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CLINICAL INVESTIGATION

RANDOMIZED CONTROLLED TRIAL OF FORWARD-PLANNED INTENSITY-MODULATED RADIOTHERAPY FOR EARLY BREAST CANCER: INTERIM RESULTS AT 2 YEARS

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Purpose: This single-center randomized trial was designed to investigate whether intensity-modulated radiotherapy (IMRT) reduces late toxicity in patients with early-stage breast cancer.
Methods and Materials: The standard tangential plans of 1,145 nonselected patients were analyzed. The patients with inhomogeneous plans were randomized to a simple method of forward-planned IMRT or standard radiotherapy (RT). The primary endpoint was serial photographic assessment of breast shrinkage.
Results: At 2 years, no significant difference was found in the development of any photographically assessed breast shrinkage between the patients randomized to the interventional or control group (odds ratio, 1.51; 95% confidence interval, 0.83–1.58; $p = .41$). The patients in the control group were more likely to develop telangiectasia than those in the IMRT group (odds ratio, 1.68; 95% confidence interval 1.13–2.40; $p = .009$). Poor baseline surgical cosmesis resulted in poor overall cosmesis at 2 years after RT. In patients who had good surgical cosmesis, those randomized to IMRT were less likely to deteriorate to a moderate or poor overall cosmesis than those in the control group (odds ratio, 0.63; 95% confidence interval, 0.39–1.03, $p = .061$).
Conclusions: IMRT can lead to a significant reduction in telangiectasia at comparatively early follow-up of only 2 years after RT completion. An important component of breast induration and shrinkage will actually result from the surgery and not from the RT. Surgical cosmesis is an important determinant of overall cosmesis and could partially mask the longer term benefits of IMRT at this early stage. © 2011 Elsevier Inc.

Breast cancer, Intensity-modulated radiotherapy, IMRT, Clinical trials.

INTRODUCTION

Radiotherapy (RT) has an established role in the management of early, invasive breast cancer to increase both locoregional control and survival (1). The current challenge has been to minimize the morbidity caused by this treatment without losing efficacy. Conventional two-dimensional RT breast plans can produce substantial dose inhomogeneities, particularly in women with larger breasts. This can result in a worse cosmetic outcome and lead to other late normal tissue side effects such as breast pain (2). These toxicities have been shown to have a considerable effect on patients' physical and psychological well-being (3).

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Conflict of interest: none.

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Intensity-modulated RT (IMRT) allows the radiation fluence to vary across the beam and can be used to improve the dose homogeneity in an irradiated volume (4). We have recently shown that the dosimetry was significantly improved with a simple method of forward-planned IMRT compared with two-dimensional RT in 815 randomized patients (5). This has been supported by many dosimetry studies that also demonstrated improvement with IMRT compared with two-field tangential RT plans. Currently, only limited randomized control trial evidence is available that these dosimetry improvements with IMRT translate into clinical benefit for these patients (6, 7). Only one randomized trial has shown a beneficial effect of forward-planned IMRT on late toxicity in patients with larger breasts (6).

The primary aim of the Cambridge Breast IMRT trial was to investigate, in a larger trial that included patients with all breast sizes, whether correction of RT dose inhomogeneities, using a simple method of forward-planned IMRT, would decrease late normal tissue toxicity in patients with early breast cancer.

METHODS AND MATERIALS

The Cambridge Breast IMRT trial opened in April 2003 and was closed to recruitment in June 2007. The trial protocol was developed at the "Methods in Clinical Cancer Research" workshop in Flims, Switzerland, in June 2001. This was jointly organized by the Federation of European Cancer Societies, the American Association for Cancer Research, and the American Society of Clinical Oncology. The protocol development included specific statistical advice for the present study. The Cambridge Research Ethics Committee provided ethical approval for the present study. The National Cancer Research Institute Radiotherapy Studies Group accepted the trial as a portfolio trial in April 2002, and it was adopted by the National Cancer Research Network in March 2003. The patient characteristics and RT technique used in the Cambridge Breast IMRT trial have been previously described (5) and have only been summarized in the present report.

Patients

Women were eligible if they had operable unilateral histologically confirmed invasive breast cancer (Stage T1-T3N0-N1M0) or ductal carcinoma *in situ* and required RT after complete macroscopic excision of the tumor using breast-conserving surgery. Other eligibility criteria included age >18 years, no history of contralateral breast cancer, no previous malignancy in the previous 5 years (except for skin basal cell or squamous carcinoma or *in situ* carcinoma of the cervix), and availability for follow-up. All patients provided written informed consent.

Sample size

A standard event rate of 40% in the control group at 2 years was assumed. 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 and 80% power, and a type I error of 0.05, 358 patients and 125 events were required in each of the randomized arms. This sample size was increased by 10% to adjust for possible loss of patient follow-up.

RT technique

Patients with significant dose inhomogeneities, defined by a $\geq$2-cm^3 volume that was >107% of the prescribed dose, were randomized to either standard breast RT (control arm) or IMRT (interventional arm). Randomization was performed by the Birmingham Clinical Trials Unit using random permuted blocks of mixed block sizes and stratified for T stage and adjuvant therapy. Patients in the control arm were treated with wedged tangential fields to the breast. The women randomized to the interventional arm underwent repeat treatment planning with a simple, manual forward-planned IMRT technique to reduce the volumes receiving

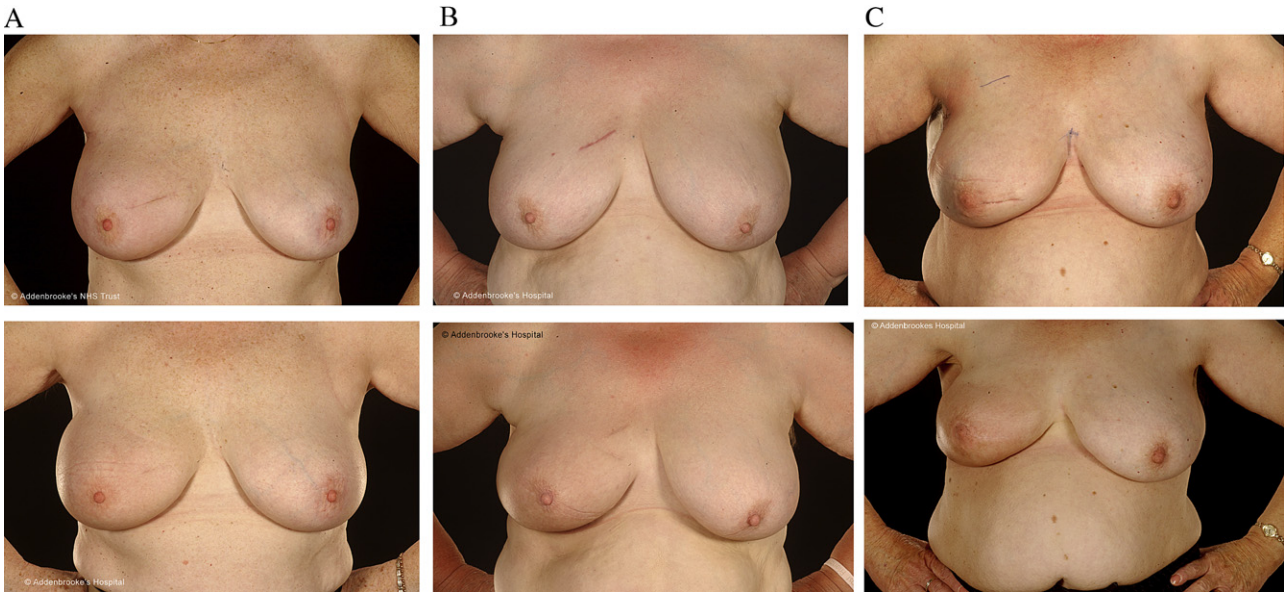

Fig. 1. Example of photographic scoring of breast shrinkage. (Top) Photographs of 3 patients immediately after surgery to right breast. (Lower) Two years after radiotherapy showing Patient A without shrinkage, Patient B with mild shrinkage, and Patient C with marked breast shrinkage.

Table 1. Patient, tumor, and treatment characteristics of 1,145 trial participants

Characteristic	Treatment group				*p*		
					Heterogeneity		
	Nonrandomized	Randomized, control	Randomised, IMRT	Total	Nonrandomized vs. randomized	Control vs. IMRT	Trend
Age (y)					< .00005		
Mean	56	59	59	58			
Range	26–82	29–81	32–84	26–84			
Breast volume (cm^3)					< .00005	.37	
Mean	728	1,341	1,305	1,154			
Range	116–2,120	329–4,194	229–3,436	116–4,194			
Absolute volume >107% (cm^3)					< .00005	< .00005	
Mean	0.54	44.5	10.5	19.8			
Range	0–2	0–540	0–368.9	0–540			
Diabetes mellitus (*n*)							
No	310 (94)	375 (93)	374 (91)	1059 (93)	.25		
Not known	8 (2)	9 (2)	10 (2)	27 (2)			
Yes	12 (4)	21 (5)	26 (6)	59 (5)			
Smoking status (*n*)							
Nonsmoker	269 (82)	344 (85)	346 (84)	959 (84)	.31		
Unknown	4 (1)	8 (2)	1 (1)	13 (1)			
Smoker	57 (17)	53 (13)	63 (15)	173 (15)			
Cardio/peripheral vascular disease (*n*)							
No	297 (90)	348 (86)	357 (87)	1002 (87)	.25		
Unknown	8 (2)	12 (3)	12 (3)	32 (3)			
Yes	25 (8)	45 (11)	41 (10)	111 (10)			
Postoperative infection requiring antibiotics (*n*)							
Absent	261 (79)	322 (79)	322 (78)	905 (79)	.96		
Not known	5 (2)	8 (2)	11 (3)	24 (2)			
Present	64 (19)	75 (19)	77 (19)	216 (19)			
Postoperative hematoma (*n*)							
Absent	272 (82)	329 (81)	330 (80)	931 (81)	.92		
Not known	33 (10)	49 (12)	52 (13)	134 (12)			
Present	25 (8)	27 (7)	28 (7)	80 (7)			
Pathologic tumor size (mm)					< .00005		
Mean	14	16	17	16		.17	
Range	2–40	1.5–45	2–45	1.5–45			
Mean specimen weight* (g)	46 ± 38	64 ± 45	72 ± 72	62 ± 63	< .00005	.29	
Histologic grade (*n*)							
1	82	76	65	223	.038	.41	.14
2	147	194	195	536			
3	62	84	98	244			
Unknown or not available	39	51	52	142			
Histologic type (*n*)					.73		
Invasive ductal	231	283	275	789			
Invasive lobular	21	28	39	88			
DCIS	32	39	44	115			
Other	38	42	45	125			
Unknown	8	13	7	28			
Axillary surgery (*n*)							
Yes	302 (92)	364 (91)	368 (90)	1034 (91)	.69		
No	27 (8)	36 (9)	41 (10)	104 (9)			
Unknown	1	5	1	7			
RT breast boost (*n*)					.33		
Yes	216 (66)	246 (61)	266 (65)	728 (64)			
No	114 (34)	159 (39)	144 (35)	417 (36)			
Axillary RT (*n*)							
Yes	0 (0)	2 (<1)	1 (<1)	3 (<1)	.64		
No	330 (100)	403 (>99)	409 (>99)	1142 (>99)			
Supraclavicular RT (*n*)							
Yes	10 (3)	16 (4)	17 (4)	43 (4)	.71		

(*Continued*)

Table 1. Patient, tumor, and treatment characteristics of 1,145 trial participants (*Continued*)

	Treatment group				*p*		
					Heterogeneity		
Characteristic	Nonrandomized	Randomized, control	Randomised, IMRT	Total	Nonrandomized vs. randomized	Control vs. IMRT	Trend
No	320 (97)	389 (96)	393 (96)	1102 (96)			
Tamoxifen (*n*)							
Yes	216 (66)	263 (65)	260 (63)	739 (65)	.82		
No	110 (33)	128 (32)	139 (34)	377 (33)			
Unknown	4 (1)	14 (3)	11 (3)	29 (2)			
Treatment with AI (*n*)							
Yes	15 (6)	31 (7)	31 (7)	80 (7)	.38		
No	308 (93)	359 (89)	368 (90)	1034 (90)			
Unknown	4 (1)	15 (4)	12 (3)	31 (3)			
Chemotherapy (*n*)							
Yes	55 (17)	89 (22)	87 (21)	231 (20)	.16		
No	272 (82)	311 (77)	321 (78)	904 (79)			
Unknown	3 (1)	5 (1)	2 (1)	10 (1)			
Gonadorelin ovarian ablation (*n*)					.033		
Yes	18 (6)	12 (3)	8 (2)	38 (3)		.53	
No	292 (88)	363 (90)	366 (89)	1021 (89)			
Unknown	20 (6)	30 (7)	36 (9)	86 (8)			

Abbreviations: DCIS = ductal carcinoma *in situ;* AI = aromatase inhibitor; RT = radiotherapy.
*Available for 986 of 1,145 patients.

>107% and <95% of the prescribed dose (5). Patients with satisfactory dose homogeneity were not randomized but treated with standard RT and followed up the same as were the randomized patients.

All patients were treated to a dose of 40 Gy in 15 fractions, 5 d/wk within 3 weeks, with 6-MV photons prescribed to the International Commission on Radiation Units and Measurements report 50 reference point. Mixed energies of 6- and 15-MV photons were used, when required, in patients with larger separations. Nodal RT and a tumor bed boost were administered according to the local protocol (5). After RT, all patients were treated equally, irrespective of the treatment arm to which they had been allocated.

Study endpoints

The primary endpoint was serial photographic assessment of breast shrinkage. Frontal photographs of both breasts were taken after primary surgery and before the start of RT (baseline) and repeated at 2 years after RT. Two photographs were taken, one with the hands resting on the hips and one with the arms raised above the head. Follow-up photographs were terminated in the case of local tumor relapse, additional breast surgery, poor health, or patient refusal. Changes in breast shrinkage were scored on a validated 3-point scale (none/minimal, 1; mild, 2; marked, 3; Fig. 1). A multidisciplinary team of seven clinicians (four oncologists, 1 radiographer, 1 surgeon, and 1 breast care nurse) were involved in the photographic assessment, with a panel of three present at any one time. At the photographic assessment, all clinicians were unaware of the treatment arm to which the patient had been allocated. This method has been validated and shown to be as sensitive as, but quicker than, using three independent scorers, with repeat scoring of discrepancies and final resolution through discussion (8–10).

In addition, the baseline surgical cosmesis and estimated surgical deficit were assessed after surgery and before RT. Overall cosmesis was assessed using the photographs taken at 2 years, taking into account the effects of breast surgery and RT. The baseline surgical cosmesis, surgical deficit, and overall cosmesis were all scored using a 3-point scale.

The secondary endpoints included the photographic assessment of overall cosmesis at 2 years (described in the previous paragraphs), acute skin toxicity, clinical assessment of late normal tissue effects, and quality-of-life self-assessment questionnaires. Acute skin reactions were assessed and recorded according to the Radiation Therapy Oncology Group grading system (11). The patients were assessed weekly during treatment, at RT completion, and 16 weeks after the end of treatment (*i.e.,* at the routine clinic appointments).

The clinical assessment was made at a trial follow-up appointment at 2 and 5 years after RT completion. The initial 70 patients were assessed by an oncologist (C.E.C.) who had trained the breast research radiographer (J.W.) in clinical assessment at the same time. A single observer (J.W.) then assessed the remainder of the patients. Both clinicians were unaware of the allocated treatment arm at the assessment. The treated breast was examined for the presence of breast edema, telangiectasia, breast shrinkage, pigmentation changes, and palpable induration of the breast. Each of the secondary clinical endpoints was graded 0–3 (none, a little, quite a bit, or very much) on the scale used in the UK Standardisation of Breast Radiotherapy (START) trials (8, 9). Pigmentation change was scored from 0 to 2 according to the Late Effects of Normal Tissue–Subjective Objective Management Analytical score (12, 13). Locoregional recurrence, metastasis development, and death were recorded at 2 years from RT completion but were not included as secondary endpoints.

The quality of life was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 with the breast cancer module, "Additional Body Image items" (START trial), and the Hospital Anxiety and Depression Scale (14–16). The patient self-assessment questionnaires were completed at 6, 24, and 60 months after RT completion. A full quality-of-life analysis will be reported in a subsequent publication. However, in the present study, the results from the European Organization for Research and

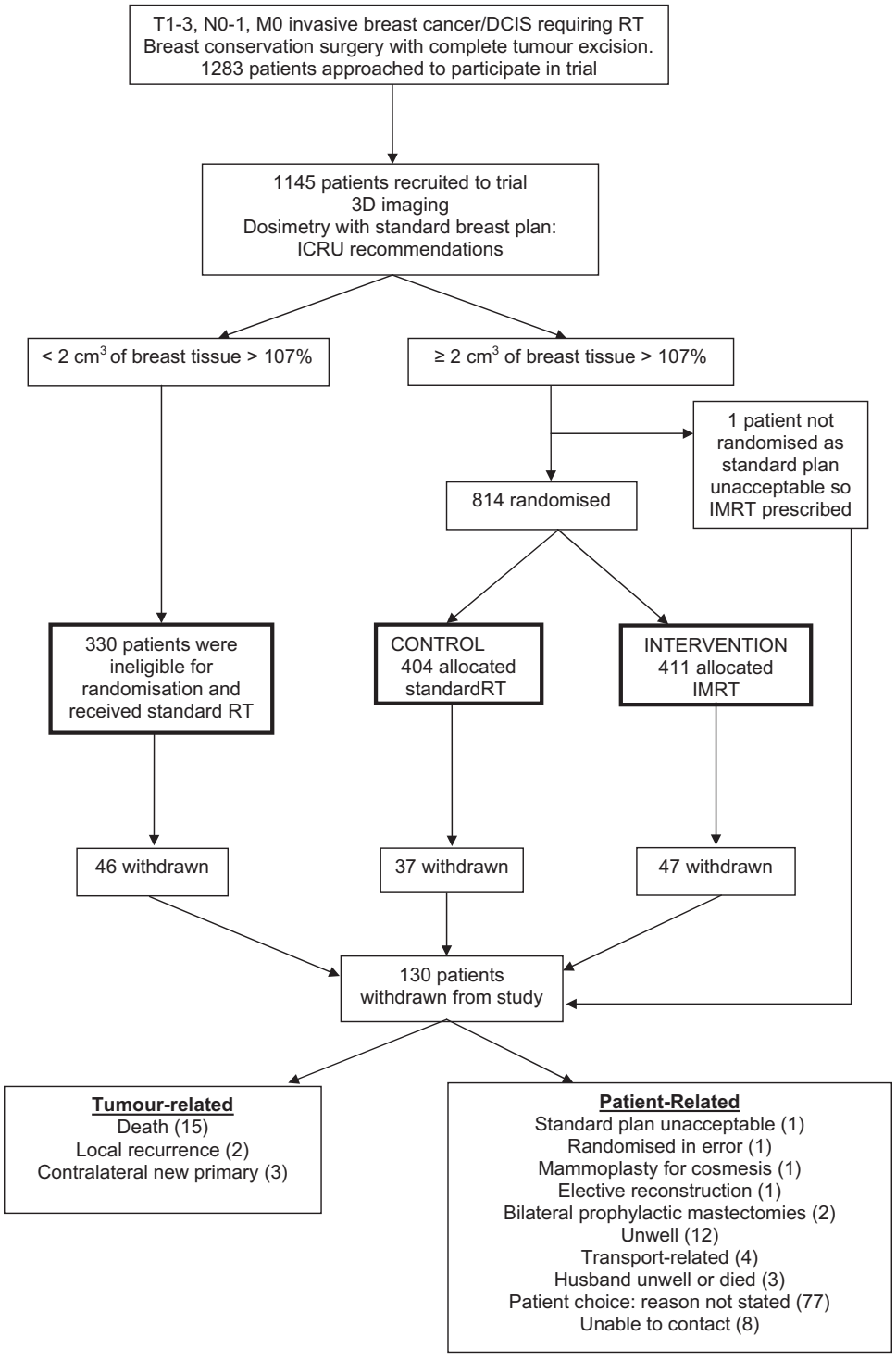

Fig. 2. Consolidated Standards Of Reporting Trials diagram of trial. RT = radiotherapy; IMRT = intensity-modulated radiotherapy.

Treatment of Cancer BR23 questionnaire were used to assess the pain and hypersensitivity in the treated breast at 2 years after RT (17). The pain and oversensitivity experienced in the last week were scored on a scale from 1 to 4 (not at all, a little, quite a bit, and very much).

Statistical analysis

The baseline data was compared using the Student *t* test, Pearson's chi-square test for heterogeneity and trend, and Fisher's exact test, as appropriate. The reproducibility of the primary endpoint was checked by rescoring the photographic assessment of breast shrinkage on a random 10% subset of the study sample. The pairs of scores obtained at these two points were compared within patients, and the weighted κ statistic was calculated as a measure of agreement. The photographic assessment of RT shrinkage and overall cosmesis were dichotomized by grouping the scores 2 and 3. The clinical endpoints were dichotomized, with scores of 0 as one group and ≥ 1 as the second group. The toxicity endpoints

were compared across the two treatment arms using the chi-square test. Polychotomous logistic regression analysis was also performed and produced similar results. The analysis was performed on an intention-to-treat basis.

RESULTS

Baseline data

Between April 2003 and June 2007, 1,145 patients were recruited into the trial. The baseline demographic, clinical, and tumor characteristics of the study participants have previously been published (5) and are summarized in Table 1. Of these 1,145 patients, 815 (71%) were eligible for randomization on the basis of significant dose inhomogeneity using a standard breast plan. The baseline demographic and clinical characteristics of the patients and tumors in the randomized arms were well balanced, with no statistically significant differences between the IMRT and control arms. The mean age was 58.3 years (range, 26–84). As expected, the mean breast volume and separation were significantly larger in the randomized group than in the nonrandomized group.

The differences in dosimetry among the three trial arms have been previously reported (5), and the differences between the volume receiving >107% of the prescribed dose are listed in Table 1. In the randomized patients, the decrease in mean volume receiving >107% and <95% of the prescribed dose in the IMRT group compared with the control group was 34.0 cm^3 (95% confidence interval [CI] 26.4–41.6; $p < .0001$) and 48.1 cm^3 (95% CI 34.4–61.9; $p < .0001$), respectively. By definition, the patients in the nonrandomized arm had a volume receiving >107% of <2 cm^3.

Two-year follow-up data

Some form of toxicity data was available for 1,013 patients. The photographic assessment of RT shrinkage was available for 852 patients (618 randomized) and the 2-year clinical toxicity data for 921 patients (667 randomized). Data from the self-assessment questionnaires were available for 913 patients (656 randomized). After 2 years of follow-up, 7 patients (0.6%) had developed local recurrence, 16 had developed systemic metastases (including 5 with local recurrence), 7 had developed a new primary tumor in the contralateral breast, and 15 (1.3%) had died, with the cause of death known to be metastatic breast cancer for 3. At 2 years, 130 patients (84 randomized) had withdrawn from the present study. Two patients had not withdrawn but had not attended the 2-year follow-up appointment. Figure 2 shows the Consolidated Standards Of Reporting Trials (CONSORT) diagram of the present trial. Of the patients who had withdrawn, no significant differences were found in the numbers allocated to each trial arm.

A major protocol deviation was made for 1 patient on clinical grounds because of a significant region of low dose on the patient's standard plan that might have led to an increased risk of local recurrence. The patients had been allocated to the nonrandomized arm, because the volume receiving >107% was <2 cm^3. The clinician therefore decided to treat with IMRT and prescribed a dose of 50 Gy in 25 fractions. Therefore, the patient was withdrawn from the late toxicity analysis.

Primary endpoint

At 2 years, no significant difference was found in the development of any photographically assessed breast shrinkage between the patients randomized to the interventional or control group (odds ratio [OR], 1.51; 95% CI 0.83–1.58; $p = .41$). A comparison of the initial photographic assessment of the RT-induced shrinkage scores with the repeated scores in 10% of the population showed an agreement of 81.1%, with a weighted κ statistic of 0.63, reflecting good agreement between the scores of the primary endpoint at these two points. The photographic scores for each patient never differed between the assessors by more than one point.

Secondary endpoints

No significant difference was found in the incidence of any acute toxicity between the control and IMRT groups. The risk of developing acute toxicity of Grade 2a or greater was the same in the control and interventional groups (OR, 1.00; 95% CI, 0.76–1.34; $p = .97$). In terms of the late effects, the patients randomized to the control group were more likely to develop telangiectasia than those who had undergone IMRT. The OR for any telangiectasia (score, 1, 2, or 3) in the control group compared with the IMRT group was 1.68 (95% CI 1.13–2.50; $p = .009$). The incidence of the different grades of telangiectasia in the IMRT and control arms is listed in Table 2. No significant differences were found between the two groups for any other clinically assessed outcome (Table 3).

In patients with good baseline surgical cosmesis, a trend was seen for patients randomized to the IMRT group to be less likely to deteriorate to a moderate or poor overall cosmesis than those in the control group (OR, 0.63; 95% CI, 0.39–1.03; $p = .061$).

Effect of surgery on late toxicity

The effect of the initial surgical outcome on the assessment at 2 years was examined further. The pre-RT baseline surgical defects and cosmesis significantly affected the score in the photographic assessment of overall cosmesis and the clinical assessment of breast shrinkage and induration ($p < .0001$). As expected, the patients with moderate or poor

Table 2. Incidence of different grades of telangiectasia in IMRT and control arms

	Telangiectasia score (*n*)				
Variable	0	1	2	3	Total
IMRT	280 (85)	22 (7)	19 (6)	8 (2)	329 (49)
Control	265 (77)	40 (12)	26 (8)	12 (3)	343 (51)
Total	545 (81)	62 (9)	45 (7)	20 (3)	672 (100)

Abbreviation: IMRT = intensity-modulate radiotherapy.
Data in parentheses are percentages.

Table 3. Incidence of all toxicity endpoints in IMRT and control arms

Variable	IMRT (n = 362)		Control (n = 365)		
	No toxicity	Any toxicity	No toxicity	Any toxicity	p
Photographic					
Shrinkage after RT	178	120	180	139	.41
Overall cosmesis	114	184	113	207	.45
Clinical					
Telangiectasia	280	49	266	76	.015
Breast edema	175	154	167	176	.24
Breast shrinkage	137	192	126	217	.19
Any induration	57	272	72	271	.23
Pigmentation	229	57	234	70	.36
Patient reported					
Breast pain	155	169	157	172	.98
Oversensitivity	188	135	202	128	.43

Table 4. Effect of surgical factors on surgical deficit and cosmesis using Spearman's correlation coefficient

Variable	Surgical deficit		Surgical cosmesis	
	Spearman's rho	p	Spearman's rho	p
Pathologic tumor size	0.096	.0060	0.027	.0010
Specimen weight	0.18	< .00005	0.006	< .00005
Grade		.16		.089
Age	0.070	.042	0.029	.0003
Estrogen receptor status		.53		.64
Histologic group		.48		.60
Lymph node status		.93		.72
Body mass index		.12	0.037	.0065
Smoker status		.53		.24
Breast volume		.44		.75
Postoperative infection		.64		.13
Postoperative hematoma		.67		.091
Primary side		.077		.072

surgical cosmesis had a greatly increased risk of moderate or poor overall cosmesis (OR, 40.9; 95% CI, 25.4–65.8) at 2 years. The patients with moderate or poor surgical cosmesis had an increased risk of developing any clinically assessed breast shrinkage (OR, 4.96; 95% CI, 3.67–6.71) and breast induration (OR, 2.78; 95% CI, 1.92–4.01). The score for photographically assessed shrinkage due to RT was significantly associated with surgical cosmesis; however, the magnitude of this effect size was much smaller (OR, 1.40; 95% CI, 1.06–1.86; p = .02).

Increased surgical deficit and poorer surgical cosmesis were significantly associated with increased pathological tumor size, greater specimen weight, and older age (Table 4). Surgical cosmesis was also adversely influenced by an increased body mass index.

DISCUSSION

In the present study, no significant difference was found in the development of the primary endpoint of photographic assessment score for breast shrinkage between the patients randomized to the interventional or control group. The follow-up was only 2 years; therefore, it is likely that not all patients had experienced their final toxicity level. This follow-up period might have been insufficient to detect a difference in breast shrinkage with IMRT. The study is on-going, with a repeat analysis planned at 5 years after RT completion.

We have previously shown that the use of forward-planned IMRT can significantly improve dose homogeneity (5). This improvement translates into an improvement in the incidence of telangiectasia between the IMRT group and the control group at 2 years after RT completion. One explanation is that telangiectasia develops before subcutaneous fibrosis. Data on the course of the development of these two late toxicity endpoints have been limited but suggest that, in fact, the reverse is true, and the latent period for subcutaneous fibrosis is less than that for telangiectasia (18, 19). An alternative explanation is that telangiectasia is consistently documented and more specific to the effects of RT than fibrosis and breast shrinkage. Finally, it is possible that the results have arisen by chance (falsely positive).

In addition, for patients who had a good postoperative cosmetic result, a trend was seen toward better overall cosmesis in the IMRT group than in the control group. We believe this could become statistically significant at the later analysis, because evidence has shown that the late effects at 2 years can be predictive of those at 5 years (20). Surgical cosmesis appears to be a very important determinant of overall cosmesis after 2 years of follow-up and might mask any beneficial effects of IMRT at this early stage.

A statistically significant association was found between the surgical cosmesis and the clinical assessment of either breast shrinkage or induration. Patients with moderate or poor surgical cosmesis at baseline were more likely to be scored as having any category of either clinically assessed breast shrinkage (OR, 4.96; 95% CI, 3.67–6.71) or breast induration (OR, 2.78; 95% CI, 1.92–4.01) at 2 years, although it was not possible to determine whether such induration resulted predominantly from surgery or RT.

The results of the present trial therefore have shown that the clinical assessment of breast shrinkage and induration should be used with caution because of the confounding effect of surgery, at least at the 2-year point. This was because the clinical assessment was made compared with the contralateral side, and it was not possible to determine the relative contributions of surgery and RT to these end points (Fig. 3). Despite this, the patient assessment of breast hardness was sensitive to the effects of dose in the START trial (9, 15). The advantage of using the photographic endpoints is clearly that a comparison with baseline can be made.

The 5-year results of the START trial have been reported. That trial used the same whole breast fractionation regimen as was used in our trial. These showed no significant difference in late normal tissue toxicity compared with 50 Gy in 2-Gy fractions (8, 21). In addition, the Canadian trial, which compared 50 Gy in 25 fractions within 35 days with 42.5

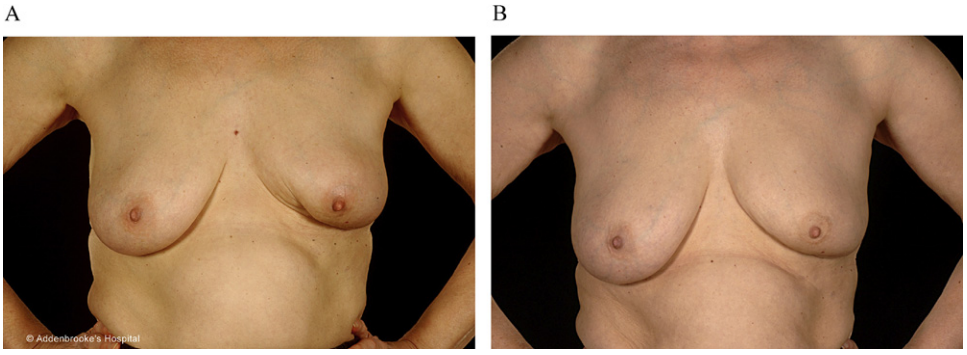

Fig. 3. Example of effect of surgery at 2 years. (A) After surgery, but before radiotherapy, showing substantial surgical deficit with resulting poor cosmesis. (B) At 2 years after radiotherapy showing no additional change. If baseline photographs had not been available, surgical deficit might have been attributed to radiotherapy shrinkage.

Gy in 16 fractions within 22 days, has 10 years of follow-up. They also found no significant difference in late normal toxicity (22). Yarnold *et al.* (23) discussed in detail the effect of hypofractionated breast RT on both local control and late normal tissue toxicity in their comprehensive review of the published studies.

Donovan *et al.* (6) reported the results of the first randomized controlled trial designed to investigate the effect of IMRT on the incidence of late radiation toxicity. In their study, 306 patients with early-stage breast cancer were randomized to either standard RT or forward-planned IMRT. The primary endpoint was the change in breast appearance after RT, measured using serial photographs. This was similar to the endpoint of overall cosmesis used in the present study. At 2 years, a nonsignificant trend was seen for a greater change in breast appearance in the control than in the IMRT arm (24). The analysis was also performed at 5 years, and at that point, the patients in the control arm were 1.7 times (95% CI, 1.6–2.5) more likely to have had a change in breast appearance than those in the IMRT arm ($p = .008$).

One of the inclusion criteria for the Royal Marsden Hospital trial was an anticipated increased risk of radiation toxicity because of a larger breast size and/or distortion of breast shape after surgery owing to these patients having the greatest dose inhomogeneities (6). In contrast, the Cambridge IMRT trial included all patients for whom a volume of ≥ 2 cm^3 received >107% of the prescribed dose. Therefore, it is possible that, for some patients, the volume of "hot spots" might have been too small to be clinically significant.

Another multicenter randomized trial of breast IMRT was performed by Pignol *et al.* (7) to investigate a possible reduction in acute radiation dermatitis. The use of breast IMRT significantly reduced the number of patients experiencing moist desquamation during, or ≤ 6 weeks after, RT (*i.e.,* 31.2% with IMRT compared with 47.8% with standard treatment; $p = .002$). In the present study, we did not find a difference in the incidence of acute toxicity between the IMRT and control groups, but acute toxicity was measured during the third week of treatment to integrate with the standard clinical care in our department. It was, therefore, possible that a difference was not detected because, with the dose regimen used, acute toxicity peaks at about 2 weeks after RT completion, and this level of increased follow-up was not possible in our trial.

CONCLUSIONS

The results of the present study have demonstrated evidence of a decrease in the incidence of late toxicity with the use of simple forward-planned IMRT compared with a standard two-field technique at only 2 years after RT. The results of the present study have suggested that much of the clinically assessed breast induration and shrinkage at 2 years was actually due to the effects of surgery rather than the RT. Baseline surgical cosmesis is an important determinant of overall cosmesis and might, at this early stage of follow-up, mask the potential beneficial effects of improved RT from the use of IMRT.

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