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ORIGINAL REPORT

A Multicenter Randomized Trial of Breast Intensity-Modulated Radiation Therapy to Reduce Acute Radiation Dermatitis

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

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ABSTRACT

Purpose
Dermatitis is a frequent adverse effect of adjuvant breast radiotherapy. It is more likely in full-breasted women and when the radiation is distributed nonhomogeneously in the breast. Breast intensity-modulated radiation therapy (IMRT) is a technique that ensures a more homogeneous dose distribution.

Patients and Methods
A multicenter, double-blind, randomized clinical trial was performed to test if breast IMRT would reduce the rate of acute skin reaction (notably moist desquamation), decrease pain, and improve quality of life compared with standard radiotherapy using wedges. Patients were assessed each week during and up to 6 weeks after radiotherapy.

Results
A total of 358 patients were randomly assigned between July 2003 and March 2005 in two Canadian centers, and 331 were included in the analysis. Breast IMRT significantly improved the dose distribution compared with standard radiation. This translated into a lower proportion of patients experiencing moist desquamation during or up to 6 weeks after their radiation treatment; 31.2% with IMRT compared with 47.8% with standard treatment ($P = .002$). A multivariate analysis found the use of breast IMRT ($P = .003$) and smaller breast size ($P < .001$) were significantly associated with a decreased risk of moist desquamation. The use of IMRT did not correlate with pain and quality of life, but the presence of moist desquamation did significantly correlate with pain ($P = .002$) and a reduced quality of life ($P = .003$).

Conclusion
Breast IMRT significantly reduced the occurrence of moist desquamation compared with a standard wedged technique. Moist desquamation was correlated with increased pain and reduction in the quality of life.

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INTRODUCTION

Because of the widespread use of mammography, breast cancer is commonly diagnosed at an early stage.[1,2] The standard treatment for early-stage disease is breast-conserving surgery followed by adjuvant radiation therapy (RT) to the whole breast. This approach leads to low recurrence rates with a good cosmesis and provides an effective alternative to mastectomy.[3-10] However, about one third of women will develop significant acute skin toxicity after whole breast irradiation.[11] These reactions are painful and typically occur in the inframammary fold, and have also been associated with a reduction in health-related quality of life.[11,12] Previous studies have attempted to identify factors associated with an increased risk of acute radiation-induced toxicity after conventional whole breast irradiation. These include large breast size and the delivery of excessive radiation dose (> 10% of prescribed dose) to areas within the breast.[12] The areas receiving excessive dose are known as radiation hot spots, and are due to the limitations of conventional RT techniques to account for the complex three-dimensional (3D) shape of the breast, resulting in the inability to deliver a homogeneous dose throughout the breast.[13] Breast intensity-modulated radiation therapy (IMRT) is a novel technique that can deliver a more homogeneous dose of radiation throughout the breast and efficiently removes the radiation hot spots.[13-17] This raises the possibility that breast irradiation using

IMRT may lead to a significant reduction in severe radiation-induced skin toxicity.[13] IMRT is more complex than conventional techniques and it is unknown to what extent, if any, breast IMRT can provide a clinical benefit to patients with early-stage breast cancer.

We report the results of a multicenter, phase III, double-blinded clinical trial in which patients were randomly assigned to receive either breast IMRT or a standard RT treatment after complete excision of an early-stage breast cancer.

PATIENTS AND METHODS

Study Design

Patients with early-stage breast cancer referred for adjuvant RT to the Sunnybrook Health Sciences Centre (SHSC; Toronto, Ontario, Canada) or the British Columbia Cancer Agency–Vancouver Island Centre (VIC; Victoria, British Columbia, Canada) were enrolled onto a phase III, double-blinded, multicenter, randomized, controlled trial. Patients received adjuvant RT using either a standard wedge missing-tissue compensation technique or breast IMRT. The primary end points were the rates of acute dermatitis and moist desquamation. The sample size was calculated to identify an absolute 15% improvement from a previously reported 36% rate of moderate to severe acute skin toxicity.[11] A planned sample size of 308 patients (154 for each arm) was needed for an 80% power to test this hypothesis ($\alpha = .05$, two sided).[18] A total sample size of 340 was planned to allow for a 10% dropout or lost to follow-up rate. The study protocol was approved by the institutional research ethics board of each participating center, and was registered at the National Institutes of Health (www.clinicaltrials.gov No. NCT00187343).

Eligibility

Eligibility criteria included women with early-stage breast cancer referred for adjuvant RT to the breast alone. Patients were treated by breast-conserving surgery with a confirmed histologic diagnosis of invasive carcinoma or ductal carcinoma in situ, with three or fewer involved lymph nodes. Patients were excluded if they had four or more positive nodes, an Eastern Cooperative Oncology Group performance status ≤ 1, bilateral breast cancer, a postoperative wound infection, previous radiation to the same breast, a connective tissue disorder, or were pregnant. All patients provided written informed consent.

Random Assignment

Eligible patients were randomly assigned to receive 50 Gy in 25 fractions (2 Gy per fraction) to the whole breast using either standard RT with wedge compensation or breast IMRT. An additional boost dose of 16 Gy was used at the discretion of the radiation oncologist in accordance with the results of the European Organisation for Research and Treatment of Cancer (EORTC) randomized clinical trial.[9] Given that the breast size and the total dose were factors associated with increased skin toxicity,[11,12] the random assignment was stratified for the use of a boost and breast size, and blocked 1:1 to ensure that the two arms were equally balanced.[19] Breast size was defined as small (bra sizes 32A or 32B, 34A or 34B, and 36A), medium (bra sizes 32C, 34C, 36B or 36C, and 38A, 38B, or 38C), or large (larger bra sizes).[11] The randomization was performed centrally at SHSC after the patient had completed computed tomography (CT) simulation.

Interventions

All patients underwent CT simulation for RT planning. The involved breast was treated using a pair of parallel-opposed megavoltage beams to cover the whole glandular breast tissue. The two treatment arms differed by the missing tissue compensation method (two dimensional [2D] *v* 3D) used to account for variations in breast shape. The standard arm used a tungsten wedge inserted in the beam path and the experimental arm used breast IMRT. For the standard arm, the selection of the optimal wedge angle was done iteratively, minimizing hot spots in the whole breast volume. The experimental arm technique was called breast IMRT for consistency with previous reports,[13-17] and to follow the definition of compensating filter IMRT by Purdy.[20] Details of the dosimetry steps were reported elsewhere.[21] Briefly, a

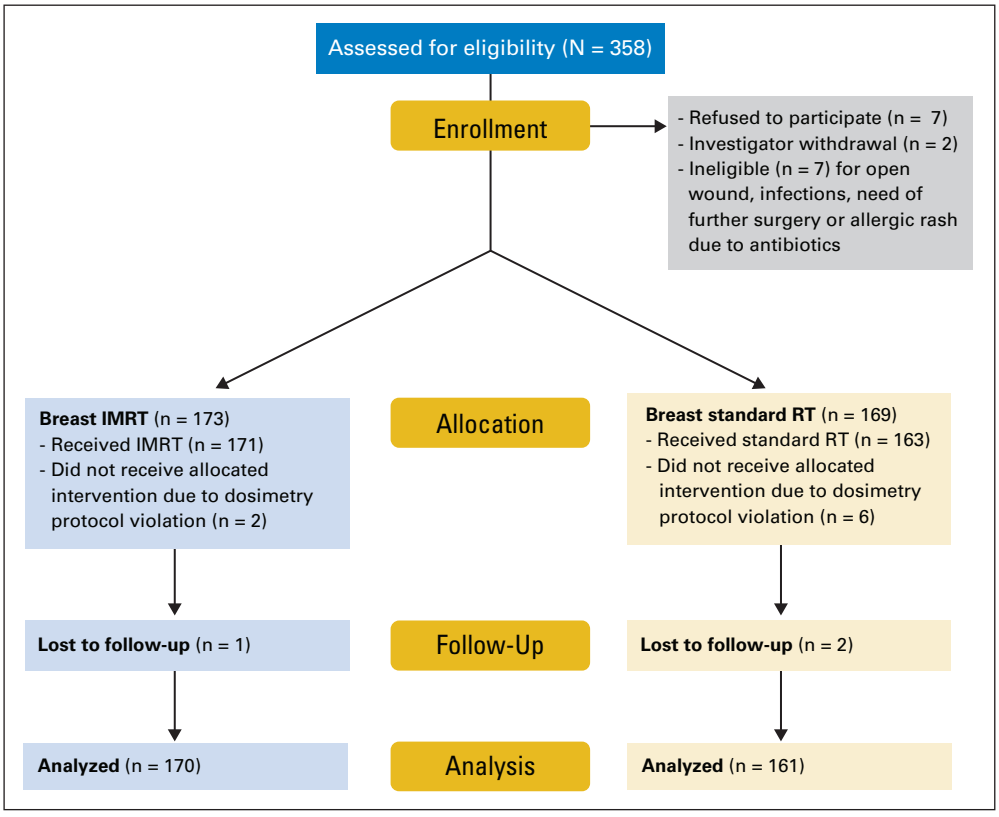

Fig 1. Patient flow chart. IMRT, intensity-modulated radiation therapy; RT, radiation therapy.

Table 1. Patient, Treatment, and Dosimetry Characteristics Between the Two Arms

Clinical Characteristics	BIMRT (n = 170) No.	BIMRT (n = 170) %	Standard RT* (n = 161) No.	Standard RT* (n = 161) %	P†
Age, years					
Mean		57.1		56.4	
SD		10.7		10.5	.71
Body mass index					.99
Mean	27.2		27.2		
SD	5.6		5.0		
Chemotherapy	52	30.8	60	37.3	.21
Hormone therapy	67	39.9	67	41.9	.71
Skin type (Fitzpatrick[26])					.61
Melanocompromised	63	37.0	56	34.8	
Melanocompetent	96	56.5	90	55.6	
Melanoprotected	11	6.5	15	9.3	
Smoking habit	19	11.2	12	7.5	.25
Diabetes	8	4.7	11	6.8	.41
High blood pressure	42	24.7	40	24.8	.98
Connective tissue disorder	1	0.6	0	0.0	.33
Breast size					.99
Small (sizes 32A, 32B; 34A, 34B; 36A)	29	17.1	27	16.8	
Medium (Sizes 32C; 34C; 36B, 36C; 38A, 38B, 38C)	85	50.0	80	49.7	
Larger sizes	56	32.9	54	33.5	
Treatment characteristics					
Boost	51	30.0	51	31.7	.74
6-MV energy only	137	80.6	78	48.5	< .001
Median wedge angle in degrees	NA		30		
Median No. of segments	4		NA		
Dosimetry characteristics					
Volume receiving 95% of the prescribed dose (mL; median)		958		973	.14
Breast separation (cm, median)		21.0		20.6	.92
Clinically significant maximum (median)		105.0		110.0	< .001
Sagittal dose gradient (median)		0.6		10.0	< .001
Relative volume receiving (mean)					
> 105% of the prescribed dose (V_{105})		7.7		16.9	< .001
> 107% of the prescribed dose (V_{107})		2.6		7.9	< .001
> 110% of the prescribed dose (V_{110})		0.5		2.1	< .001
> 115% of the prescribed dose (V_{115})		0.02		0.12	< .001

Abbreviations: RT, radiation therapy; BIMRT, two-field, breast intensity-modulated RT; SD, standard deviation.
*RT using wedge compensation.
†χ^2 test or Wilcoxon.

multileaf collimator was used to generate several field-in-fields to compensate for missing tissue. Based on treatment planning availability at each site, an inverse algorithm was used to select the breast IMRT segment weights at SHSC, and a forward-planning method was used at VIC. It resulted in a smaller number of segments added to the open beam at SHSC (mean, 4.0 ± 1.1 standard deviation) compared to VIC (mean, 5.7 ± 0.6 standard deviation). In previously published work, we demonstrated that the two techniques were equivalent to minimize the dose distribution heterogeneity.[21] For both arms, differential dose-volume histograms were calculated to evaluate various dosimetry end points for each patient. No contouring of normal tissue was done, and to eliminate the buildup area automatically, the clinical target volume was defined as the volume receiving at least 95% of the prescribed dose.

The beam energy (6 MV or mixed energies) was selected depending on the breast separation (> or < 25 cm) and/or the presence of an excessive dose hot spot on the dose distribution. If a boost was required, the planning involved a clinical mark-up and the use of a direct electron beam. The electron beam energy was selected using CT images to ensure that the surgical cavity was covered appropriately. The planning technique and dose prescription was similar at both sites, and it involved the dose calculation using heterogeneity correction and the plan normalization to a prescription point set at mid-separation, two thirds of the distance between the skin and the base of the tangential fields, such that the clinical target volume was covered by the 50 Gy isodose line. Dosimetry quality assurance included a central medical record review for each of the VIC patients and two thirds of the SHSC patients. Standard skin care during the radiation treatment was similar between sites.

Study End Points

Clinical outcomes included the intensity of acute skin reaction or pain using the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0 scale[22] and the occurrence of moist desquamation.[11,12,23] The type and maximal intensity of each symptom and its location in the breast were recorded weekly during the 5 to 7 weeks of RT and at weeks 1, 2, 4, and 6 after treatment by trained clinical research assistants. Quality-of-life data were coded using the EORTC Quality of Life Questionnaire C-30 general module and the BR-23 module self-assessment questionnaires at baseline, the last week of treatment, and 1 month later.[24,25] To ensure unbiased symptom measurement, both patients and the clinical research assistants were blinded to the

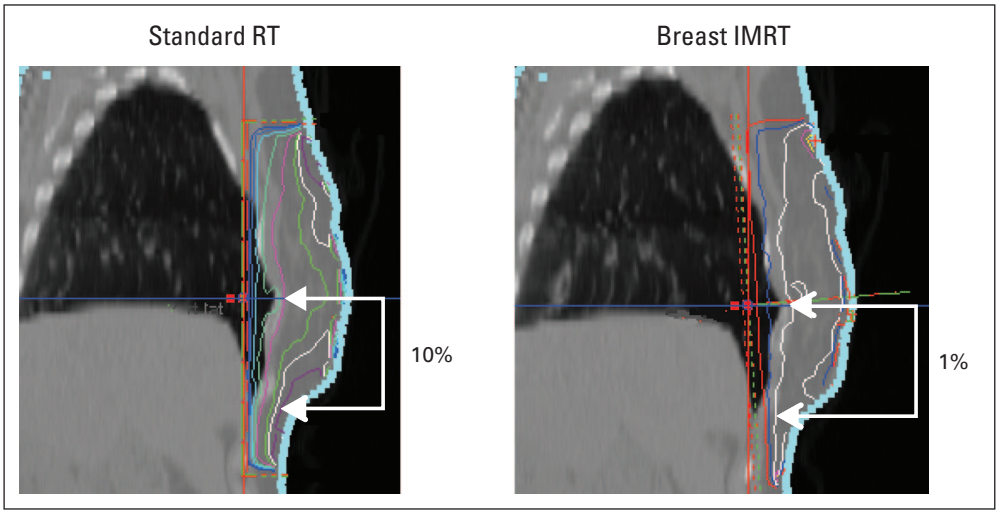

Fig 2. The sagittal dose gradient, defined as the gradient between the dose prescription point and the dose calculated in the breast crease 1 cm from the skin surface at mid-separation, is improved for breast intensity-modulated radiation therapy (IMRT) compared with the standard wedge technique. RT, radiation therapy.

treatment arm. Moreover, the skin assessment was done in a separate clinic, and to ensure consistency and accuracy in the skin symptom coding, each clinical research assistant was trained for 3 weeks by the local principal investigator. Each patient's baseline information included height and weight, breast size measured by bra size, age, skin type coded using the Fitzpatrick classification,[26] smoking habits, and the existence of diabetes or high blood pressure.

Statistical Analysis

The comparisons of patient characteristics and dosimetry outcomes between the two treatment arms were done using χ^2 tests for categoric variables and using the Wilcoxon rank sum test for continuous variables.[27] The proportions of maximum observed toxicity were compared across the two treatment arms using the χ^2 test.[27] A comparison was considered significant at the 5% level of significance for two-sided tests. Univariate and multivariate logistic regression models including technical, dosimetry, and clinical parameters were developed to evaluate the factors associated with moist desquamation.[28] The multivariate model was adjusted for boost delivery and breast size (the stratification variables), but the continuous dosimetry variable breast volume receiving at least 95% of the dose was used instead of bra size. The EORTC Quality of Life Questionnaire C-30 and BR-23 data were processed to calculate the global health status/quality of life and breast symptoms scale values at each assessment. The outcomes used for analysis were change in scale values from baseline to end of treatment. Changes in scale from baseline were compared with treatment and pain grade using the Wilcoxon rank sum test. Pain grade was compared to treatment and grade of moist desquamation at the end of treatment using the χ^2 test.[27] All statistical analysis was performed using the SAS software (SAS Institute Inc, Cary, NC).

RESULTS

Patient and Treatment Characteristics

Between July 2003 and March 2005, 358 patients were enrolled onto the study and 331 patients met eligibility for analysis. Twenty-seven patients (7.5%) were excluded from the analysis, mainly because of treatment protocol violation or withdrawal of the consent. Of the 331 patients, 170 received breast IMRT and 161 received a standard wedge technique (Fig 1).

Table 1 lists the patient, treatment, and dosimetry characteristics. The treatment arms were well balanced regarding clinical and treatment factors. The beam energy was different between the two arms, with significantly more patients receiving mixed-energy beams (> 6 MV) in the standard treatment arm (51.6%) compared with the breast IMRT arm (19.8%), given that the standard arm generated a plan with unacceptable off-axis hot spots in the majority of the patients.

Regarding the dosimetry characteristics, breast IMRT significantly improved the radiation treatment quality as reflected on all dosimetry parameters including the clinically significant maximum,[29] the sagittal dose gradient (Fig 2),[21] and removed the hot spot in the inframammary fold (Table 1).

Comparison Between Treatment Arms

The comparison of clinical outcomes between the two treatment arms is summarized in Table 2. There was a trend toward fewer NCI CTC version 2.0 grade 3 to 4 acute skin reactions in the experimental arm, with an absolute reduction of 9.5%, but this difference did not reach statistical significance ($P = .06$). Breast IMRT significantly reduced the occurrence of moist desquamation anywhere in the breast, with an absolute reduction of 16.6% ($P = .002$), and moist desquamation in the inframammary fold, with an absolute reduction of 17% ($P = .001$).

Time of Occurrence of Acute Skin Toxicity

Figure 3 shows the differential (Figs 3A and 3B) and cumulative (Figs 3C and 3D) occurrence of acute skin reaction over time. There was a significant amount of edema present at the baseline; the redness rose abruptly after the second week of treatment and peaked after the

Table 2. χ^2 Analysis Between the True Arms

End Point	BIMRT (%) (n = 170)	Standard RT* (%) (n = 161)	*P*
Skin toxicity grade 3-4 (NCI CTC 2.0)	27.1	36.7	.06
Moist desquamation, all breast	31.2	47.8	.002
Moist desquamation, inframammary crease	26.5	43.5	.001
Pain grade 2-4 (NCI CTC 2.0)	23.5	25.5	.68

Abbreviations: BIMRT, two-field, breast intensity-modulated RT; NCIC CTC 2.0, National Cancer Institute Common Toxicity Criteria version 2.0.
*RT using wedge compensation.

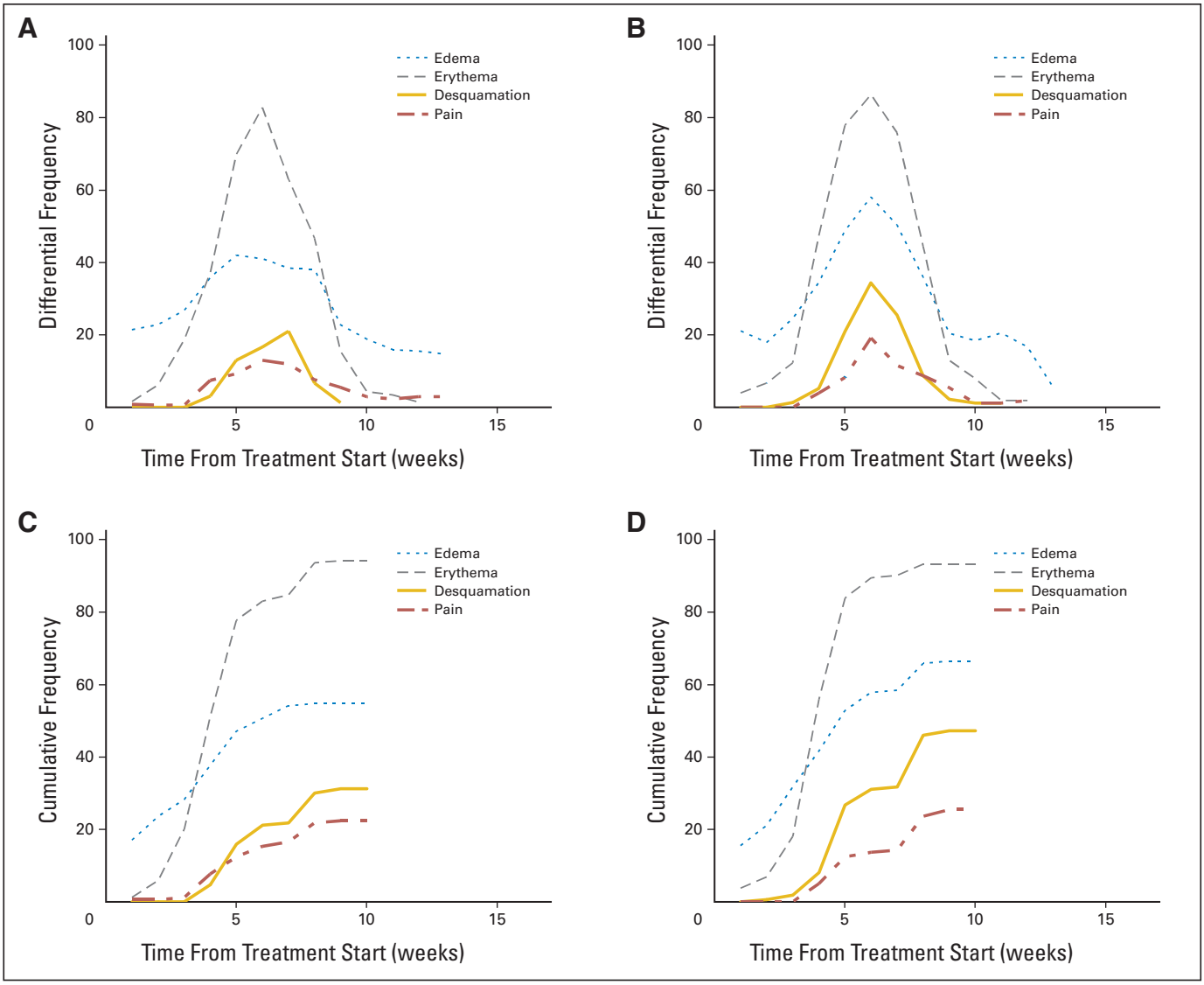

Fig 3. Differential and cumulative frequencies of various toxicities (grade 3 to 4, moist desquamation and pain) from treatment start to the last clinical assessment for (A, C) breast intensity-modulated radiation therapy and (B, D) standard radiation therapy.

fifth week. Moist desquamation occurred after 4 weeks of treatment and peaked between the fifth and the sixth week. The occurrence of pain measured by a visual analog scale closely followed the occurrence of moist desquamation.

Factors Associated With Skin Toxicity

Table 3 summarizes the univariate analysis of factors associated with an increased risk of moist desquamation anywhere in the breast. The factors found significantly associated with increased skin toxicity included the body mass index, breast size, the use of breast IMRT, the beam energy, the clinically significant maximum dose, and sagittal dose gradient. Several patient-related factors showed a trend toward increased skin toxicity but did not reach significance, including the patient's age, the skin type,[26] or the existence of diabetes or high blood pressure.

Table 4 summarizes the logistic regression model used for the multivariate analysis. In addition to the radiation technique and the breast volume, technical factors traditionally associated with a higher rate of skin toxicity were forced into the model. They included the volume of breast receiving more than 10% of the prescribed dose ($V_{110\%}$), the delivery of a boost, and the beam energy. Moreover, we wanted to adjust for potential differences in patient population demographics and treatment between sites, so the variable treatment site was also included in our model. The two factors strongly associated with a decreased risk of moist desquamation were smaller breast size ($P < .001$) and use of breast IMRT ($P = .003$). The delivery of a boost and the volume receiving more than 10% of the prescribed dose were not significantly associated with an increased risk of moist desquamation. Unlike the univariate analysis, the use of a 6-MV beam alone would increase skin toxicity, but this did not reach statistical significance.

Pain and Quality of Life

There was no statistically significant difference in the quality of life or pain between the two treatment arms. However, because the

Table 3. Univariate Analysis of Factors Associated With Increased Moist Desquamation Anywhere in the Breast

Factor	OR	95% CI	*P*
Age (per year, 10-year OR = 1.211)	1.019	0.998 to 1.041	.074
Body mass index	1.159	1.102 to 1.219	< .001
Diabetes	2.230	0.872 to 5.702	.09
Smoking history	0.974	0.456 to 2.081	.95
High blood pressure	1.574	0.951 to 2.608	.08
Melanocompetent *v* skin melanocompromised	0.647	0.404 to 1.035	.07
Melanoprotected *v* skin melanocompromised	0.883	0.374 to 2.081	.78
Chemotherapy	0.760	0.473 to 1.219	.26
Tamoxifen	1.038	0.661 to 1.630	.87
Medium *v* small breast size (ref small, OR = 1)	3.596	1.529 to 8.456	.003
Large *v* small breast size	10.907	4.525 to 26.28	< .001
Toronto *v* Victoria Treatment Centre	0.761	0.449 to 1.291	.31
BIMRT technique *v* standard RT*	0.494	0.316 to 0.774	.002
Beam energy 6 MV *v* mixed energies	0.594	0.375 to 0.941	.03
Boost to the primary site	0.884	0.547 to 1.430	.62
V_{95}, per excess cm^3	1.002	1.001 to 1.003	< .001
Breast separation, cm	1.293	1.181 to 1.415	< .001
Clinically significant maximum, per % of excess dose	1.094	1.030 to 1.161	.003
Sagittal dose gradient, per % of excess dose	1.076	1.029 to 1.250	.001
V_{110} (> 0 *v* 0)	1.491	0.956 to 2.326	.08

Abbreviations: OR, odds ratio; BIMRT, two-field, breast intensity-modulated RT; RT, radiation therapy; V_{95}, volume of breast receiving 95% of the prescribed dose; V_{110}, volume of breast receiving > 10% of the prescribed dose.
*RT using wedge compensation.

quality of life assessment timing did not correspond to the maximal skin toxicity timing, we tested the correlation between skin toxicity occurring the last week of treatment, and the quality of life and pain scores assessed at the same time. There was a highly significant correlation ($P < .0001$) between the occurrence of a moist desquamation and an NCI CTC version 2.0 grade 2 to 3 pain score. Regarding quality of life, there was a highly significant correlation between the occurrence of moist desquamation and a reduction in the global health status scale ($P = .0019$), and there was also a highly significant correlation between the occurrence of moist desquamation and an increase in the breast symptoms scale ($P = .0028$).

Table 4. Logistic Multivariate Analysis for Moist Desquamation Anywhere in the Breast

Factor	Odds Ratio	95% CI	*P*
BIMRT technique	0.418	0.232 to 0.753	.0034
Breast size (per 100 cm^3)	1.236	1.157 to 1.321	< .0001
6-MV energies	1.299	0.733 to 2.304	.3703
V_{110} (0 *v* > 0%)	0.773	0.441 to 1.355	.3691
Boost	1.162	0.677 to 1.993	.5856

Abbreviations: BIMRT, breast intensity-modulated radiation therapy; V_{110}, volume of breast receiving > 10% of the prescribed dose.

DISCUSSION

Numerous trials aiming to prevent acute radiation adverse effects to skin using creams or hygiene have been reported, but none of these trials demonstrated an effective prevention of skin reactions.[30-33] To our knowledge, our study is the first multicenter randomized trial demonstrating a successful reduction in acute radiation skin toxicity using an improved radiation technique, breast IMRT.

In 2002, Vicini et al[13] reported the first clinical use of breast IMRT in a prospective series and suggested a reduced occurrence of acute skin adverse effects. In 2006, Freedman et al[34] reported the results of a matched-pair analysis of 131 patients treated using either breast IMRT (73 patients) or standard RT (58 historical patients). There was a significant reduction in the rate of moist desquamation using breast IMRT compared with the standard technique using wedge compensation. In that study, the two groups were not comparable regarding the total radiation dose, the use of mixed beam energy, and chemotherapy delivery. In the absence of a randomization, it is unknown if these factors might have increased the rate of acute skin reactions.[12,35,36]

Our multicenter, randomized trial confirmed the dramatic improvement in the dose distribution homogeneity using breast IMRT, and demonstrated that it translated into a significant 17% absolute reduction in the frequency of moist desquamation. There was a trend toward improved acute grade 3 to 4 skin reactions (9.5% lower for breast IMRT), but this difference was not statistically significant. The lack of statistical significance may result from the nonspecificity and frequency of some symptoms included in the scale. For example, edema was often present at the time of the first skin assessment, before the radiation treatment, and might be due to the effects of breast and axillary surgery. In addition, the majority of the patients experienced erythema at some point of their treatment for both techniques (Fig 2), such that this parameter has no discriminative value. Conversely, moist desquamation is a parameter that is more specifically induced by radiation. It is easily recognized and measured by clinical research assistant, and it is the most clinically significant acute toxicity induced by radiation. Nearly 48% of patients had moist desquamation at some point of their treatment in the standard treatment arm using wedges. Compared with other series reporting rates of moist desquamation captured the last week or the week after the end of RT and ranging from 20% to 38%,[30,31,34] our rates look high. However, we are reporting cumulative and not differential rates of moist desquamation (Fig 2). To ensure this, the maximal skin toxicity was recorded; patients were asked to return to the treatment center 1, 2, 4, and 6 weeks after the end of the RT. In the standard treatment arm of our series, only 20.9% of our patients experienced moist desquamation the last week of treatment, and this value is consistent with those reported by other authors. In our study, there was no significant difference in the pain scores or quality of life scores between the two arms at the end of the radiation treatment. However, when moist desquamation was present at the time the quality-of-life questionnaire for pain assessment was completed, there was also an increased level of pain and a worsening of the quality of life score. This finding further justifies attempts to reduce the occurrence of moist desquamation.

There are possibly additional benefits of breast IMRT. There is accumulating clinical evidence showing that telangiectasia is a late sequelae of acute skin reactions,[37] and that dose inhomogeneity causes

an increased risk of fibrosis and inferior cosmetic outcome.[38] Recently, Donovan et al[39] reported the results of a single-institution randomized trial of breast IMRT versus standard 2D compensation for large breasted women. This study found a significant change in the breast appearance after 5 years. In addition, Haffty et al suggested that increasing dose distribution homogeneity would benefit patients receiving chemotherapy in regard to the possible additional detrimental effect on the cosmetic outcome.[40-42] Similarly, the low acceptance of shorter courses of breast RT outside Canada and United Kingdom is related to concern regarding delayed complications and reduced cosmetic outcome.[10,41] The increased homogeneity produced by breast IMRT could improve the acceptance of a shorter course, which will impact on the cost of the technique. Finally, using of a lower number of monitor units and avoiding a beam modifier reduces the scatter dose, hence possibly reducing the risk of secondary cancer.[42]

The present results support the shift from 2D to 3D dose compensation. CT simulation, 3D dose distribution treatment planning systems, and treatment unit with multileaf collimation are now becoming standard equipment in radiation oncology, such that breast IMRT should be offered to patients receiving adjuvant breast RT instead of the standard wedge technique.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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