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# Long-Term Breast Cancer Patient Outcomes After Adjuvant Radiotherapy Using Intensity-Modulated Radiotherapy or Conventional Tangential Radiotherapy

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**Abstract:** The aim of the article is to analyze breast cancer patient clinical outcomes after long-term follow-up using intensity-modulated radiotherapy (IMRT) or conventional tangential radiotherapy (cRT).

We retrospectively reviewed patients with stage 0–III breast cancer who received breast conserving therapy between April 2004 and December 2007. Of the 234 patients, 103 (44%) were treated with IMRT and 131 (56%) were treated with cRT. A total prescription dose of 45 to 50 Gy (1.8–2 Gy per fraction) was delivered to the whole breast. A 14 Gy boost dose was delivered in 7 fractions. The median follow-up was 8.2 years.

Five of 131 (3.8%) cRT-treated patients and 2 of 103 (1.9%) IMRT-treated patients had loco-regional failure. The 8-year loco-regional failure-free survival rates were 96.7% and 97.6% ( $P = 0.393$ ) in the cRT and IMRT groups, respectively, whereas the 8-year disease-free survival (DFS) rates were 91.2% and 93.1%, respectively ( $P = 0.243$ ). Patients treated with IMRT developed  $\geq$  grade 2 acute dermatitis less frequently than patients treated with cRT (40.8% vs 56.5%;  $P = 0.017$ ). There were no differences in late toxicity.

IMRT reduces  $\geq$  grade 2 acute skin toxicity. Local control, DFS, and overall survival were equivalent with IMRT and cRT. IMRT can be considered a standard technique for breast cancer treatment.

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**Abbreviations:** BCS = breast-conserving surgery, CI = confidence interval, cRT = conventional tangential radiotherapy, CTV = clinical target volume, DFS = disease-free survival, HR = hazard ratio, IMRT = intensity-modulated radiotherapy, LC = local control, LRRFS = loco-regional failure-free survival, MLC = multileaf collimator, OS = overall survival, PTV = planning target volume, RT = radiotherapy.

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## INTRODUCTION

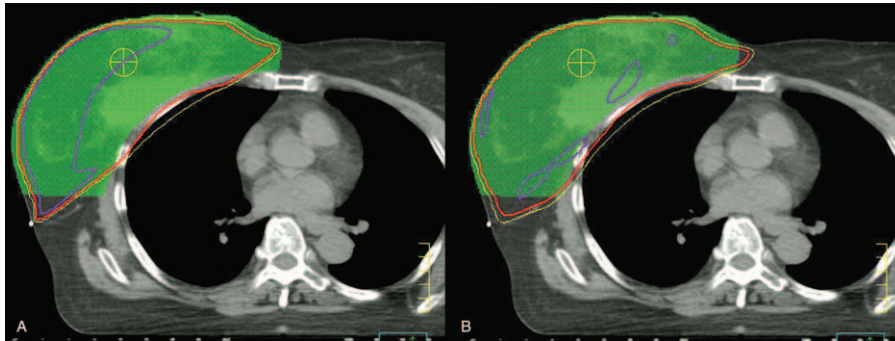
Breast-conserving surgery (BCS) followed by adjuvant radiotherapy (RT) for patients with early breast cancer reduces local recurrence more than surgery alone. Numerous randomized trials have demonstrated that this standard of care can achieve an overall survival (OS) that is equivalent to that achieved with a mastectomy.<sup>1,2</sup> RT is beneficial for breast cancer treatment but is also associated with acute and late toxicity.<sup>3,4</sup> Because most patients with breast cancer survive for long periods of time, radiation toxicity is a significant concern. Acute toxicities include erythema and dry or moist desquamation. A small number of patients develop late skin toxicities such as telangiectasia, lymphedema, and skin fibrosis. Most patients can tolerate skin toxicity well but the side effects worsen breast cosmesis and patient quality of life.<sup>3,4</sup> Additionally, inhomogeneity of the dose delivered to the breast leads to both acute and late skin effects. When using conventional tangential RT (cRT), a 15% to 20% higher dose in the superior and inferior regions of the breast compared to the prescribed dose is likely, which can result in increased skin toxicity.<sup>5,6</sup>

Intensity-modulated RT (IMRT) is a novel technique in breast cancer treatment that involves a combination of computed tomography simulation, inverse planning, optimization, and multileaf collimator (MLC). Inhomogeneity in the dose can be corrected using this technique. Some studies have shown that the treatment volume that received 110% of the prescribed dose decreased from a median of 10% with cRT to 0.1% with IMRT.<sup>7,8</sup> Therefore, less skin toxicity is expected.<sup>9</sup> However, there are also potential disadvantages. It has been postulated that removing hotspots with IMRT can lead to dose de-escalation, especially to the skin.<sup>10,11</sup> Furthermore, the distribution of the planned dose differs from the distribution delivered to the moving target due to the interplay effect between the MLC and respiratory motion during dose delivery.<sup>12</sup> All of these effects may compromise disease control.

Although the application of IMRT to breast cancer treatment is emerging, the long-term results of comparisons between patients treated with IMRT or cRT have seldom been reported. Moreover, previous studies have focused on Caucasians and results for Asians are still unclear. Here, we report the clinical results of a comparison between cRT and IMRT for breast cancer treatment after long-term follow-up, with a particular focus on loco-regional control and skin toxicity.

## METHODS

We evaluated medical notes to identify breast cancer patients who received adjuvant RT after surgery at our institute between April 2004 and December 2007. Patients were included in the study if they had unilateral stage 0–III breast cancer with



**FIGURE 1.** (A) An example of the isodose curves in conventional tangential radiotherapy. A total dose of 50 Gy, 2 Gy per fraction, was prescribed to the reference point (yellow circle), located near the breast center. The dose to the margins of the target was ~45 Gy. The green color wash represents the clinical target volume. The yellow, red, and purple lines represent the dose curves of 40, 45, and 50 Gy (B) An example of the isodose curves in intensity-modulated radiotherapy. A total dose of 45 Gy, 1.8 Gy per fraction, was prescribed to the margin of the PTV. The green color wash represents the clinical target volume. The yellow, red, and purple lines represent the dose curves of 40, 45, and 50 Gy.

histological validation, underwent BCS, were > 18 years of age and had no previous history of breast cancer or other malignancies. A review of the pathological reports was mandatory for an accurate diagnosis. All patients were retrospectively restaged according to the 7th Edition of the American Joint Committee on Cancer.<sup>13</sup> Exclusion criteria included the performance of modified radical mastectomy, male breast cancer, previous RT to the same breast, connective tissue disease, or stage IV disease and RT with a palliative intent.

Following surgery, patients received chemotherapy first if postoperative RT and chemotherapy were clinically indicated. Hormone therapy was administered depending on oestrogen receptor and progesterone receptor status and was administered after completion of RT.

When IMRT was first introduced at our institute, we agreed that the choice of technique would be determined based on the side of the breast that required treatment. Left-sided breast cancer was treated with IMRT to reduce the dose to the heart whereas right-sided breast cancer was treated using cRT. All of the patients provided the informed consent before treatment.

Computed tomography (Siemens Somatom Emotion) simulation of the chest wall with a 3 mm slice thickness was utilized in all cases. During the scan, patients were in a supine position on a breast board (Med-Tec MT-350-N) with the ipsilateral arm externally rotated and abducted overhead.

A parallel-opposed tangential technique was used for cRT. The clinical target volume (CTV) was set at the first intercostal space cranially, 1 to 2 cm below the breast tissue caudally, at the mid-sternum line medially, at the midaxillary line laterally, at skin anteriorly and at the anterior aspect of pectoralis muscle posteriorly. To account for set-up uncertainty and respiratory target motion, the planning target volume (PTV) was generally generated by expanding the CTV by 8 mm. It was also allowed to adjust the expansion of the CTV border by the physician's discretion when tumor size, tumor location, and the dose to the contralateral breast tissue were taken into consideration. The collimator was rotated to accommodate the slope of the chest wall. A nondivergent, deep beam edge was achieved by adjusting the gantry angle with acceptable 1 to 2 cm of underlying lung in the field. A flash distance of at least 2 cm was allowed above the breast. Nucletron Plato RTS v2.6.3 planning system with pencil beam dose calculation algorithm was used for tangential field design. The whole breast was treated with a daily dose of 2 Gy, 5 fractions per week, with a total prescription

dose of 50 Gy to the reference point, which was located near the center of the breast (Figure 1A). The margin areas around the target received ~45 Gy. Mega-voltage equipment was used to deliver a standard 6 MV photon beam. If patients had pathological lymph node involvement, the supraclavicular field was irradiated with the delivery of 45 to 50 Gy, 1.8 to 2 Gy per fraction, 5 fractions per week. Geometric matching to the tangential field was necessary to achieve using different methods. The field was angled 10 to 15° laterally to spare the spinal cord, which was limited superiorly by the thyrocricoid groove, inferiorly by the caudal edge of the clavicular head, medially by the lateral edge of the vertebral body, and laterally by the lateral edge of the humeral head. The tumour bed was boosted in all patients. The electron energy was selected to encompass the target volume depth in an 85% to 90% iso-dose line, which was based on a physical examination, imaging, or the location of the metallic surgical clips. An appositional technique was used to deliver 14 Gy at a daily dose of 2 Gy.

IMRT was performed using a step-and-shoot MLC technique. The orientation and margin of the field border was the same as that of conventional techniques for CTV and PTV. A total dose of 45 Gy, 1.8 Gy per fraction, 5 fractions per week was prescribed to the margin of the PTV with a 6 MV photon beam (Figure 1B). If supraclavicular irradiation or tumor bed boost was clinically indicated, the same dose and fractionation was scheduled as cRT. The dose-volume histogram was plotted using the same planning system as the one used in cRT. The inverse planning method was performed to design a plan which was required to contain 3 to 7 gantry angles and a 90% to 95% iso-dose volume that received a total prescription dose.

Physicians evaluated patients each week during treatment. The physicians maintained a record of any skin changes in the medical notes. After treatment, all patients were followed with clinical examinations at regular intervals. All medical notes were thoroughly reviewed for toxicity grade and disease status. We checked the specific terms that were used to describe the skin toxicity to assist with grading. Acute skin toxicities were graded retrospectively using the Common Terminology Criteria for Adverse Events, version 4 (CTCAE, v 4.0). We also identified any possible radiation-related late toxicities including telangiectasia, lymphedema, pigmentation, and fibrosis.

Discontinuous variables associated with treatment techniques were examined by chi-square tests. Student's independent *t* tests were used to determine the statistical significance of

the differences in the mean between continuous variables. Skin toxicity was compared between the 2 groups using the chi-square test. The follow-up times were measured from the last day of RT. Patients were censored at the day of event, death from any cause or the day of last hospital visit, whichever came first. For loco-regional failure-free survival (LRFFS) analysis, only loco-regional failure was the event of interest which was defined as the appearance of tumors at the chest wall, axilla, or supraclavicular or infra-clavicular area with pathological confirmation. Disease-free survival (DFS) was defined as the length of time of survival without loco-regional failure, distant metastasis, development of second primary cancer or death from any cause. Second primary cancer was determined through tumor board discussion as the ipsilateral tumors with distinct features from the first one. The Kaplan–Meier method was used to estimate survival and the differences between groups were assessed using the log-rank test. The Cox Proportional Hazards regression model was used to calculate the adjusted LRFFS and DFS curves and also to identify univariates and multivariates associated with LRFFS and DFS.  $P < 0.05$  was considered statistically significant for all tests. SPSS (SPSS Inc. Chicago, IL) version 22 was used for data analysis.

**RESULTS**

The characteristics of patients included in the study are shown in Table 1. Out of a total of 234 patients that were treated, 103 received IMRT and 131 received cRT. There were no significant differences in the distribution of characteristics between the 2 groups. At the time of the analysis, the median follow up was 8.2 years. Loco-regional failure was observed in 5 of 131 (3.8%) of patients treated with cRT and in 2 of 103 (1.9%) of patients treated with IMRT. The 8-year LRFFS rates were 96.7% and 97.6% ( $P = 0.393$ ) for the cRT and IMRT groups, respectively, whereas the 8-year DFS rates were 91.2% and 93.1%, respectively ( $P = 0.243$ ). A sensitivity analysis was conducted in which death from any cause was included as an event. The 8-year LRFFS was still not statistically significant with 94.4% in the cRT group and 96.5% in the IMRT group ( $P = 0.244$ ).

The univariate and multivariate analysis of factors associated with loco-regional failure are summarized in Table 2. A Cox proportional hazards regression model indicated that the risk of loco-regional failure was higher in patients with age  $\leq 45$  years (hazard ratio [HR], 11.23; 95% confidence interval [CI], 1.40–93.46;  $P = 0.025$ ),  $\geq 4$  positive lymph nodes (HR, 11.82; 95% CI, 2.64–53.01;  $P = 0.001$ ), a positive margin (HR, 7.27; 95% CI, 0.87–60.51;  $P = 0.067$ ), and the presence of lymphovascular space invasion (HR, 5.19; 95% CI, 1.14–23.61;  $P = 0.033$ ). The factors that remained independently significant in the multivariate analysis included age  $\leq 45$  years (HR, 9.00; 95% CI, 1.06–76.57;  $P = 0.044$ ) and  $\geq 4$  positive lymph nodes (HR, 5.55; 95% CI, 1.01–30.42;  $P = 0.048$ ). The adjusted LRFFS curves for the IMRT and cRT groups after adjusting for these 2 factors did not differ significantly (Figure 2,  $P = 0.569$ ).

The univariate and multivariate analyses of factors associated with DFS are summarized in Table 3. Based on the univariate analysis,  $\geq 4$  positive lymph nodes, the presence of lymphovascular space invasion, and the use of chemotherapy were significant prognostic factors for DFS. A multivariate analysis indicated that only  $\geq 4$  positive lymph nodes (HR, 3.62; 95% CI, 1.21–10.80;  $P = 0.021$ ) remained independently significant. After adjusting for the factor of  $\geq 4$  positive lymph nodes, there was no significant difference in the DFS curves for

**TABLE 1. Patient Characteristics**

Variable	IMRT	cRT	P Value
	No. of Patients (%)	No. of Patients (%)	
No. of patients	103 (44)	131 (56)	
Age (y)			0.432
Mean (SD)*	49.3 (7.8)	48.4 (9.6)	
Range	32–73	26–85	
BMI (kg/m <sup>2</sup> )			0.326
Mean (SD)*	23.9 (3.7)	23.3 (4.6)	
Tumor size, cm			0.633
$\leq 2$	75 (72.8)	88 (67.2)	
2–5	27 (26.2)	41 (31.3)	
$> 5$	1 (1)	2 (1.5)	
pLN			0.217
0	89 (86.4)	102 (77.9)	
1–3	8 (7.8)	19 (14.5)	
$\geq 4$	6 (5.8)	10 (7.6)	
Stage			0.406
In situ disease	17 (16.5)	20 (15.3)	
I	52 (50.5)	54 (41.2)	
II	27 (26.2)	47 (35.9)	
III	7 (6.8)	10 (7.6)	
Grade			0.942
1	20 (19.4)	27 (20.6)	
2	38 (36.9)	48 (36.6)	
3	41 (39.8)	49 (37.4)	
Unknown	4 (3.9)	7 (5.3)	
Surgical margin			0.237
Positive	2 (1.9)	3 (2.3)	
$\leq 2$ mm	20 (19.4)	15 (11.5)	
$> 2$ mm	81 (78.6)	113 (86.3)	
LVSI			0.718
Positive	14 (13.6)	20 (15.3)	
Negative	89 (86.4)	111 (84.7)	
ER status			0.960
Positive	75 (72.8)	95 (72.5)	
Negative	28 (27.2)	36 (27.5)	
PR status			0.931
Positive	76 (73.8)	96 (73.3)	
Negative	27 (26.2)	35 (26.7)	
Her2/neu status			0.821
Positive	20 (19.4)	27 (20.6)	
Negative	83 (80.6)	104 (79.4)	
Chemotherapy			0.481
Yes	59 (57.3)	81 (61.8)	
No	44 (42.7)	50 (38.2)	
Hormone therapy			0.671
Yes	78 (75.7)	96 (73.3)	
No	25 (24.3)	35 (26.7)	

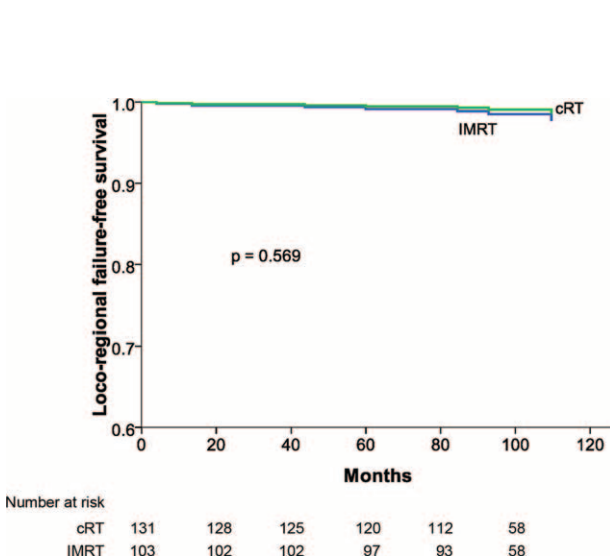
BMI = body mass index, cRT = conventional radiotherapy, ER = estrogen receptor, IMRT = intensity-modulated radiotherapy, LVSI = lymphovascular space involvement, pLN = positive lymph node, PR = progesterone receptor, SD = standard deviation.  
\*t test.

the IMRT and cRT groups (Figure 3,  $P = 0.263$ ). The OS rate at 8 years was 97.6% for women treated with cRT and 98.9% for woman treated with IMRT ( $P = 0.429$ ).

**TABLE 2.** Prognostic Factors on LRFFS by Cox Proportional-Hazards Model

Variable	8-Year LRFFS (%) (All Patients)	Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P
Age, y					
≤45 vs >45	93.9 vs 99	11.23 (1.40–93.46)	0.025	9.00 (1.06–76.57)	0.044
Tumor size					
≤2 vs >2	97.7 vs 95.8	0.57 (0.13–2.53)	0.458		
pLN					
≥4 vs <4	87.1 vs 97.9	11.82 (2.64–53.01)	0.001	5.55 (1.01–30.42)	0.048
Grade > 2					
Yes vs no	96.8 vs 97.3	1.04 (0.23–4.64)	0.960		
Positive margin					
Yes vs no	80.0 vs 97.5	7.27 (0.87–60.51)	0.067	3.28 (0.30–36.73)	0.335
LVSI					
Yes vs no	89.6 vs 98.4	5.19 (1.14–23.61)	0.033	2.68 (0.47–15.29)	0.268
ER positive					
Yes vs no	97.9 vs 95.1	0.51 (0.11–2.28)	0.378		
PR positive					
Yes vs no	96.9 vs 98.0	2.48 (0.30–20.66)	0.402		
Her2/neu positive					
Yes vs no	95.7 vs 97.5	1.64 (0.32–8.44)	0.556		
Chemotherapy					
No vs yes	100 vs 95.2	0.02 (0–10.35)	0.221		
Hormone therapy					
No vs yes	96.4 vs 97.4	1.15 (0.22–5.92)	0.869		
RT technique					
IMRT vs cRT	97.6 vs 96.7	0.50 (0.10–2.56)	0.402		

CI = confidence interval, cRT = conventional radiotherapy, ER = estrogen receptor, HR = hazard ratio, IMRT = intensity-modulated radiotherapy, LRFFS = locoregional failure free survival, LVSI = lymphovascular space involvement, pLN = positive lymph node, PR = progesterone receptor, RT = radiotherapy.



**FIGURE 2.** A comparison of the loco-regional failure-free survival (LRFFS) curves for patients treated with intensity-modulated radiotherapy (IMRT) or conventional tangential radiotherapy (cRT) after adjusting for potential prognostic factors using a Cox regression hazard model. cRT=conventional radiotherapy, IMRT=intensity-modulated radiotherapy, LRFFS= loco-regional failure-free survival.

Treatment interruption occurred in 9 patients: 8 patients in the cRT group and 1 patient in the IMRT group (6.1% vs 1.0%, respectively;  $P = 0.043$ ). All of interruptions were caused by skin toxicity. They all eventually completed radiotherapy after improvement of dermatitis except 1 patient in the cRT group who did not complete planned treatment dose. Differences in acute and late toxicities between the IMRT and cRT groups are shown in Table 4. For patients treated with IMRT, 36.9% had grade 2 and 3.9% had grade 3 dermatitis. For patients treated with cRT, 45% had grade 2 and 11.5% had grade 3 dermatitis. The frequency of grade 2 or 3 dermatitis decreased significantly in the IMRT group compared with the cRT group (40.8% vs 56.5%, respectively;  $P = 0.017$ ). In addition, patients treated with IMRT developed less moist desquamation compared to patients treated with cRT. In terms of late toxicity, there was no statistically significant difference between the IMRT and cRT groups.

A high body mass index (BMI) tended to be associated with increased skin toxicity. Patients with grade  $\geq 2$  dermatitis had higher BMI values than those with grade 0–1 dermatitis (median BMI: 24.07 vs 23.08, respectively;  $P = 0.077$ ). Furthermore, a high BMI was significantly associated with an increased risk of moist desquamation (median BMI: 25.82 vs 23.12, respectively;  $P < 0.001$ ).

**DISCUSSION**

The introduction of IMRT provided an opportunity to reduce side effects by improving dose inhomogeneity and

**TABLE 3.** Prognostic Factors on DFS by Cox Proportional-Hazards Model

Variable	8-y DFS (%) (All Patients)	Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P
Age, y					
≤45 vs > 45	91.3 vs 92.5	1.30 (0.52–3.24)	0.572		
Tumor size					
≤2 vs >2	93.7 vs 88.1	0.57 (0.23–1.42)	0.226		
pLNs					
≥4 vs <4	75 vs 93.4	6.19 (2.22–17.23)	<0.001	3.62 (1.21–10.80)	0.021
Grade >2					
Yes vs no	92.8 vs 91.4	0.74 (0.29–1.89)	0.535		
Positive margin					
Yes vs no	80 vs 92.3	2.58 (0.34–19.32)	0.357		
LVSI					
Yes vs no	81 vs 94	3.94 (1.54–10.07)	0.004	2.37 (0.86–6.49)	0.095
ER positive					
Yes vs no	92 vs 92	0.84 (0.32–2.20)	0.714		
PR positive					
Yes vs no	91.2 vs 94.7	1.50 (0.50–4.53)	0.473		
Her2/neu positive					
Yes vs no	91.2 vs 92.2	1.10 (0.36–3.30)	0.871		
Chemotherapy					
No vs yes	96.2 vs 89.3	0.27 (0.08–0.91)	0.035	0.42 (0.11–1.57)	0.200
Hormone therapy					
No vs yes	94.7 vs 91.1	0.54 (0.16–1.85)	0.325		
RT technique					
IMRT vs cRT	93.1 vs 91.2	0.57 (0.22–1.50)	0.250		

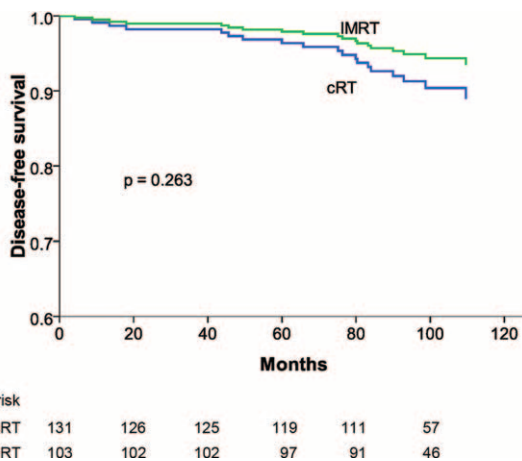
CI = confidence interval, cRT = conventional radiotherapy, DFS = disease-free survival, ER = estrogen receptor, HR = hazard ratio, IMRT = intensity-modulated radiotherapy, LVSI = lymphovascular space involvement, pLN = positive lymph node, PR = progesterone receptor, RT = radiotherapy.

sparing the normal tissue. Although many institutions have shifted to IMRT for treatment of breast cancer, the use of IMRT still is criticized due to the lack of large-scale, long-term clinical results. In this study, we demonstrated that IMRT

is superior to cRT in terms of reducing acute radiation dermatitis. The efficacy of IMRT for disease control is comparable to that of cRT after an 8-year follow-up period.

Dosimetric comparison between different radiotherapy techniques indicated IMRT has dosimetric superiority than cRT. Barnett et al reported IMRT decreases mean volumes receiving >107% (vol > 107) and <95% (vol < 95) of the prescribed dose by 34.0 cm<sup>3</sup> and 48.1 cm<sup>3</sup>, respectively, when compared with standard tangential plans.<sup>14</sup> Zhang and Zheng reported IMRT has the not only best index of the PTV but also lower Dmax than cRT and 3-dimensional conformal radiation therapy.<sup>15</sup> These phenomenon could explain why IMRT can reduce dermatitis compared with cRT.

The advantages of dose homogeneity achieved with IMRT did translate into clinical benefits. Pignol et al reported the results of the first randomized trial of breast IMRT versus cRT in evaluation of acute radiation skin toxicity.<sup>3</sup> The study demonstrated that 31.2% of breast cancer patients in the IMRT group experienced moist desquamation compared to 47.8% of patients that received standard treatment (P = 0.002). In a retrospective analysis, Harsolia et al reported that ≥ grade 2 acute breast dermatitis was significantly reduced with IMRT compared to conventional wedges (41% vs 85%, respectively; P < 0.001).<sup>16</sup> In a single-institution study, McDonald et al reported that treatment with IMRT resulted in decreased acute RTOG grade 2 or 3 dermatitis compared to cRT (39% vs 52%, respectively; P = 0.047).<sup>17</sup> Our study results indicated that IMRT reduced the frequency



**FIGURE 3.** A comparison of the disease-free survival (DFS) curves for patients treated with intensity-modulated radiotherapy (IMRT) or conventional tangential radiotherapy (cRT) after adjusting for potential prognostic factors using a Cox regression hazard model. cRT = conventional radiotherapy, DFS = disease-free survival, IMRT = intensity-modulated radiotherapy.

**TABLE 4.** Acute and Late Toxicity Between IMRT and cRT

	IMRT No. of Patients (%)	cRT No. of Patients (%)	P Value
Acute toxicity			
Grade 2–3	42 (40.8)	74 (56.5)	0.017
Dry desquamation	24 (23.3)	27 (20.6)	0.621
Moist desquamation	11 (10.7)	28 (21.4)	0.029
Late toxicity			
Induration/fibrosis	4 (3.9)	10 (7.6)	0.230
Telangiectasia	0 (0)	4 (3.1)	0.074
Pigmentation	10 (9.7)	20 (15.3)	0.207
Arm lymphedema	22 (21.4)	17 (13.0)	0.088

cRT = conventional radiotherapy, IMRT = intensity-modulated radiotherapy.

of  $\geq$  grade 2 dermatitis and moist desquamation, which was consistent with the previous study.

Many large, randomized trials have demonstrated long-term LC (local control) rates, DFS or OS of adjuvant radiotherapy in breast cancer treatment using conventional techniques. The treatment efficacy of IMRT compared to cRT has rarely been reported. Mukesh et al<sup>18</sup> reported that there was no statistically significant difference in the 5-year loco-regional recurrence and OS rates in a randomized controlled trial. In the study by McDonald et al, no significant difference in the 7-year LC, DFS, and OS rates was found between patients treated with IMRT and cRT.<sup>17</sup> In our study, there was no difference in 8-year LC, DFS, and OS between treatment arms. Based on these results, IMRT may not compromise LC. Further prospective, randomized trials are necessary to confirm the equivalent outcomes achieved with IMRT and cRT.

Death is a competing event of loco-regional recurrence; however, we did not conduct a competing risk analysis. In this study, only 3 patients died in the cRT group whereas 1 patient died in the IMRT group. Of those died, 2 died of breast cancer with distant metastasis and 2 died of other causes. No patient had locoregional recurrence. We could not exclude the possibility that those died had further locoregional recurrence if they did not die. However, those patients did not possess factors associated with loco-regional failure, such as young age, positive margin. Loco-regional failure in those patients may be less likely. Furthermore, there were only few death events. We included death from any cause as an event for sensitivity analysis and the LRFFS was still not statistically significant between 2 groups. So, we considered death being a competing event would not be a serious issue.

The rationale for the use of IMRT in breast cancer treatment has been questioned in recent publications.<sup>19,20</sup> The main argument is that better target coverage does not translate into better tumor control. Even so, IMRT undoubtedly represents the refinement of cancer treatment. It is irrefutable that the use of IMRT reduces toxicity. Given that the incidence of breast cancer has been increasing worldwide, more patients may gain quality of life and psychological comfort with IMRT treatment, which are almost as important as tumor control. Another argument is the cost-effectiveness of IMRT. Some studies show IMRT is a more expensive approach.<sup>21,22</sup> Many factors should be taken into consideration for patient selection in order to implant IMRT in patients who will benefit more. Then, the balance between medical costs and the potential benefits of IMRT can be achieved in clinical practice.

There were some limitations in our study. First, it was a retrospective, single-institution study. Therefore, it is possible that not all the toxicities were captured. Second, the study included a relatively small number of patients. Nevertheless, this is one of few studies to date that has reported clinical outcomes after long-term follow-up of patients with breast cancer after IMRT.

## CONCLUSION

IMRT not only showed promise in reducing acute skin toxicity in patients with breast cancer but also showed comparable long-term LC, DFS, and OS to cRT. IMRT can therefore be considered a standard technique for breast cancer treatment.

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