expansion (mm), and the image guidance method used (e.g., none, implanted fiducial markers, electronic portal imaging device (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 study						
Freedman et al, 2009 (21)	Inverse-planned	Step & shoot	Combination of open and segmented fields	Whole breast with and without regional nodal expansion	20 mm in the superior, inferior, and lateral directions	CT and fluoroscopy
Harsolia et al, 2007 (17)	(Pinnacle)	Beam's eye	Coplanar tangential beams	Breast and lumpectomy cavity	10-20mm	CT

McDonald et al, 2008 (18)	Forward-planned (CadPlan)	NR	Medial and lateral tangential fields	Whole breast	20mm	CT
Historically controlled trial						
Freedman et al, 2006 (16)	NR	Step & shoot	Tangential fields delivered via multileaf collimators	NR	20 mm in the superior, inferior, and lateral directions	CT and fluoroscopy
Prospective cohort study						
Morganti et al, 2009 (19)	Forward-planned (Plato)	NR	Tangential beams	Whole breast	8mm in the cranial, caudal, medial, and lateral directions	CT
Randomized controlled trial						
Pignol et al, 2008 (20)	Inverse (Toronto) and forward-planned (Vancouver)	NR	NR	NR	NR	CT

Note: mm, millimetres; CT, computed tomography; NR, not reported.

Study Quality

The six included papers included one RCT (20), three retrospective cohort studies (17,18,21), one historically controlled trial (16), and one prospective cohort study (19). The reported quality of the RCT by Pignol et al (20) was acceptable, with all components fully detailed except length of follow-up. The other study designs 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.

None of the non-randomized studies (16-19,21) reported on groups that had a disproportionate number of patients in one of the groups. All five of the non-randomized studies identified prognostic factors that were used to determine differences in the baseline characteristics of each group. Four (16-18,21) of these studies detected differences in the baseline characteristics. The retrospective cohort study by Freedman et al (21) reported differences between the groups for bra size (any D or 40+, 36% IMRT: 26 tangential RT [TanRT]; $p<0.0001$), chest wall separation (22.2 IMRT: 21.4 TanRT; $p=0.002$), tumour stage (19.5 IMRT: 12% TanRT; $p=0.02$), chemotherapy received (no, 57% IMRT: 67% TanRT; $p=0.005$ and yes [before radiation], 40% IMRT: 29% TanRT; $p=0.006$), and tamoxifen received (yes [before or current with radiation], 17.5% IMRT: 54% TanRT; $p=0.006$). The retrospective cohort study by Harsolia et al (17) reported differences in mixed beams (yes, 32% IMRT: 9% TanRT; $p<0.05$ and no, 68% IMRT: 91% TanRT; $p<0.05$). The retrospective cohort study reported by McDonald et al (18) reported differences in adjuvant hormonal treatment received (no, 62% IMRT: 8% TanRT). The historically controlled trial reported by Freedman et al (16) matched IMRT patients with a control group according to bra size and chest wall separation, but due to the two different time periods that the two patients groups belonged to, the systemic therapies administered differed both in type and dosage pattern. The IMRT

patients received chemotherapy before radiation, started tamoxifen after radiation, and typically received an adriamycin-based regimen. In contrast, the TanRT patients received chemotherapy both before and after radiation, started tamoxifen concurrently with radiation, and typically received a cytoxan/methotrexate/5-fluorouracil-based regimen. The prospective cohort study by Morganti et al (19) reported no differences between groups.

None of the retrospective cohort studies adjusted the comparison groups according to the measured prognostic factors (17,18,21). The historically controlled trial (16) achieved parity between the groups by matching IMRT patients with patients who received conventional radiation on a 1:1 basis. The prospective cohort study (19) reported no differences between groups; therefore, no adjustments were necessary.

Table 4 describes the components of quality for the RCT.

Table 4. Study quality, RCT.

Study	Pignol JP et al, 2008 (20)
Randomization	Stratified by use of boost and breast size and blocked 1:1 to ensure balance
Blinding	Double-blinded
Analysis details	Toxicity was compared using the X^2 test with a two-sided level of significance at 5%. Multivariate logistic regression models were used to explore the factors associated with moist desquamation
Expected effect size and power calculation details	The minimum sample that would provide 80% power was determined to be 308 patients. A total sample size of 340 was planned to allow for drop-outs and losses to follow-up
Length of follow-up (months)	NR
Differences in patient characteristics	The treatment arms were balanced for clinical and treatment factors

Note: NR, not reported.

Outcomes: Treatment-Related

Only two of the obtained papers reported on any treatment-related outcomes, the retrospective cohort study by McDonald et al (18), with a total of 240 patients, and the prospective cohort study by Morganti et al (19), with a total of 332 patients. McDonald et al (18) compared IMRT with TanRT, and Morganti et al compared two different IMRT regimens with TanRT. Neither of these studies reported statistically significant differences between treatment groups for contralateral breast cancer rates, clinical recurrence-free survival, or disease-specific survival. Treatment-related outcomes appear in Table 5.

Table 5: Treatment-related outcomes.

Author, year published	Comparison	Freedom from contralateral breast cancer recurrence %	Clinical recurrence-free survival %	Disease-specific survival %
Retrospective cohort study				
McDonald et al, 2008 (18)	IMRT	96±2.7	95±2.9	97±2.2
	TanRT	98±1.6 p=0.99	90±3.3 p=0.36	95±2.4 p=0.42
Prospective cohort study				
Morganti et al, 2009 (19)	MARA1-IMRT	NR	100	100
	MARA2-IMRT	NR	100	100
	TanRT	NR	100	100

Note: IMRT, intensity modulated radiotherapy; TanRT, tangential radiotherapy; NR, not reported.

Outcomes: Adverse Effects

Acute Adverse Effects

All six of the obtained papers reported on acute adverse effects (16-21) (Table 6). The three retrospective cohort studies reported on acute dermatitis (17,18,21). All three reported significant benefits associated with the use of IMRT compared with TanRT: Freeman et al (21) (804 patients total) (Grade 2-3: 52% versus [vs.] 75%, p<0.0001), Harsolia et al (17) (172 patients total) (Grade 2+: 41% vs. 85%, p<0.001), and McDonald et al (18) (240 patients total) (Grade 2-3: 39% vs. 52%, p=0.047). A subgroup analysis performed by Freedman et al (21) detected significant improvements in Grade 2-3 dermatitis, favouring IMRT over TanRT for all patients regardless of breast size (small, medium, and large, all p<0.05).

Only the retrospective cohort study by Freedman et al (21) reported on the proportion of treatment time with acute dermatitis, finding a significant benefit for IMRT compared with TanRT (18% vs. 71%, p<0.0001).

Two studies reported on moist desquamation (16,20). Both reported significant differences for IMRT compared with TanRT: the historically controlled trial reported by Freedman et al (16) (21% vs. 38%, p=0.001) and the RCT reported by Pignol et al (20) (31.2% vs. 47.8%, p=0.002). The RCT also reported on moist desquamation in the inframammary crease and detected a significant benefit for IMRT over TanRT (26.5% vs. 43.5%, p=0.001).

The retrospective cohort study reported by Harsolia et al (17) detected significant benefits favouring IMRT over TanRT for breast edema (1% vs. 28%, p<0.001) and hyperpigmentation (5% vs. 50%, p<0.001).

The retrospective cohort study reported by Morganti et al (19) reported a significant benefit favouring the MARA1-IMRT regimen over TanRT for all skin-related acute toxicity effects (p<0.05), albeit with a lower total dose.

Late Adverse Effects

Only the retrospective cohort studies reported by Harsolia et al (17) (172 patients total) and McDonald et al (18) (240 patients total) reported on late toxicity effects. The Harsolia study demonstrated a significant difference between IMRT and TanRT in favour of IMRT for breast edema (IMRT, 1% vs. TanRT, 25%; p<0.001), with no differences in fat necrosis, induration/fibrosis, or cosmesis. The study by McDonald et al (18) found a trend towards a reduction in lymphedema rates (p=0.06), with no reduction in pneumonitis, fat necrosis, or second malignancies.

Table 6: Adverse effects.

Author, year published	**Adverse effects**			
Retrospective cohort study				
Freedman et al, 2009 (21)	Acute dermatitis			
		IMRT %	TanRT %	p-value
	Grade 0/1	48	25	**<0.0001**
	Grade 2/3	52	75	
	Time with acute dermatitis			
	Grade 0/1	82	29	**<0.0001**
	Grade 2/3	18	71	
	Subgroup analysis detected significant improvements in Grade 2/3 toxicity in favour of treatment with IMRT for patients with small (**p=0.0015**), medium (**p<0.0001**), and large (**p<0.0001**) breast sizes.			

Harsolia et al, 2007 (17)	Acute toxicity (Grade ≥2)			
		IMRT %	TanRT %	p-value
	Dermatitis	41	85	**<0.001**
	Breast edema	1	28	**<0.001**
	Pain	8	8	0.78
	Hyperpigmentation	5	50	**<0.001**
	Late toxicity (Grade ≥2)			
	Hyperpigmentation	7	17	0.06
	Breast edema	1	25	**<0.001**
	Fat necrosis	0	1	0.46
	Induration/fibrosis	0	6	0.11
	Good/excellent cosmesis	99	97	0.60
McDonald et al, 2008 (18)	Acute toxicity (RTOG Scale)			
		IMRT %	TanRT %	p-value
	Grade 2-3 dermatitis	39	52	**0.047**
	Breast cellulitis	2	4	0.45
	Late toxicity			
	Radiation pneumonitis	1	2	1.0
	Lymphedema	0	4	0.06
	Fat necrosis	0	2	0.5
	Second malignancy	3	4	0.84
Historically controlled trial				
Freedman et al, 2006 (16)	Acute skin toxicity	IMRT %	TanRT %	
	CTC Grade			
	0	0	0	
	1	30	28	
	2	70	72	
	3+	0	0	
	p-value	p>0.05		
	Grade of erythema			
	0- None	0	0	
	1- Mild	33	32	
	2- Moderate/severe	67	68	
	p-value	p>0.05		
	Grade of desquamation			
	0- None	42	52	
	1- Dry	37	10	
	2- Moist	21	38	
	p-value	**p=0.001**		
Prospective cohort study				
Morganti et al, 2009 (19)	Acute skin toxicity			
		MARA1-IMRT %	MARA2-IMRT %	TanRT %
	Grade			
	0	NR	NR	NR
	1	NR	NR	NR
	2	13.1	45.1	33.6
	3	1.0	2.0	3.1
	MARA1 vs. TanRT: OR=0.28, **p=0.0002** in favour of MARA1			

	MARA2 vs. TanRT: OR=1.47, p=0.16			
Randomized controlled trial				
Pignol et al, 2008 (20)	Acute toxicity			
		IMRT %	TanRT (WC) %	p-value
	Skin toxicity (Grade 3-4, NCI CTC 2.0)	27.1	36.7	0.06
	Moist desquamation (all breast)	31.2	47.8	**0.002**
	Moist desquamation, inframammary crease	26.5	43.5	**0.001**
	Pain (Grade 2-4, NCI CTC 2.0)	23.5	25.5	0.68

Note: IMRT, intensity modulated radiotherapy; TanRT, tangential radiotherapy; CTC, Common Toxicity Criteria; NR, not reported; RTOG, Radiation Therapy Oncology Group; NCI, National Cancer Institute (U.S.); vs., versus.

ONGOING TRIALS

The National Cancer Institute (NCI) clinical trials database (located at: http://www.cancer.gov/clinicaltrials) was searched on May 12, 2009 for listings of relevant trials. The details of the four relevant trials that were found appear in Table 7.

Table 7: Ongoing trials.

Post-operative radiation with IMRT in the management of Stage IIB-III breast cancer Phase: Phase II, Phase I Type: Treatment Status: Active Age: 18 and over Sponsor: Other Protocol IDs: 2006277-01H, OTT 06-03, NCT00508352 Description: The purpose of this trial is to improve on the results of conventional radiation by decreasing the amount of radiation-induced toxicity in patients with stage IIb-III breast cancer.
Partial breast radiation to the lumpectomy cavity with IMRT in elderly women Phase: Phase II, Phase I Type: Treatment Status: Active Age: 65 and over Sponsor: Other Protocol IDs: VCC0601, NCT00337064 Description: The goal of this study is to determine the toxicity and efficacy of giving the radiation in a shorter time, using higher daily doses of radiation.
Phase III randomized study of intensity-modulated radiotherapy in women who have undergone breast conservation surgery and systemic therapy for early breast cancer Phase: Phase III Type: Treatment Status: Active Age: 18 and over Sponsor: Other Protocol IDs: ICR-IMPORT-HIGH, IMPORT HIGH, ICR-CTSU/2007/10013, ISRCTN47437448, EU-20897, NCT00818051 Description: The goal of this study is to test dose-escalated intensity-modulated radiotherapy after breast conservation surgery in women with early breast cancer who are at higher than average risk for local

recurrence.

Phase III randomized study of intensity-modulated and partial organ radiotherapy in women who have undergone breast conservation surgery for early stage breast cancer
Phase: Phase III
Type: Biomarker/Laboratory analysis, Treatment
Status: Active
Age: 50 and over
Sponsor: Other
Protocol IDs: ICR-IMPORT-LOW, IMPORT LOW, ICR-CTSU/2006/10001, ISRCTN12852634, EU-20896, NCT00814567
Description:
The goal of this study is to test partial breast radiotherapy using intensity-modulated techniques following complete local tumour excision in women with low-risk, early-stage breast cancer.

DISCUSSION

With only one (20) of six retrieved reports being a randomized trial, concerns can be raised regarding the study findings (22,23), particularly as the majority of the other studies reported retrospectively collected data.

However, in all cases, comparisons were made against standard tangent RT, to typically prescribed doses, which allows for good external validity. No studies reported on IMRT-based locoregional radiation.

In any review of the benefits of therapy, disease control is of paramount importance. Only two papers (18,19) reported on breast cancer outcomes, perhaps due to the short follow-up times in some studies. In these two studies (18,19), there appeared to be no evidence for differences in local recurrence rates, with less follow-up for patients receiving IMRT-based treatment. The study with the longest follow-up (19) reported on the IMRT group after a median time exceeding six years. Local recurrence rates were acceptable, with no evidence of increased rates of contralateral breast cancer.

Acute toxicity was the most commonly reported outcome, being reported in all six studies. Rates using standard techniques were approximately 50% or higher. Despite differences in reported outcomes, all six found a significant reduction in acute skin toxicity. Only Freedman et al (21) reported on rates of erythema and desquamation as separate issues. They found no difference in the rates of erythema, although it could be argued that this finding is of little clinical significance in that it is short lived and in and of itself does not lead to patient discomfort. Three studies reported on acute dermatitis (17,18,21), while two others reported rates of moist desquamation (16,20). As these two outcomes were reported in a mutually exclusive manner, it may be that authors are reporting the same phenomenon. In all five of these studies, the relative reduction in acute skin toxicity ranged from 25-52% (median: 35%). The remaining study (19) reported acute skin toxicity as a composite, with a 62% reduction, although this may be the result of confounding as the MARA1 group also received a reduced radiation dose. The study by Pignol et al (20) found a reduction of moist desquamation specific to the inframammary fold by 39%. This area is particularly susceptible to acute skin toxicity with standard radiation techniques, while IMRT provides a distinct dosimetric advantage through its ability to provide wedging in the superior-inferior dimension.

Despite being of greater clinical significance, late toxicity was reported in only two studies, again likely due to the short follow-up in most studies. Harsolia et al (17) found a large reduction in the rate of breast edema and a reduction of hyperpigmentation of borderline significance. Of late toxicities causing major clinical concern, McDonald et al (18) suggested that arm lymphedema may be reduced, with low numbers in both groups. This is not a major concern with tangent-only techniques. Whether this potential advantage is true

of locoregional IMRT treatments remains unknown. Serious potential late toxicities from postoperative breast tangent irradiation include pulmonary fibrosis, secondary non-breast malignancies, and cardiac mortality (17,18). Due to relatively short follow-up times and small patient numbers, it is not surprising that none of the studies reported a difference in these outcomes. Future research should aim at providing long-term data from prospective, randomized trials (20,24).

CONCLUSIONS

The available data provided by this evidence-based systematic review suggests that at similar doses IMRT is associated with reduced acute side effects when compared with standard tangential techniques. IMRT is associated with a 25-50% reduction in acute skin toxicity when compared with TanRT. There may be a reduction in late toxicity, although this is not borne out by the available studies. Based on our current understanding of IMRT radiation delivery methods, these results were expected. As IMRT has the capacity to deliver biologically effective doses to the planned target volume while avoiding nearby tissue and OAR, the expected result would be fewer adverse effects but similar treatment-related outcomes, and this evidence review continues to support this. Therefore, clinicians and patients choosing IMRT over TanRT in the treatment of breast cancer can expect significantly fewer adverse effects while experiencing similar treatment outcomes. No evidence was found to suggest that this reduction in toxicity comes at a price of higher recurrence rates, although no study was designed to address this as its primary outcome.

CONFLICT OF INTEREST

None declared.

JOURNAL REFERENCES

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

Steering Panel

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Mr. Eric Gutierrez Program Manager, Radiation Treatment Program, Cancer Care Ontario
Ms. Kate Bak Project Coordinator, Radiation Treatment Program, Cancer Care Ontario
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Dr. Peter Dixon Radiation Oncologist, Durham Regional Cancer Centre Associate Professor, Department of Oncology, Queen's University
Dr. Julie Bowen Radiation Oncologist, Radiation Treatment Program Leader, Northeastern Ontario Regional Cancer Centre

Appendix 2. Literature search strategies.

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

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1 breast cancer.mp. or exp Breast Neoplasms/ (101326)
2 imrt.mp. or exp Radiotherapy, Intensity-Modulated/ (2546)
3 protons.mp. or exp Protons/ (15329)
4 biological marker.mp. or exp Biological Markers/ (307683)
5 gene therapy.mp. or exp Gene Therapy/ (32885)
6 children.mp. or exp Child/ (528413)
7 pediatric cancer.mp. (657)
8 childhood cancer.mp. (1924)
9 exp Quality Assurance, Health Care/ or quality assurance.mp. (136285)
10 treatment plan comparison.mp. (5)
11 aperture optimization.mp. (27)
12 independent dose calculation.mp. (13)
13 EPID dosimetry.mp. (13)
14 set up errors.mp. (85)
15 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (990421)
16 1 and 2 (150)
17 1 and 15 (16645)
18 16 not 17 (133)
19 limit 18 to (english language and humans and yr="2000 - 2009") (125)
20 from 19 keep 1-125 (125)

Database: EMBASE <1996 to 2009 Week 11>

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1 breast cancer.mp. or exp Breast Cancer/ (115520)
2 imrt.mp. or exp Intensity Modulated Radiation Therapy/ (3312)
3 proton therapy.mp. or exp Proton Therapy/ (680)
4 biological marker.mp. or exp Biological Marker/ (31873)
5 gene therapy.mp. or exp Gene Therapy/ (34502)
6 quality assurance.mp. or exp Quality Control/ (110835)
7 child/ or child.mp. or children.mp. (457760)
8 exp Childhood Cancer/ or pediatric cancer.mp. (9951)
9 treatment plan comparison.mp. (5)
10 aperture optimization.mp. (28)
11 independent dose calculation.mp. (12)
12 EPID dosimetry.mp. (14)
13 set up errors.mp. (88)
14 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (628144)
15 1 and 2 (242)
16 1 and 14 (6832)
17 15 not 16 (203)
18 limit 17 to (human and english language and yr="2000 - 2009") (173)
19 from 18 keep 1-173 (173)

Appendix 3. Excluded papers (N=10).

Title	Reason(s) for exclusion
Guideline	
National Collaborating Centre for Cancer Early and locally advanced breast cancer: diagnosis and treatment February 2009	No comparative data with IMRT provided No explicit IMRT recommendations provided
Papers	
Vicini FA, Sharpe M, Kestin L, Martinez A, Mitchell CK, Wallace MF, et al. Optimizing breast cancer treatment efficacy with intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2002;54(5):1336-44.	No comparative data with IMRT provided
Fourquet A, Bollet MA, Kirova Y, Dendale R, Campana F. Optimal management of breast cancer with locoregional radiotherapy Eur J Cancer Suppl. 2005;3(3):137-47. ECCO 13 Education Book	Review
Yarnold J. Latest developments in local treatment: radiotherapy for early breast cancer Ann Oncol 2005;16(2):170-3.	Review
Pignol J, Olivotto I, Rakovitch E, Gardner S, Ackerman I, Sixel K, et al. Phase III randomized study of intensity modulated radiation therapy versus standard wedging technique for adjuvant breast radiotherapy [abstract]. Int J Radiat Oncol Biol Phys. 2006;66(3) Suppl 1;Plenary 1.	Duplicate publication: same as Pignol et al, 2008
Woo TCS, Pignol JP, Rakovitch E, Vu T, Hicks D, et al. Body radiation exposure in breast cancer radiotherapy: impact of breast IMRT and virtual wedge compensation techniques. Int J Radiat Oncol Biol Phys. 2006;65(1):52-8.	No outcomes of interest reported on
Chronowski GM, Buchholz TA. Accelerated partial breast irradiation Curr Probl Cancer. 2007;31:7-25.	Review
Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, et al. Randomized trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol. 2007;82:254-64.	No outcomes of interest reported on
Stelzer KJ, Bailey B, Davidson M, Dugick S, Mullins M. Determination of critical dosimetric parameters for breast radiation using forward-planned segmented fields for intensity modulation. Med Dosim. 2007;32(1):23-32.	Planning/dosimetry study, no outcomes of interest reported on
Haffty BG, Buchholz TA, McCormick B. Should intensity-modulated radiation therapy be the standard of care in the conservatively managed breast cancer patient? J Clin Oncol. 2008;26(13):2072-4.	Editorial (re: Pignol et al, 2008)

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

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

I. Dayes, R.B. Rumble, J. Bowen, P. Dixon, 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 27, 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). 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 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/RTP. The series is a convenient and up-to-date source of the best available evidence on the role of IMRT in breast cancer, developed through a review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel

Prior to the submission of this EBS draft report for Expert Panel review, the report was submitted to the PEBC Report Approval Panel (RAP) for review on September 10, 2009. 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:

- The inherent weaknesses of the available evidence
- The RCT evidence should be emphasized
- Resource allocation issues were noted but no supporting evidence was described

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

- The authors acknowledge that the lack of RCT evidence makes definitive recommendations problematic; however, the comparative data available do support our recommendations. Until larger patient populations are studied in a randomized setting, we are confident that the evidence included in this report comprises the most relevant data available.
- The RCT evidence is now presented separately from the other evidence.
- Gathering evidence on the resource issues associated with IMRT was beyond the scope of this report, but the authors believed it was important that the reader be made aware that there will be implications on resources should IMRT be implemented.

No resubmission was requested by RAP; however, changes were made as a result of the feedback obtained from the IMRT Expert Panel Conference, and the revised draft was submitted to the RAP for consideration. No further feedback was obtained.

Breast Cancer DSG Review

On September 9, 2009, the current draft was sent out to the 24 members of the Breast Cancer DSG concurrent with the initial RAP review. Of these 24, the two members who were

guideline authors were excluded from commenting. Of the 22 remaining members, four responded (18% response rate), and all approved of the guideline (100% approval rate) (three with no changes, and one with minor changes that were addressed).

IMRT Expert Panel Conference

On December 3, 2009, the IMRT breast guideline was presented to members of the IMRT Expert Panel (n=26), 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	11	15	0	26	0
%	42.3	57.7	0	100	0

Rate the overall quality of the guideline report							
Response	1. Lowest	2.	3.	4.	5. Highest	TOTALS	Missing
N	0	0	3	21	2	26	0
%	0	0	11.5	80.8	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	17	5	24	2
%	0	0	8.3	70.8	20.8	99.9	7.7
I would recommend this guideline for use in practice							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
N	0	0	3	18	5	26	0
%	0	0	11.5	69.2	19.2	99.9	0

RECOMMENDATIONS

1. If acute toxic effects are the main outcomes of interest, then IMRT is the recommended treatment option over tangential RT (TanRT) to patients undergoing adjuvant radiotherapy following breast-conserving surgery.							
Response	1. Lowest	2.	3.	4.	5. Highest	TOTALS	Missing
N	0	0	3	15	7	25	1
%	0	0	12	60	28	100	3.8
Do you agree with this Recommendation?							
Response	Yes	No	Unsure	TOTALS	Missing		
N	23	0	2	25	1		
%	92	0	8	100	3.8		

2. If treatment-related outcomes are the main outcomes of interest, there is no evidence to support or refute a recommendation of IMRT over TanRT to patients undergoing adjuvant RT following breast-conserving surgery.							
Response	1. Lowest	2.	3.	4.	5. Highest	TOTALS	Missing
N	0	0	2	16	7	25	1
%	0	0	8	64	28	100	3.8
Do you agree with this Recommendation?							
Response	Yes	No	Unsure	TOTALS	Missing		
N	25	1	0	26	0		
%	96	4	0	100	0		

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?
• Ambiguity as to type of IMRT being recommended (forward planned versus inverse planned), please specify.
Comments Recommendation Two:
• Specify what IMRT fields and techniques used in the recommendation. • Reword "treatment-related outcomes" as "disease-related outcomes". Comment on local control.

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 20 submitted responses (16% 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	3	11	6	20	0
%	0	0	15	55	30	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	2	2	9	7	20	0
%	0	10	10	45	35	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	3	11	6	20	0
%	0	0	15	55	30	100	0

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

Barriers:

- Availability, cost, local staff expertise, and the funding of sufficient trained staff.
- The availability of IMRT for use in breast cancer treatment at all cancer centres.
- In centres that have limited resources for planning and delivery of IMRT the use of IMRT for breast patients may not be the highest priority.

Enablers:

- The technology for IMRT is becoming more routinely available.

5. Additional comments.

No additional comments were obtained.

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time, and at its sole discretion, to change or revoke this authorization.

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