Published Ahead of Print on September 16, 2013 as 10.1200/JCO.2013.49.7842
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.49.7842

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Controlled Trial of Intensity-Modulated Radiotherapy for Early Breast Cancer: 5-Year Results Confirm Superior Overall Cosmesis

Mukesh B. Mukesh, Gillian C. Barnett, Jennifer S. Wilkinson, Anne M. Moody, Charles Wilson, Leila Dorling, Charleen Chan Wah Hak, Wendi Qian, Nicola Twyman, Neil G. Burnet, Gordon C. Wishart, and Charlotte E. Coles

Processed as a Rapid Communication manuscript.

Mukesh B. Mukesh, Gillian C. Barnett, Jennifer S. Wilkinson, Anne M. Moody, Charles Wilson, Wendi Qian, Nicola Twyman, Neil G. Burnet, and Charlotte E. Coles, Cambridge University Hospitals National Health Service Foundation Trust; Gillian C. Barnett, Charleen Chan Wah Hak, and Neil G. Burnet, University of Cambridge; and Gordon C. Wishart, Anglia Ruskin University, Cambridge, United Kingdom.

Published online ahead of print at www.jco.org on September 16, 2013.

Supported by Efficacy and Mechanism Evaluation Program Grant No. 09/150/16 from the Medical Research Council (M.B.M.), by a fellowship from Cancer Research UK and the Royal College of Radiologists (G.C.B.), by Addenbrooke's Charitable Trust (G.C.B., L.D.), by the Breast Cancer Campaign and Comprehensive Local Research Network (J.S.W.), by Cancer Research UK (L.D.), and by the Cambridge National Institute of Health Research Biomedical Research Centre (N.G.B., G.C.W., C.E.C.).

Presented at the Second European Society for Radiotherapy and Oncology Forum, Geneva, Switzerland, April 19-23, 2013.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: ISRCTN21474421.

Corresponding author: Charlotte E. Coles, MRCP, FRCR, PhD, Oncology Centre, Box 193, Cambridge University Hospitals NHS Foundation Trust, Hills Rd, Cambridge, CB2 0QQ, United Kingdom; e-mail: charlotte.coles@addenbrookes.nhs.uk.

0732-183X/13/3199-1/$20.00

DOI: 10.1200/JCO.2013.49.7842

ABSTRACT

Purpose
There are few randomized controlled trial data to confirm that improved homogeneity with simple intensity-modulated radiotherapy (IMRT) decreases late breast tissue toxicity. The Cambridge Breast IMRT trial investigated this hypothesis, and the 5-year results are reported.

Patients and Methods
Standard tangential plans of 1,145 trial patients were analyzed; 815 patients had inhomogeneous plans (≥ 2 cm^3 receiving 107% of prescribed dose: 40 Gy in 15 fractions over 3 weeks) and were randomly assigned to standard radiotherapy (RT) or replanned with simple IMRT; 330 patients with satisfactory dose homogeneity were treated with standard RT and underwent the same follow-up as the randomly assigned patients. Breast tissue toxicities were assessed at 5 years using validated methods: photographic assessment (overall cosmesis and breast shrinkage compared with baseline pre-RT photographs) and clinical assessment (telangiectasia, induration, edema, and pigmentation). Comparisons between different groups were analyzed using polychotomous logistic regression.

Results
On univariate analysis, compared with standard RT, fewer patients in the simple IMRT group developed suboptimal overall cosmesis (odds ratio [OR], 0.68; 95% CI, 0.48 to 0.96; $P = .027$) and skin telangiectasia (OR, 0.58; 95% CI, 0.36 to 0.92; $P = .021$). No evidence of difference was seen for breast shrinkage, breast edema, tumor bed induration, or pigmentation. The benefit of IMRT was maintained on multivariate analysis for both overall cosmesis ($P = .038$) and skin telangiectasia ($P = .031$).

Conclusion
Improved dose homogeneity with simple IMRT translates into superior overall cosmesis and reduces the risk of skin telangiectasia. These results are practice changing and should encourage centers still using two-dimensional RT to implement simple breast IMRT.

J Clin Oncol 31. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Radiation therapy (RT) has an established role in the management of early-stage breast cancer.[1] However, some patients develop RT-related complications, including breast fibrosis, breast shrinkage, poor breast cosmesis, and telangiectasia, which contribute to their psychological morbidity.[2] With improving breast cancer survival, there is increasing focus on reducing treatment-related complications. The use of advanced RT techniques like intensity-modulated RT (IMRT) offers an opportunity to reduce RT-related complications. The overall aim of IMRT is to improve coverage of the RT target and/or to minimize dose to surrounding normal tissues. The term IMRT covers a spectrum of techniques, ranging from relatively simple to highly complex. For the majority of patients treated with breast RT, it seems that a simple form of IMRT may be the most appropriate technique. This simple IMRT uses additional irradiation fields to smooth out the dose to the breast (ie, target). More complex IMRT techniques can produce a large volume of low-dose radiation to surrounding tissues. As a result, complex IMRT tends to be restricted to cases in which a steep dose gradient is required (eg, in patients with pectus

excavatum, who would otherwise receive unacceptably high dose to surrounding organs at risk [ie, lungs and heart]).

Studies have shown improved dose homogeneity across the breast with the use of simple and complex IMRT,[3,4] and it would be expected that improved dose homogeneity would reduce late breast tissue toxicity. However, there are few randomized controlled trial data to confirm the advantage of IMRT over standard RT in breast cancer.[5-7] Donovan et al[5] showed reduction in late breast tissue toxicity with IMRT among women who were judged to be at higher than average risk of radiation-induced toxicity based on breast size and/or breast shape. Worldwide, the practice of whole-breast RT is gradually shifting from standard two-dimensional RT to IMRT.[8,9] However, skeptics have pointed out that breast IMRT is being clinically implemented with a paucity of data on its long-term benefits.[10,11]

The large randomized Cambridge Breast IMRT trial was designed to investigate whether the correction of dose inhomogeneity using simple IMRT would decrease late breast tissue toxicity.[12] It included women with all breast sizes, and the interim results at 2 years showed statistically significant reduction in the risk of telangiectasia with IMRT as compared with standard RT.[6] However, the 2-year time point was considered insufficient for patients to experience their final level of toxicity and demonstrate the full benefits of IMRT. The preplanned long-term results of the trial at 5 years are reported here to determine if improved dose homogeneity with simple IMRT translates into clinical benefits of reduced late breast tissue toxicity.

PATIENTS AND METHODS

The single-center Cambridge Breast IMRT trial opened in April 2003 and was closed to recruitment in June 2007. The Cambridge Research Ethics Committee provided ethical approval of the study. The National Cancer Research Institute Studies group accepted this trial as a portfolio trial in April 2002, and it was adopted by the National Cancer Research Network in March 2003.

Study Population

Women with operable unilateral, histologically confirmed invasive breast cancer (T1-3, N0-1, M0) or ductal carcinoma in situ requiring RT after breast-conservation surgery were eligible for the trial (Fig 1). All patients with

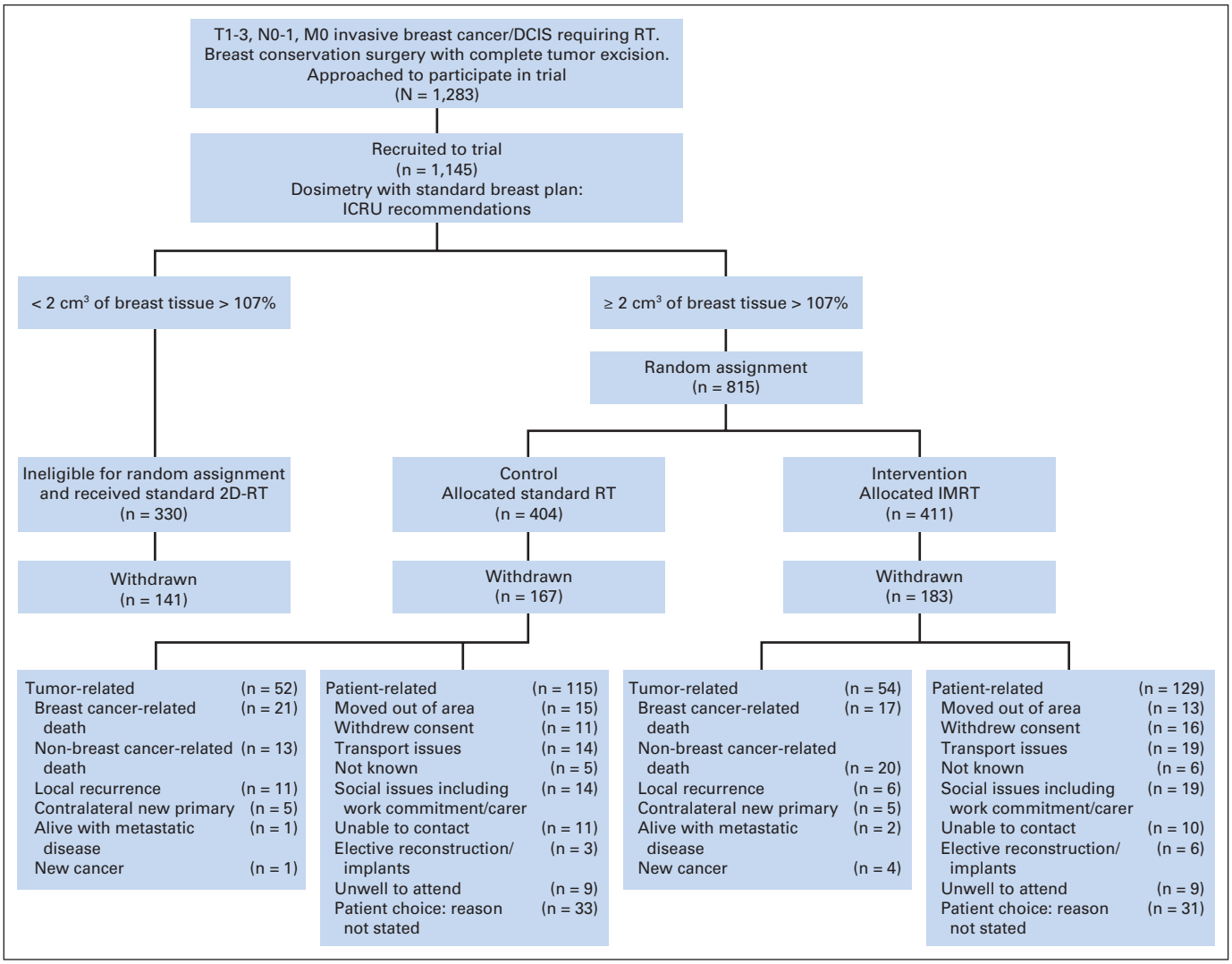

Fig 1. CONSORT diagram of Cambridge Breast Intensity-Modulated Radiotherapy (IMRT) trial. 2D, two dimensional; DCIS, ductal carcinoma in situ; ICRU, International Commission on Radiation Units; RT, radiotherapy.

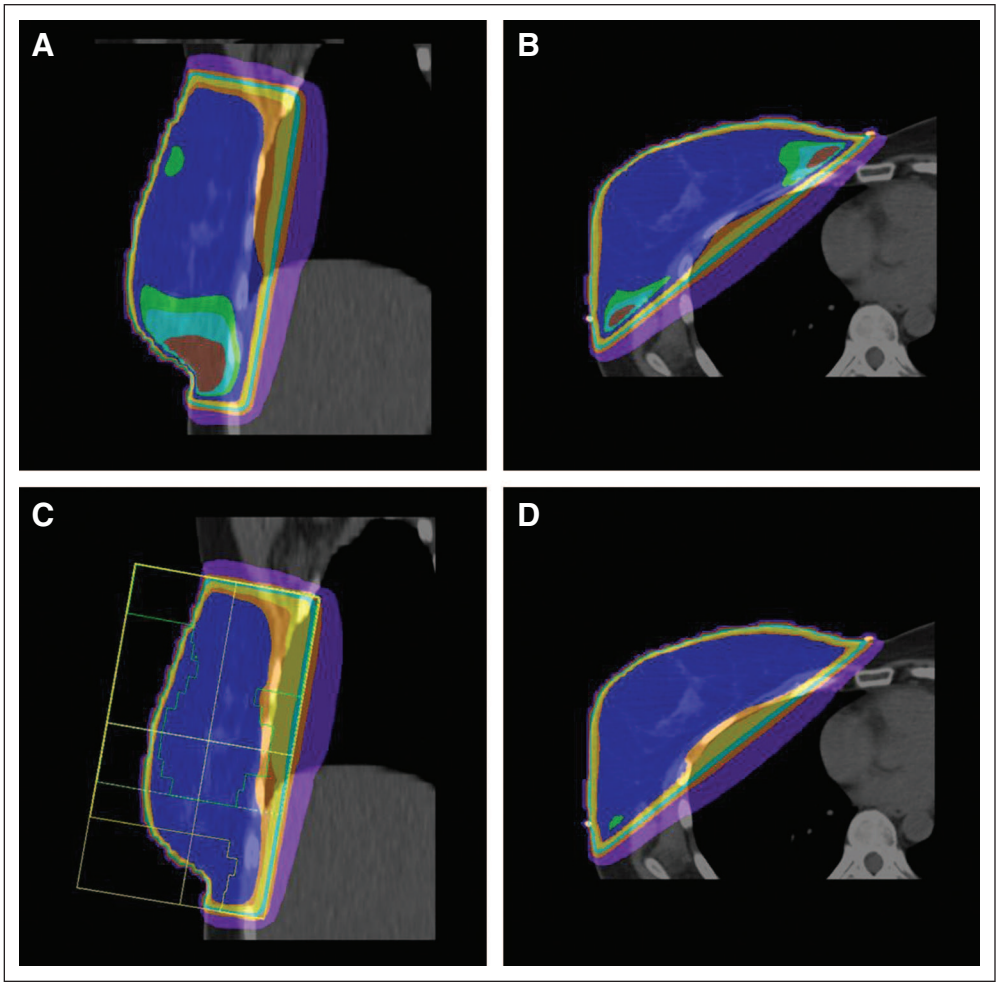

Fig 2. Comparison of dose homogeneity between standard radiotherapy (RT; control arm) and forward-planned intensity-modulated RT (IMRT; intervention arm). Blue color wash displays 95% of prescribed dose (PD), green represents 105% PD, turquoise represents 107% PD, and dark brown represents 110% PD. (A, B) Dose distribution using standard two-wedged tangential fields in (A) beam field view and (B) axial view. Regions of unplanned high dose can be seen medially, laterally, and in inframammary region. (C, D) Dose distribution with forward-planned IMRT with addition of two top-up fields. There is better dose homogeneity across breast tissue; previous regions of unplanned high dose of $\geq$ 107% of prescribed dose have been avoided.

invasive breast cancer underwent sentinel node biopsy and/or axillary clearance (if lymph node positive). Other eligibility criteria included age $>$ 18 years, no history of contralateral breast cancer, no malignancy in the previous 5 years (except skin basal cell or squamous carcinoma or in situ carcinoma of cervix), and availability for follow-up. All patients provided written informed consent. A total of 1,145 patients were recruited.

Sample Size Calculation

The sample size was based on a standard event rate of 40% in the control arm at 2 years. The difference to be detected was estimated to be 10%, with a hazard ratio of 0.7. Assuming a minimal average follow-up of 2 years, 80% power, and type I error of 0.05, 358 patients and 125 events were required in each of the randomly assigned arms. This sample size was increased by 10% to adjust for possible loss to follow-up by 2 years.

Random Assignment

A standard RT plan consisting of paired wedged tangents was produced for all trial patients. Patients with satisfactory dose homogeneity (29%) were not randomly assigned but instead treated with standard RT and observed for the same follow-up as the randomly assigned patients. Patients whose plan had significant dose inhomogeneity, defined as ≥ 2 cm^3 volume receiving $>$ 107% of the prescribed dose, were randomly assigned between standard RT (control arm) and forward-planned field-in-field dose homogenization IMRT (simple IMRT; interventional arm; Fig 2). Random assignment was performed using permuted blocks of mixed block size and was stratified for T stage and adjuvant therapy. Patients were informed of their randomly assigned arm if they enquired at the time of RT treatment.

RT Technique

Patients in the control arm were treated with wedged tangential fields to the breast, and patients in the interventional arm were replanned with a simple IMRT technique to reduce the volume receiving $>$ 107% and $<$ 95% of the prescribed dose. The full details of the RT planning technique are described in the Appendix (online only).

All patients were treated to a dose of 40 Gy in 15 fractions, 5 days per week over 3 weeks, with 6-MV photons prescribed to the ICRU (International Commission on Radiation Units) 50 reference point. Mixed energies of 6- and 15-MV photons were used in patients with large breast separation. Nodal irradiation and sequential tumor bed boost were administered according to local protocol. After completion of RT, all patients were treated similarly irrespective of their allocated treatment arm.

Outcome Measures: Breast Toxicity End Points

Patients were assessed at 2 and 5 years after completion of RT using serial photographs and clinical examination. The primary outcome of the study was photographic assessment of late cosmetic effects, and the secondary outcome was clinical assessment of breast late normal tissue changes (induration, telangiectasia, and breast edema). Toxicity assessors were unaware of a patient's treatment arm. This article reports these end points at 5 years from completion of RT.

Photographic assessment. Frontal photographs of both breasts were taken after primary surgery and before RT (baseline) and repeated at 2 and 5 years post-RT. Two photographs were taken: one with the hands resting on the

hips, and the other with the arms raised above the head. The 5-year photographs were compared with postoperative baseline photographs for RT-associated breast shrinkage and scored on a validated three-point scale (1, none/minimal; 2, mild; 3, marked). A multidisciplinary team of seven clinicians (four oncologists, one radiographer, one surgeon, and one breast care nurse) were involved in photographic assessment, with a panel of three being present at any one time. This method has been validated and shown to be quicker than using three independent scorers with rescoring of discrepancies and final resolution through discussion and was used to score the UK START (Standardisation of Breast Radiotherapy) trial photographs.[13] The interobserver variability of this assessment has been validated before by our group.[6] The panel also scored overall cosmesis on photographs taken at 5 years by assessing the global breast appearance (looking at breast shrinkage, breast distortion, and skin changes), independent of baseline cosmetic appearance. The overall breast appearance (cosmesis) was scored using a three-point score (good, moderate, and poor cosmesis) as per the United Kingdom FAST (Faster Radiotherapy for Breast Cancer Patients) study[14] and Royal Marsden Hospital IMRT trial,[5] with moderate to poor scores regarded as suboptimal cosmesis. In addition, postoperative baseline photographs were scored for surgical cosmesis using a three-point score (good, moderate, and poor). Other computerized methods for photo scoring, like BCCT (breast cancer conservative treatment).core software (Breast Research Group, Porto, Portugal),[15] were not available at the time of study design and hence not used in this study.

Clinical assessment. The treated breast was assessed at 5 years for breast edema, skin telangiectasia, breast shrinkage, pigmentation changes, and palpable induration. Each of these end points was graded from 0 to 3 (none, a little, quite a bit, very much) on the scale used in the START trials.[16,17] All 5-year clinical assessments were performed by a single trained research radiographer (J.S.W.).

The planned photographic and clinical assessments were not performed in cases of local tumor relapse, metastatic disease, new cancer diagnosis, additional breast surgery, poor health, and patient refusal. Patients who were unable to attend the 5-year follow-up appointment were contacted via telephone to assess their well being.

Statistical Analysis

The baseline demographics for patients with 5-year follow-up data were compared using the student *t* test, Pearson's χ^2 test, and Fisher's exact test for heterogeneity and trend. Toxicity end points were compared between the randomly assigned patients on univariate analysis using polychotomous logistic regression analysis. Stepwise multivariate polychotomous logistic regression was used to analyze the patient- and treatment-related factors that were significantly associated with late toxicity after RT on univariate analysis ($P < .1$). Univariate and multivariate odds ratios (ORs) were generated.

Baseline surgical cosmesis was an important determinant factor for breast toxicity end points at 2 years in this trial.[6] Hence, data from all trial patients (those randomly assigned and not randomly assigned) were used to assess the effect of baseline (pre-RT) surgical cosmesis on late toxicity end points at 5 years using polychotomous logistic regression. In addition, baseline surgical cosmesis was included in the multivariate analysis of final overall cosmesis between the randomly assigned patients.

The 5-year locoregional recurrence (LRR) and overall survival (OS) rates were compared between randomly assigned patients using the Mantel-Haenszel (log-rank) test. The length of follow-up or time to an event was measured from the date of random assignment, and analysis was performed according to intention to treat. All randomly assigned patients were included in this analysis, not just those who were available for the 5-year toxicity assessment. Details of local recurrences and deaths were obtained from local hospital and cancer registry records. All statistical analyses were performed using STATA statistical software (version 10.1; STATA, College Station, TX).

RESULTS

The late breast tissue toxicity outcomes of 654 (57%) of 1,145 patients (control arm, 237; IMRT arm, 228; non–randomly assigned arm, 189) were available at 5 years. Baseline patient, tumor, and treatment characteristics of the 654 patients are summarized in Table 1. The characteristics are well balanced between the two randomly assigned arms, with the exception of volume of breast tissue receiving > 107% of the prescribed dose (as expected). Patients in the non–randomly assigned arm were younger, with smaller tumor size, and less frequently received systemic chemotherapy. The mean breast volume was also significantly larger in the two randomly assigned arms as compared with the non–randomly assigned arm. Reasons for patients with no 5-year assessments from the study are summarized in the CONSORT diagram (Fig 1).

Five-Year Toxicity in Control (standard RT) Versus Intervention Arm (IMRT)

On univariate analysis, fewer patients in the simple IMRT arm developed suboptimal overall cosmesis (OR, 0.68; 95% CI, 0.48 to 0.96; $P = .027$) or skin telangiectasia (OR, 0.58; 95% CI, 0.36 to 0.92; $P = .021$) as compared with the control arm (Table 2). However, no significant difference was seen for photographically assessed breast shrinkage (OR, 0.79; 95% CI, 0.55 to 1.14; $P = .21$), breast edema (OR, 0.74; 95% CI, 0.48 to 1.15; $P = .18$), tumor bed induration (OR, 0.76; 95% CI, 0.54 to 1.06; $P = .11$), or pigmentation (OR, 0.80; 95% CI, 0.46 to 1.38; $P = .42$) between the randomly assigned patients.

On multivariate analysis, the benefits of simple IMRT over standard RT (control arm) were maintained for both overall cosmesis (OR, 0.65; 95% CI, 0.44 to 0.98; $P = .038$) and skin telangiectasia (OR, 0.57; 95% CI, 0.34 to 0.95; $P = .031$). Large breast volume ($P = .02$), poorer baseline surgical cosmesis ($P < .001$), and tumor bed boost ($P = .003$) were also associated with suboptimal overall cosmesis on multivariate analysis. Skin telangiectasia was also associated with older age ($P = .005$), postoperative breast infection ($P < .001$), increasing breast volume ($P < .001$), and tumor bed boost ($P = .023$). The full details of the covariates included in the multivariate analysis are summarized in Appendix Tables A1 and A2 (online only).

Impact of Pre-RT Surgical Cosmesis on Late Toxicity End Points

Patients with moderate to poor baseline surgical cosmesis more frequently developed suboptimal final cosmesis (OR, 8.15; 95% CI, 6.09 to 10.92; $P < .001$), tumor bed induration (OR, 1.80; 95% CI, 1.44 to 2.26; $P < .001$), and photographically assessed breast shrinkage (OR, 1.54; 95% CI, 1.21 to 1.96; $P < .001$) at 5 years in the study.

LRR and OS

There was no statistically significant difference in 5-year LRR and OS rates between the randomly assigned patients (control arm, 404 patients; IMRT arm, 410 patients). The 5-year LRR rates for the control and IMRT arms were 2.56% and 1.35% respectively ($P = .36$). The 5-year OS rates for the control and IMRT arms were 92.5% and 91.7%, respectively ($P = .88$).

DISCUSSION

This large single-center trial confirms that improved dose homogeneity with simple IMRT decreases late breast tissue toxicity. At 5 years, patients receiving simple IMRT had superior overall cosmesis and reduced risk of skin telangiectasia as compared with patients receiving

Table 1. Patient, Tumor, and Treatment Characteristics of Patients With 5-Year Toxicity Data (n = 654)

Characteristic	Non–Randomly Assigned		Randomly Assigned				*P* for Heterogeneity*	
			Control Arm		IMRT Arm		Randomly Assigned Versus Non–Randomly Assigned	Control Versus IMRT
	No.	%	No.	%	No.	%		
Age, years							**.003**	.12
Mean	57		60		58			
Range	27-82		33-80		34-78			
Diabetes mellitus							.19	
No	178	94	214	90	213	93		
Yes	5	3	14	6	9	4		
Unknown	6	3	9	4	6	3		
Smoking status							.33	
No	163	86	208	88	205	90		
Yes	24	13	25	11	22	10		
Unknown	2	1	4	2	1	1		
Cardiovascular disease							.84	
No	171	90	211	89	207	91		
Yes	13	7	18	8	16	7		
Unknown	5	3	8	3	5	2		
Postoperative infection requiring antibiotics							.67	
No	144	76	180	76	176	77		
Yes	42	22	51	22	44	19		
Unknown	3	2	6	3	8	4		
Postoperative hematoma							.65	
No	151	80	189	80	182	80		
Yes	16	8	18	8	16	7		
Unknown	22	12	30	13	30	13		
Tumor size, mm							**.01**	.54
Mean	14.5		16		16.4			
Range	2-40		0-40		2-45			
Histology							.48	
DCIS	19	10	22	9	22	10		
Ductal carcinoma	134	71	156	66	155	68		
Lobular carcinoma	13	7	23	10	26	11		
Other invasive histology	16	8	25	11	20	9		
Unknown	7	4	11	5	5	2		
Histologic grade							.34†	.34
1	49	26	56	24	42	18		
2	86	46	109	46	111	49		
3	32	17	44	19	49	22		
Unknown	22	12	28	12	26	11		
Axillary surgery							.57	
No	18	10	18	8	20	9		
Yes	170	90	218	92	208	91		
Unknown	1	0.5	1	0.5	0	0		
Breast volume, cm^3							**< .001**	.12
Mean	710		1,339		1,260			
Range	136-1,974		329-3,179		285-3,436			
V107, cm^3‡							**< .001**	**< .001**
Mean	0.55		43.5		9.6			
Range	0-2		0-540		0-369			
Tumor bed boost							.18	
No	65	34	99	42	87	38		
Yes	124	66	138	58	141	62		
Radiotherapy (axilla)							.51	
No	189	100	235	99	228	100		
Yes	0	0	2	1	0	0		
Radiotherapy (SCF)							.46	
No	184	97	226	95	224	98		
Yes	5	3	11	5	4	2		

(continued on following page)

Table 1. Patient, Tumor, and Treatment Characteristics of Patients With 5-Year Toxicity Data (n = 654) (continued)

Characteristic	Non–Randomly Assigned		Randomly Assigned				*P* for Heterogeneity*	
			Control Arm		IMRT Arm		Randomly Assigned Versus Non–Randomly Assigned	Control Versus IMRT
	No.	%	No.	%	No.	%		
Tamoxifen							.51	
No	63	33	63	27	76	33		
Yes	126	67	165	70	149	65		
Unknown	0	0	9	4	3	1		
Aromatase inhibitor							.44	
No	178	94	214	90	204	89		
Yes	11	6	15	6	19	8		
Unknown	0	0	8	3	5	2		
Chemotherapy							**.03**	.74
No	163	86	182	77	181	79		
Yes	26	14	50	21	46	20		
Unknown	0	0	5	2	1	1		

Abbreviations: DCIS, ductal carcinoma in situ; IMRT, intensity-modulated radiotherapy; SCF, supraclavicular fossa; V107, breast volume receiving > 107% of prescribed dose.
*Fisher's exact test.
†$P = .18$ for trend.
‡Breast volume receiving > 107% of the prescribed dose.

standard RT. However, no significant difference was observed for photographically assessed breast shrinkage or clinically assessed breast edema, breast pigmentation, or breast induration.

To date, only two other randomized trials have compared standard RT with IMRT for early breast cancer. The multicenter Canadian study compared acute toxicity for 331 patients randomly assigned after breast-conservation surgery between IMRT (forward or inverse planned) and standard RT using wedges.[7] Patients in the IMRT arm experienced significantly less moist desquamation during or up to 6 weeks post-RT as compared with standard treatment (31.2% *v* 47.8%; $P = .002$). Women of all breast sizes were included in the study, and on multivariate analysis, use of IMRT and small breast size were significantly associated with decreased risk of moist desquamation. Late toxicity has not yet been reported. Donovan et al[5] reported a single-center study in which 306 patients were randomly assigned between forward-planned IMRT and standard RT. Of the 240 patients evaluated at 5 years, patients who received standard RT were 1.7× more likely to develop any change in breast appearance on photographic assessment (95% CI, 1.2 to 2.5; $P = .008$) as compared with patients treated with IMRT. In addition, fewer patients developed palpable induration in the center of the breast, pectoral fold, inframammary fold, and boost site with IMRT. Retrospective case-matched studies have also compared standard RT with IMRT for breast cancer (Appendix Table A3, online only).

Fewer patients developed breast induration with IMRT in the Donovan et al[5] study; however, a similar reduction in induration was not seen in the interventional arm of the larger Cambridge Breast IMRT trial. The different entry criteria for the two trials may explain these dissimilar results. In the Donovan et al study, women were eligible if they were judged to be at higher than average risk of radiation-induced toxicity based on breast size and/or breast shape. The mean percentages of breast volumes receiving > 105% of the prescribed dose between standard and IMRT arm were 11.7% versus 1%, respectively.[18] In contrast, women of all breast sizes were eligible

Table 2. Comparison of Skin Telangiectasia and Overall Final Cosmesis Between Control and IMRT Arms at 5 Years

Effect	Control Arm		IMRT Arm		Univariate Analysis		Multivariate Analysis	
	No.	%	No.	%	OR*	*P*	OR*	*P*
Skin telangiectasia					0.58	.021	.57	.031
None	179	76	193	85				
A little	24	10	16	7				
Quite a bit	18	8	12	5				
Very much	14	6	7	3				
Overall final cosmesis					0.68	.027	0.65	.038
Good	84	37	95	43				
Moderate	95	41	102	45				
Poor	50	22	26	12				

Abbreviations: IMRT, intensity-modulated radiotherapy; OR, odds ratio.
*Based on polychotomous logistic regression analysis.

for the Cambridge Breast IMRT trial, if their breast volume receiving > 107% of the prescribed dose was ≥ 2 cm^3 on a standard RT plan. The mean percentage of breast volume receiving > 107% of the prescribed dose was only 2.9% in the control arm of the trial, which decreased to 0·6% with IMRT.[12] It is also possible that these dissimilar results resulted from the subjective nature of clinical assessment, with different interpretation of induration between clinicians of the two studies.

Our study found tumor bed boost to be an independent risk factor for suboptimal cosmesis and skin telangiectasia, as previously shown in the EORTC (European Organisation for Research and Treatment of Cancer) 22881-10882 boost-versus–no boost trial.[19] Large-breasted women more frequently develop late breast tissue toxicity, and this has been linked to their suboptimal dosimetry.[20] Our study found large breast volume to be a risk factor for suboptimal cosmesis and skin telangiectasia, independent of dose inhomogeneity. Similar results were also seen in the UK FAST hypofractionated trial at 2 years.[21] The FAST Trialists group postulated that in large-breasted women, the major component of the breast is adipose tissue, which is perhaps more sensitive to the effects of RT and hence more likely to develop late toxicity. However, one should also note that in postmenopausal patients, the major component of the breast is usually adipose tissue regardless of breast size.

Our study also highlights the importance of optimal surgical cosmesis, because patients with moderate to poor surgical cosmesis are more likely to develop breast shrinkage, breast induration, and suboptimal final cosmesis.

The local control and survival rates with both standard RT and IMRT are excellent. It is generally accepted that simple IMRT, which removes regions of high radiation dose should not affect local control and/or survival rates. Therefore, this trial was not intended to detect a difference in local control and/or survival rates between standard RT and IMRT. However, it has been postulated that removing hotspots with IMRT can lead to dose de-escalation, especially to the skin, and a theoretic increased risk of local relapse.[22] At 5 years, there was no statistical difference in LRR and OS rates between the randomly assigned patients of the study.

Our study has some limitations. A significant number of patients were withdrawn from the 5-year analysis. The routine clinical follow-up of patients post-RT was based at their regional referring hospitals, and many patients turned down their 5-year trial appointment at Cambridge because of travel difficulties, social issues, or personal choice (Fig 1). Patients were also withdrawn from the analysis because of cancer-related factors, including local or systemic relapse, new cancer, or death. The referral hospitals were contacted for information on LRR, metastasis, and survival, but data on late breast tissue toxicity were not available routinely.

In conclusion, the 5-year results from this study are practice changing. Improved dose homogeneity with simple IMRT translates into superior overall cosmesis and reduces the risk of skin telangiectasia 5 years after breast RT. Although breast IMRT has been implemented by many centers, there has not been universal adoption of this technique to date. This study should act as an evidence-based lever for change for RT centers that have yet to implement breast IMRT. In addition, surgical cosmesis should be optimized before RT delivery, becuase this also has a significant effect on late breast toxicity and overall cosmesis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Anne M. Moody, Charles B. Wilson, Nicola Twyman, Neil G. Burnet, Charlotte E. Coles
Collection and assembly of data: Mukesh B. Mukesh, Gillian C. Barnett, Jenny S. Wilkinson, Anne M. Moody, Charles B. Wilson, Charleen Chan Wah Hak, Charlotte E. Coles
Data analysis and interpretation: Mukesh B. Mukesh, Gillian C. Barnett, Jenny S. Wilkinson, Anne M. Moody, Charles B. Wilson, Leila Dorling, Wendi Qian, Gordon C. Wishart, Charlotte E. Coles
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Darby S, McGale P, Correa C, et al: Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 378:1707-1716, 2011
2. Al-Ghazal SK, Fallowfield L, Blamey RW: Does cosmetic outcome from treatment of primary breast cancer influence psychosocial morbidity? Eur J Surg Oncol 25:571-573, 1999
3. Kestin LL, Sharpe MB, Frazier RC, et al: Intensity modulation to improve dose uniformity with tangential breast radiotherapy: Initial clinical experience. Int J Radiat Oncol Biol Phys 48:1559-1568, 2000
4. Vicini FA, Sharpe M, Kestin L, et al: Optimizing breast cancer treatment efficacy with intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 54:1336-1344, 2002
5. Donovan E, Bleakley N, Denholm E, et al: Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol 82:254-264, 2007
6. Barnett GC, Wilkinson JS, Moody AM, et al: Randomized controlled trial of forward-planned intensity modulated radiotherapy for early breast cancer: Interim results at 2 years. Int J Radiat Oncol Biol Phys 82:715-723, 2012
7. Pignol JP, Olivotto I, Rakovitch E, et al: A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol 26:2085-2092, 2008
8. van der Laan HP, Hurkmans CW, Kuten A, et al: Current technological clinical practice in breast radiotherapy: Results of a survey in EORTC-Radiation Oncology Group affiliated institutions. Radiother Oncol 94:280-285, 2010
9. Smith BD, Pan IW, Shih YC, et al: Adoption of intensity-modulated radiation therapy for breast cancer in the United States. J Natl Cancer Inst 103:798-809, 2011
10. Kachnic LA, Powell SN: IMRT for breast cancer: Balancing outcomes, patient selection, and resource utilization. J Natl Cancer Inst 103:777-779, 2011
11. McCormick B, Hunt M: Intensity-modulated radiation therapy for breast: Is it for everyone? Semin Radiat Oncol 21:51-54, 2011
12. Barnett GC, Wilkinson J, Moody AM, et al: A randomised controlled trial of forward-planned radiotherapy (IMRT) for early breast cancer: Baseline characteristics and dosimetry results. Radiother Oncol 92:34-41, 2009
13. Haviland JS, Ashton A, Broad B, et al: Evaluation of a method for grading late photographic change in breast appearance after radiotherapy for early breast cancer. Clin Oncol (R Coll Radiol) 20: 497-501, 2008
14. Agrawal RK, Alhasso A, Barrett-Lee PJ, et al: First results of the randomised UK FAST trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). Radiother Oncol 100:93-100, 2011
15. Cardoso MJ, Cardoso J, Amaral N, et al: Turning subjective into objective: The BCCT.core software for evaluation of cosmetic results in breast cancer conservative treatment. Breast 16:456-461, 2007
16. Bentzen SM, Agrawal RK, Aird EG, et al: The UK Standardisation of Breast Radiotherapy (START)

Trial B of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. Lancet 371:1098-1107, 2008

17. Bentzen SM, Agrawal RK, Aird EG, et al: The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. Lancet Oncol 9:331-341, 2008

18. Donovan EM, Bleackley NJ, Evans PM, et al: Dose-position and dose-volume histogram analysis of standard wedged and intensity modulated treatments in breast radiotherapy. Br J Radiol 75:967-973, 2002

19. Vrieling C, Collette L, Fourquet A, et al: The influence of the boost in breast-conserving therapy on cosmetic outcome in the EORTC "boost versus no boost" trial: EORTC Radiotherapy and Breast Cancer Cooperative Groups—European Organisation for Research and Treatment of Cancer. Int J Radiat Oncol Biol Phys 45:677-685, 1999

20. Moody AM, Mayles WP, Bliss JM, et al: The influence of breast size on late radiation effects and association with radiotherapy dose inhomogeneity. Radiother Oncol 33:106-112, 1994

21. Goldsmith C, Haviland J, Tsang Y, et al: Large breast size as a risk factor for late adverse effects of breast radiotherapy: Is residual dose inhomogeneity, despite 3D treatment planning and delivery, the main explanation? Radiother Oncol 100:236-240, 2011

22. De Neve W, De Gersem W, Madani I: Rational use of intensity-modulated radiation therapy: The importance of clinical outcome. Semin Radiat Oncol 22:40-49, 2012

Acknowledgment

We thank all the women who participated in the study and the physicians, nurses, radiographers, and physicists who were involved in their care. We would also like to thank Tony Geater for helping with the images, Richard Hardy for helping with the trial database, and Carol McQuade for her assistance with the photographic assessments.

Appendix

Details of Standard Radiotherapy and Simple Intensity-Modulated Radiotherapy Technique Used in Study

Standard radiotherapy plan. A whole-breast planning target volume (PTV) was first contoured for the patient using a field-based approach. The PTV consisted of the volume of breast enclosed by the field: 5 mm from the skin surface, the lung–chest wall interface/posterior field edge, and superior and inferior field margins. A standard plan consisting of paired wedged tangents using 6-MV photons was produced for the patient. Mixed energies of 6- and 15-MV photons were sometimes used in patients with larger breast separations, and dose calculations were performed using a correction for lung inhomogeneity.

Simple intensity-modulated radiotherapy plan. The simple, manual forward-planned intensity-modulated radiotherapy (IMRT) plan[12] built on the original standard treatment plan by adding additional top-up fields to shield high-dose areas and boost areas of lower dose. These additional fields were based on the original treatment field sizes and were typically weighted to 10% of the original treatment beams. The dose arrays were locked, and by viewing the isodose distribution along the beam's eye view, the multileaf collimators (MLCs) were manipulated to shield the areas of the breast receiving doses $>$ 107% of the prescription (Fig 1). Occasionally, a wedge was added to the additional fields to provide a wedge in the superior/inferior direction. The isodose distributions were recalculated, and dose-volume histograms were exported and compared with the original plan. Additional adjustments to the MLC shapes and beam weightings could be made iteratively to increase the volume of the PTV receiving doses between 95% and 107% of that prescribed.

Table A1. Final Covariates Included in Multivariate Analysis for Skin Telangiectasia

Telangiectasia	OR	SE	*P*	95% CI
IMRT group	0.57	0.15	.031	0.34 to 0.95
Age	1.05	0.17	.005	1.01 to 1.08
Postoperative infection	3.53	0.91	.000	1.97 to 5.71
Breast volume	1.001	0.00022	.000	1.0009 to 1.0018
Tumor bed boost	1.86	0.51	.023	1.08 to 3.19

Abbreviations: IMRT, intensity-modulated radiotherapy; OR, odds ratio.

Table A2. Final Covariates Included in Multivariate Analysis for Final Cosmesis

Final Cosmesis	OR	SE	*P*	95% CI
IMRT group	0.65	0.13	.038	0.44 to 0.98
Breast volume	1.0004	0.00018	.020	1.000067 to 1.00078
Surgical cosmesis	8.64	1.57	.000	6.04 to 12.34
Tumor bed boost	1.89	0.40	.003	1.25 to 2.86

Abbreviations: IMRT, intensity-modulated radiotherapy; OR, odds ratio.

Table A3. Retrospective Matched Cohort Studies Comparing IMRT Versus Standard RT for Breast Cancer

Study	No. of Patients	Median Follow-Up	Acute Toxicity	Late Toxicity
Freedman GM et al: Int J Radiat Oncol Biol Phys 74: 689-694, 2009	804		Reduced risk of grade 2 to 3 acute dermatitis with IMRT (52% *v* 75%; $P < .001$)	NR
	NR		Total time spent with grade 2 to 3 dermatitis reduced with IMRT	
Morganti AG et al: Radiother Oncol 90:86-92, 2009	332	IMRT, 24 months; standard RT, 42 months	Lower grade 2 to 3 skin toxicity in MARA-1 arm compared with C-RT (14.1% *v* 36.7%)*	NR
			Higher grade 2 to 3 skin toxicity in MARA-2 arm compared with C-RT (47.1% *v* 36.7%)†	
McDonald MW et al: Int J Radiat Oncol Biol Phys 72: 1031-1040, 2008	240	IMRT, 6.3 years; standard RT, 7.5 years	Reduced risk of grade 2 to 3 skin toxicity with IMRT (39% *v* 52%; $P = .047$)	Insufficient data to report on late cosmesis
Horsolia A et al: Int J Radiat Oncol Biol Phys 68: 1375-1380, 2007	172	IMRT, 4.6 years; standard RT, 5 years	Reduced risk of grade 2 to 3 dermatitis, breast edema, and hyperpigmentation ($P < .001$) with IMRT	Reduced breast edema (1% *v* 25%; $P < .001$) and trend toward reduced hyperpigmentation with IMRT
				No difference on overall cosmetic score
Freedman GM et al: Am J Clin Oncol 29:66-70, 2006	133	NR	Reduced risk of moist desquamation with IMRT (21% *v* 38%; $P = .001$)	NR

Abbreviations: C-RT, conformal radiotherapy; IMRT, intensity-modulated radiotherapy; MARA, Modulated Accelerated Radiotherapy in Adjuvant Treatment of Breast Cancer; MARA-1, MARA protocol 1; MARA-2, MARA protocol 2; NR, not reported; RT, radiotherapy.
*60.4 Gy in 32 fractions over 6.4 weeks (C-RT) compared with 44 Gy in 16 fractions over 3.2 weeks (MARA-1).
†60.4 Gy in 32 fractions over 6.4 weeks (C-RT) compared with 60 Gy in 25 fractions over 5 weeks (MARA-2).

