

## Prone breast forward intensity-modulated radiotherapy for Asian women with early left breast cancer: factors for cardiac sparing and clinical outcomes

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(Received 10 September 2012; revised 25 January 2013; accepted 17 February 2013)

Since December 2009, after breast-conserving surgery for Stage 0–I cancer of the left breast, 21 women with relatively pendulous breasts underwent computed tomography prone and supine simulations. The adjuvant radiotherapy was 50 Gy in 25 fractions to the left breast alone. Four plans—conventional wedged tangents and forward intensity-modulated radiotherapy (fIMRT) in supine and prone positions—were generated. fIMRT generated better homogeneity in both positions. Prone position centralized the breast tissue by gravity and also shortened the breast width which led to better conformity in both planning techniques. Prone fIMRT significantly reduced doses to left lung, Level I and Level II axilla. The mean cardiac doses did not differ between positions. Among the four plans, prone fIMRT produced the best target dosimetry and normal organ sparing. In subgroup analysis, patients with absolute breast depth > 7 cm in the prone position or breast depth difference > 3 cm between positions had significant cardiac sparing with prone fIMRT. Sixteen patients with significant cardiac sparing in prone position were treated using prone fIMRT and the others using supine fIMRT. All patients received a supine electron tumor bed boost of 10 Gy in 5 fractions. No patients developed Grade 2 or worse acute or late toxicities. There was no difference in the number of segments or beams, monitor units, treatment time, or positioning reproducibility between prone and supine positions. At a median follow-up time of 26.8 months, no locoregional or distant recurrence or death was noted.

**Keywords:** breast cancer; prone breast radiotherapy; intensity-modulated radiotherapy; breast tangents; Asian women

### INTRODUCTION

Breast-conserving surgery with adjuvant radiotherapy has been shown in several large randomized controlled trials to yield survival rates equivalent to those of mastectomy in the treatment of early-stage breast cancer [1]. For patients with left breast cancer, the supine tangential fields anatomically include partial volumes of the underlying lung, heart and left anterior descending coronary artery (LAD). Clinical experiences in the last two decades have indicated

the advantages of prone position in achieving better dose distributions and in sparing normal tissue in large-breasted western women [2, 3]. Prone breast irradiation has provided consistently lower lung doses, with varied effects on cardiac dose [4–6]. The criteria for selecting patients who would benefit most from prone radiotherapy are still under investigation.

The standard technique for treating breast cancer patients is conventional wedged tangential fields. Intensity-modulated radiotherapy (IMRT)—including simplified IMRT [7],

forward IMRT (fIMRT) [8], and inverse IMRT [9, 10]—has been applied to whole-breast irradiation to achieve better dose homogeneity and to reduce acute toxicities compared with conventional wedged tangential fields. However, the IMRT procedure does not consistently prevent doses to normal tissues. Although most IMRT studies have demonstrated a potential reduction of high-dose area in cardiac and lung toxicity, divergent results for increased cardiac and lung dosage have been seen by different IMRT planning algorithms [10]. Also, low-dose spillage to normal organs, especially the contralateral breast and lung, through the use of multiple beams and longer beam-on times, which might eventually increase the risk of contralateral breast [11] or lung malignancy [12], is a concern.

The body figures and breast volumes of Asian women are generally leaner than those of western women. In recent decades, the increasing Westernization of lifestyle [13] has been associated with increased body mass indexes, enlarged breast size, and probably increased incidence of breast cancer among Asian women [14]. Large whole-breast clinical target volume (CTV) has been considered to be associated with improved cardiac dosimetry in prone position for whole-breast irradiation in a recent publication [15]. We believe that the new strategy of whole-breast irradiation in prone position may have become beneficial for more Asian women over recent decades. In preliminary studies we treated women in the prone position using a prone breast-plate, modifying the plate to fit the body type of Asian women, and found that the prone position was helpful in resolving dose heterogeneity for large breasts and in reducing ipsilateral lung, axilla and heart doses. The relationship between treatment-planning techniques (conventional wedged tangents vs fIMRT), combined with different positions (supine vs prone), and dose homogeneity or conformity has not been documented.

The purpose of this study was to assess the effects of fIMRT or prone position on better dose distributions, to determine differences in normal organ sparing between positions, to determine acute toxicities during prone

radiotherapy, to identify patient-selection criteria for prone radiotherapy, and to assess clinical outcomes after prone radiotherapy among Asian women with left breast cancer.

## MATERIALS AND METHODS

### Patient population

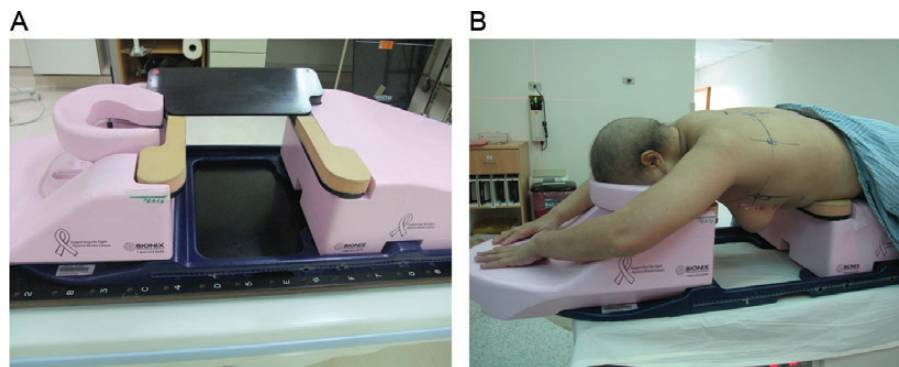
Women with left Stage 0–I breast cancer receiving breast-conserving therapy were referred for adjuvant radiotherapy. Since December 2009, patients with relatively large and pendulous breasts have been considered for prone radiotherapy. Body mass index (BMI) is calculated as weight (kg) divided by height (m) squared at the time of enrollment before simulation.

### Positioning and image acquisition

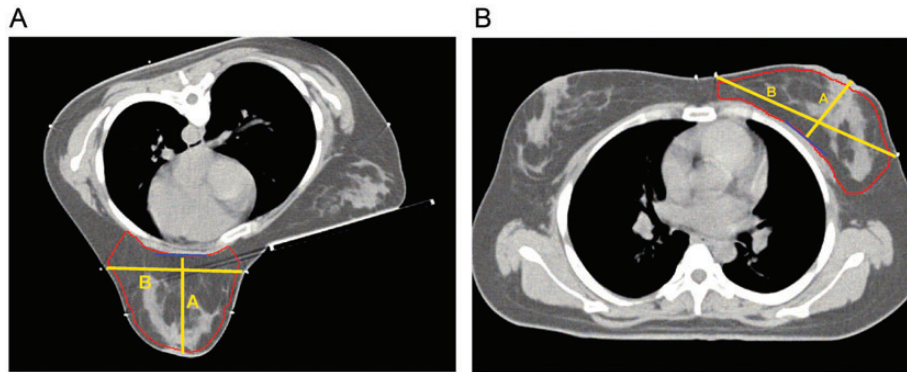
Patients underwent computed tomography (CT) simulation in the prone and supine positions. We modified the original Bionix prone breast system (Bionix, Toledo, OH, USA) (Fig. 1A) to fit the body type of Asian women, added the front handles for both arms to hold superiorly, and modified the support wedges to allow the contralateral breast to be placed laterally away from the radiation fields (the wedge could be adjusted to accommodate the appropriate slope). The patient lay prone on the plate with the left breast hanging in a dependent fashion (Fig. 1B). In the supine position, the patient lay within an individually designed vacuum cushion that immobilized the body with the left arm extending above the head. Wires were placed at the midsternum midline, at the midaxillary line, and around the palpable breast to define the breast CTV in both positions.

### Target delineation

The CTV and organs-at-risk (OARs) were contoured on the CT slices by one radiation oncologist and verified by another. The CTV, breast depth, and palpable breast width were measured (Fig. 2). The CTV was defined as the entire



**Fig. 1.** (A) The modified prone breast system was used for Asian women with left breast cancer. (B) The patient lay prone on the plate with the left breast hanging from the chest wall in a gravity-dependent fashion.



**Fig. 2.** The clinical target volume (CTV) was defined as the entire palpable breast tissue encircled by wires extending to within 5 mm of the skin surface. The breast depth A (the distance between the chest wall and the most gravity-dependent part) and breast width B (the maximal width between the posterior edge of the palpable breast, encircled by wires) were measured in prone (A) and supine (B) positions.

palpable breast tissue encircled by wires plus any additional dense breast tissue visualized on CT, extending to within 5 mm of the skin surface. The breast depth was defined as the distance between the chest wall and the most gravity-dependent part (the nipple), and the palpable breast width was defined as the maximal distance between the posterior edge of the palpable breast encircled by wires. The Level I and II axilla and the right breast were outlined according to the Radiation Therapy Oncology Group (RTOG) breast cancer atlas. The heart, right ventricle, left ventricle and LAD, which originated from the left coronary artery and ran in the interventricular groove between the right and left ventricles, were contoured based on heart atlas references [16]. A 10-mm axial margin was added to the LAD to cover delineation uncertainty, respiratory motion, and heart-beating displacements [17].

### Radiotherapy planning

The treatment-planning system (Pinnacle 3, version 8.0 c; Philips Medical Systems, Miltipias, CA, USA) was used to generate conventional wedged tangents and fIMRT plans in both positions, utilizing the collapsed cone convolution dose calculation algorithms. The medial border of the field was the anatomical midline for both positions. Appropriate tangential beam angles were decided primarily during simulation for supine and during treatment planning for prone radiotherapy. The wedged tangents plans used 6- and 10-MV beam energies, whereas the fIMRT plans used only 6-MV beam energy. A dose of 50 Gy in 25 fractions was normalized to a midplane point 1 cm anterior to the posterior field edge near the lung–chest wall junction. Single or combined wedged pairs in conventional tangential plans, or field-in-fields segments using a multileaf collimator in fIMRT plans, were forwardly superimposed on the basic tangential fields to maintain the breast tissue dose within 95–110%.

The homogeneity index (HI) was defined as  $(D_{2\%} - D_{98\%})/D_{50\%}$ .  $D_{2\%}$ ,  $D_{98\%}$ , and  $D_{50\%}$  were the dose received by 2, 98 and 50% (respectively) of the CTV. A lower HI indicated better homogeneity [18]. The conformity index was defined as  $(TV \times PV)/(TV_{PV})^2$ , where TV was the volume of CTV, PV was the prescription volume (the treatment volume of the 50-Gy isodose line), and  $TV_{PV}$  was the target volume within the prescribed isodose surface (the volume of TV within the PV) [19]. A lower CI indicated better dose conformity. The ‘ $V_{105\%}/V_{95\%}$  irradiated tissue’ was defined as the volume of tissue outside the CTV receiving  $\geq 52.5$  Gy divided by the volume receiving  $\geq 47.5$  Gy. The radiation exposures to OARs were recorded in both positions.

### Radiotherapy treatment and follow-up

Since prone fIMRT is an investigational technique expected to be beneficial on targets dosage and lung/axilla sparing, and questionable on cardiac exposure, patients without significant cardiac sparing in prone position were conventionally treated in traditional supine position. The treatment was performed using a Siemens Linear Accelerator. The number of segments or beams, monitor units and treatment time were recorded. Weekly port film obtained with an electronic portal imaging device was checked to ensure positional accuracy during treatment. Analysis of each port image involved measurements of the central lung distance (CLD, the distance from the posterior field margin to the inner chest wall along the horizontal axis of the field) and the central flash distance (CFD, the distance from the breast surface to the anterior field edge along the horizontal axis). The action level of necessity to correct the position was set at 5 mm. All patients received a sequential electron boost of up to 10 Gy in 5 fractions to the tumor bed and scar by supine position. Acute and late skin reactions (rated with RTOG Radiation Morbidity Scoring Criteria) were recorded weekly during treatment and at each visit 3–6 months after

treatment. The sites of failure were recorded for each patient, and characterized as either local (ipsilateral breast), nodal or distant.

### Analysis

Analysis was conducted using the follow-up data available on 31 May 2012. Data of target and normal tissues were organized into paired samples for comparison between positions using the two-sided Student paired *t* test. Patients were sorted by age > 50 years, BMI > 25, CTV > 450 cm<sup>3</sup>, breast depth in prone position > 7 cm, breast-depth difference (prone minus supine) > 3 cm, breast width difference (supine minus prone) > 4 cm, and tumor bed location (upper or lower breast, inner or outer breast) in order to identify patient-selection criteria for better cardiac sparing in prone position using the nonparametric Mann-Whitney

test. The number of segments or beams, monitor units, treatment time, and lengths of the displacement between positions were compared using the two-sided Student unpaired *t* test. Setup accuracy between positions was compared using the Pearson's chi-square test. *P* values of .05 were considered statistically significant. Statistical analysis was performed using SPSS version 11.5 for Windows (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Patient and treatment characteristics

A total of 21 women were considered for prone position radiotherapy. The mean age was 50.6 years (range, 21–64 years). The mean BMI was 25.1 kg/m<sup>2</sup> (range, 20.2–34.2 kg/m<sup>2</sup>). Five patients had ductal carcinoma *in situ*, three had mucinous carcinoma, and the others had invasive ductal carcinoma. Of the 21, 7 patients (33%) received adjuvant systemic therapy before the radiotherapy. The breast physical characteristics are shown in Table 1. The breast CTVs were identical for both positions (*P* = 0.336). The prone position centralized the breast tissue and resulted in a significantly greater breast depth (*P* < 0.001) and smaller palpable breast width (*P* < 0.001).

### Dose parameters for CTV

The dosimetric parameters of conventional wedged tangents and fIMRT plans in supine and prone positions are summarized in Table 2. The CTV coverage (*V*<sub>95%</sub>) was

**Table 1.** Patients' breast physical characteristics

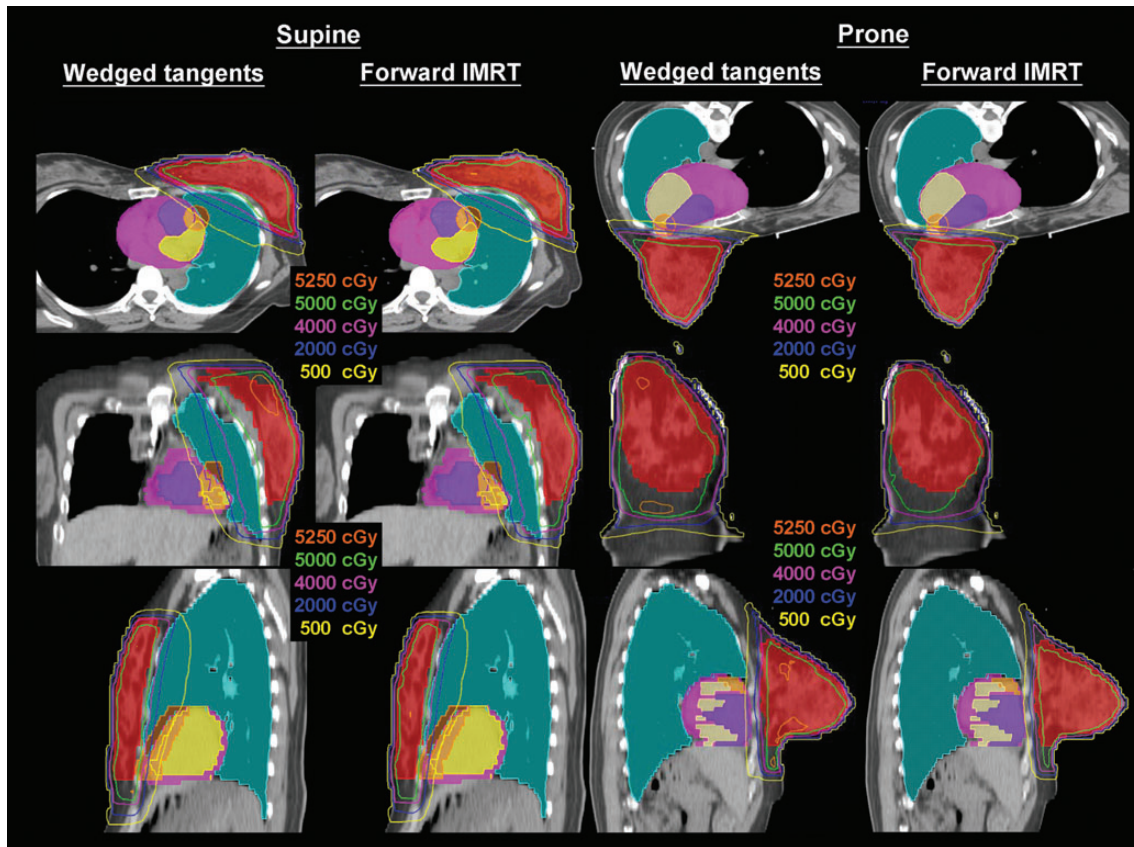
<i>n</i> = 21	Supine	Prone	<i>P</i> *
	Mean ± SD	Mean ± SD	
Breast clinical target volume (cm <sup>3</sup> )	458.7 ± 166.5	471.5 ± 204.4	0.336
Breast depth (cm)	4.4 ± 0.8	7.3 ± 1.8	<0.001
Palpable breast width (cm)	16.0 ± 1.8	12.4 ± 1.5	<0.001

SD = standard deviation, \*Significance tested using paired Student *t*-test.

**Table 2.** Dose parameters for clinical target volume (CTV)

<i>n</i> = 21	Supine wedged tangents	Supine fIMRT	<i>P</i> *	Prone wedged tangents	Prone fIMRT	<i>P</i> *	Supine vs Prone wedged tangents	Supine vs Prone fIMRT
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		<i>P</i> *	<i>P</i> *
<b>CTV</b>								
<i>D</i> <sub>max</sub> (%)	110.6 ± 2.4	105.9 ± 1.2	<0.001	111.4 ± 2.5	105.2 ± 0.6	<0.001	0.210	0.003
<i>V</i> <sub>95%</sub> (%)	94.9 ± 3.6	94.0 ± 4.4	0.004	92.4 ± 7.7	93.6 ± 6.9	0.199	0.231	0.748
<i>V</i> <sub>105%</sub> (%)	21.3 ± 9.5	0.8 ± 1.8	<0.001	23.0 ± 11.4	0.3 ± 1.0	<0.001	0.476	0.062
HI	0.128 ± 0.014	0.119 ± 0.010	0.018	0.138 ± 0.022	0.117 ± 0.011	<0.001	0.108	0.599
CI	1.803 ± 0.432	1.709 ± 0.417	0.467	1.378 ± 0.278	1.330 ± 0.237	0.545	<0.001	<0.001
<b>Irradiated tissue outside CTV</b>								
<i>D</i> <sub>max</sub> (%)	110.6 ± 2.4	106.1 ± 1.1	<0.001	111.0 ± 2.6	105.4 ± 1.6	<0.001	0.510	0.068
<i>V</i> <sub>105%</sub> (cm <sup>3</sup> )	57.6 ± 45.7	6.3 ± 14.7	<0.001	29.3 ± 34.0	0.4 ± 1.0	<0.001	0.037	0.078
<i>V</i> <sub>105%</sub> / <i>V</i> <sub>95%</sub> irradiated tissue	0.072 ± 0.056	0.013 ± 0.002	<0.001	0.047 ± 0.040	0.001 ± 0.002	<0.001	0.119	0.076

SD = standard deviation, *D*<sub>max</sub> = maximum dose, *V*<sub>95%</sub>, *V*<sub>105%</sub> = percentage of volume receiving 47.5 Gy, 52.5 Gy, HI = homogeneity index, CI = conformity index, fIMRT = forward intensity-modulated radiotherapy. \*Significance tested using paired Student *t*-test.



**Fig. 3.** The isodose distributions for one patient planned by supine wedged tangents, supine forward IMRT, prone wedged tangents, and prone forward IMRT. Color-wash areas: clinical target volume: red; left lung: light blue; heart: pink; left anterior descending coronary artery with 10-mm margin: orange; left ventricle: yellow; right ventricle: purple. The orange, green, pink, blue and yellow lines were isodose curves of 52.5, 50, 40, 20 and 5 Gy, respectively.

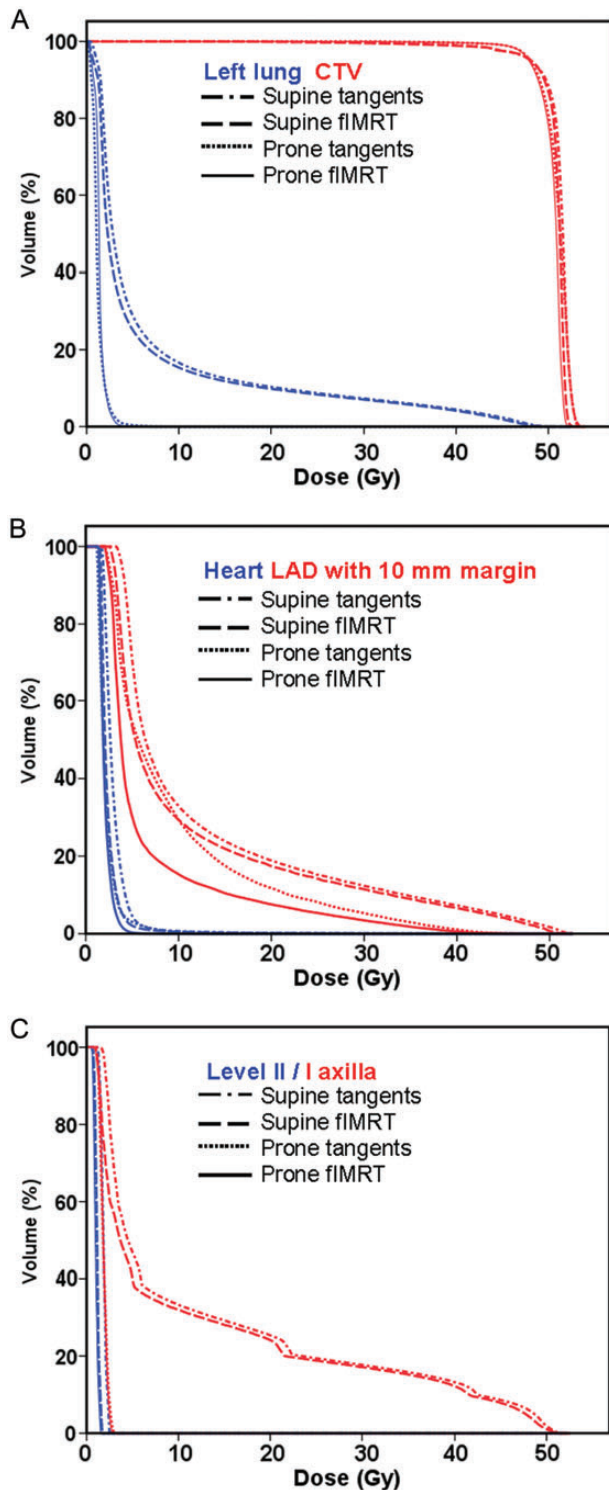
equivalently adequate in the four plans, but was slightly better in the supine wedged tangents. Compared with the wedged tangents, the fIMRT plans reduced the maximum dose and the percentage of high-dose regions inside the CTV and improved the HI in both positions ( $P = .018$  in supine position and  $P < .001$  in prone position). The fIMRT plans also reduced the maximum dose ( $D_{max}$ ), the volume of the high-dose region ( $V_{105\%}$ ), and the ratio of high-dose regions ( $V_{105\%}/V_{95\%}$ ) in irradiated tissues outside the CTV in both positions. Prone position essentially concentrated the breast tissue by gravity. In both planning techniques, the prone position led to better dose conformity by CI ( $P < 0.001$  in tangents and  $P < 0.001$  in fIMRT). Among the four plans, prone fIMRT produced the best target dosimetry. A comparison of dose distributions with dose-volume histograms for four plans for a typical case are shown in Figs. 3 and 4.

#### Dose-volume distributions in normal tissue

The mean normal tissue doses have been compared for supine and prone positions (Table 3). The left lung volume

was essentially greater in the prone position ( $P = 0.003$ ). In conventional wedged tangents plans, the doses to the left lung ( $P < 0.001$ ), Level I axilla ( $P < 0.001$ ), and Level II axilla ( $P = 0.007$ ) were significantly lower in the prone position, whereas cardiac doses were not different between positions.

The doses to the left lung, Level I and II axilla were also significantly lower in prone fIMRT plans. The irradiated volume and the dose to the left lung, represented by  $V_{20}$  and the mean lung dose, were dramatically lower in the prone position ( $P < 0.001$  and  $P < 0.001$ , respectively). The volumes of Level I and II axilla did not differ between positions. The prone position significantly spared Level I axilla by decreasing the mean dose and  $V_{47.5}$  ( $P < 0.001$  and  $P < 0.001$ , respectively). The mean dose and  $V_5$  of Level II axilla were also lower in prone position ( $P = 0.007$  and  $P = 0.003$ , respectively). The volumes and doses to the entire heart, LAD with 10-mm margin, left ventricle, and right ventricle did not differ between positions. The minimal mean doses to the right lung and right breast could be explained by scattered doses.



**Fig. 4.** The dose–volume histograms of one patient for clinical target volume (CTV) and normal organs: (A) CTV and left lung; (B) heart and left anterior descending coronary artery (LAD) with 10-mm margin; (C) Level I and II axilla.

### Subgroup analysis for cardiac doses

Five patients had no significant cardiac sparing in prone fIMRT and were treated in supine position. Among these patients, the mean doses to the heart, LAD with 10-mm margin, left ventricle and right ventricle were 4.3, 24.7, 4.3 and 6.6 Gy, respectively, in prone position and 2.9, 16.4, 3.6 and 3.0 Gy, respectively, in supine position. Of the 5 patients, 3 patients' tumor beds were in the upper outer quadrant of the left breast, and 2 in the upper inner quadrant.

In order to identify selection criteria for patients who would benefit from cardiac sparing in prone position, women were sorted by age, BMI, CTV, absolute breast depth, breast depth difference, breast width difference, and tumor bed location. The absolute mean doses to the entire heart, LAD with 10-mm margin, left ventricle and right ventricle were demonstrated in Table 3. Table 4 shows the mean differences in cardiac doses (supine minus prone) among patient subgroups. Patients with absolute breast depth in prone position > 7 cm had significantly better cardiac dosimetry for the heart and LAD in the prone position, with mean reductions in heart and LAD doses of 0.8 and 7.4 Gy ( $P = 0.023$  and  $P = 0.033$ ), respectively. Patients with breast-depth difference > 3 cm (prone minus supine) also benefited from the prone position, with mean reductions in heart and LAD doses of 1.0 and 8.1 Gy ( $P = 0.011$  and  $P = 0.020$ ), respectively.

### Radiotherapy treatments and clinical outcomes

Of the 21, 16 patients received prone fIMRT breast irradiation followed by a supine electron boost. The following approximations were used: dose rate, 300 monitor units/min; IMRT segmentation time, 16 s; gantry rotation time from lateral to medial, 30 s. No significant differences were found in the number of segments or beams, monitor units, or treatment time between the 16 prone and 5 supine patients treated by fIMRT plans (Table 5). The mean number of segments and treatment time were 8 and 2.8 min, respectively, in the prone position, and 6 and 2.2 min, respectively, in the supine position ( $P = 0.082$  and  $P = 0.057$ , respectively). The mean length of the displacement by CLD was  $3.2 \pm 2.5$  mm (range, 1–10 mm) in the prone position, and  $2.8 \pm 1.8$  mm (range, 1–5 mm) in the supine position ( $P = 0.460$ ). The mean length of the displacement by CFD was  $3.8 \pm 2.2$  mm (range, 1–9 mm) in the prone position, and  $4.3 \pm 1.2$  mm (range, 2–5 mm) in the supine position ( $P = 0.198$ ). There was no difference in positioning reproducibility or setup accuracy between supine and prone positions.

None of the patients required a treatment break. The most common acute toxicity noted was Grade 1 erythema,

**Table 3.** Dose–volume distributions in normal tissues

<i>n</i> = 21	Supine wedged tangents Mean ± SD	Prone wedged tangents Mean ± SD	<i>P</i> *	Supine fIMRT Mean ± SD	Prone fIMRT Mean ± SD	<i>P</i> *
Left lung						
Volume (cm <sup>3</sup> )	963.1 ± 206.8	1030.5 ± 188.5	0.003			
Mean dose (Gy)	7.1 ± 1.7	2.2 ± 0.9	<0.001	6.0 ± 1.7	1.9 ± 1.0	<0.001
V20 (%)	9.4 ± 4.1	1.2 ± 1.9	<0.001	9.0 ± 4.0	1.1 ± 1.8	<0.001
V5 (%)	25.1 ± 5.5	3.1 ± 3.8	<0.001	20.8 ± 5.8	3.0 ± 3.6	<0.001
Heart						
Volume (cm <sup>3</sup> )	539.8 ± 90.2	526.5 ± 94.7	0.167			
Mean dose (Gy)	4.5 ± 1.2	4.0 ± 1.9	0.189	3.7 ± 1.0	3.9 ± 2.2	0.771
V40 (%)	1.3 ± 1.3	2.1 ± 3.0	0.928	1.3 ± 1.2	2.0 ± 3.3	0.355
V5 (%)	12.7 ± 5.4	9.2 ± 7.0	0.589	8.8 ± 3.9	8.8 ± 7.2	0.960
LAD with 10-mm margin						
Mean dose (Gy)	22.7 ± 8.0	21.2 ± 11.4	0.155	22.3 ± 8.1	20.9 ± 12.2	0.629
V40 (%)	28.0 ± 16.7	28.2 ± 24.7	0.294	27.9 ± 16.3	28.0 ± 26.1	0.985
V5 (%)	84.0 ± 14.9	67.5 ± 26.0	0.113	75.1 ± 17.0	65.1 ± 27.0	0.098
Left ventricle						
Mean dose (Gy)	5.3 ± 1.8	4.5 ± 3.4	0.245	4.7 ± 1.4	4.4 ± 3.7	0.688
V40 (%)	1.8 ± 1.7	2.7 ± 5.8	0.802	1.7 ± 1.7	2.6 ± 6.0	0.465
V5 (%)	19.2 ± 7.1	10.4 ± 11.7	0.115	14.0 ± 5.9	10.0 ± 12.1	0.152
Right ventricle						
Mean dose (Gy)	5.0 ± 2.0	5.8 ± 3.3	0.764	4.1 ± 2.0	5.7 ± 4.0	0.127
V40 (%)	1.5 ± 3.4	3.2 ± 4.9	0.404	0.8 ± 1.8	3.0 ± 5.8	0.106
V5 (%)	20.8 ± 17.8	17.3 ± 14.6	0.610	11.0 ± 10.1	16.9 ± 15.3	0.112
Level I axilla						
Mean dose (Gy)	36.0 ± 9.5	11.5 ± 5.6	<0.001	33.4 ± 8.8	8.0 ± 6.6	<0.001
V47.5 (%)	40.2 ± 20.2	2.3 ± 3.7	<0.001	21.7 ± 17.0	2.2 ± 4.0	<0.001
Level II axilla						
Mean dose (Gy)	6.8 ± 4.9	3.3 ± 1.3	0.007	5.1 ± 4.5	1.9 ± 1.4	0.007
V5 (%)	29.2 ± 27.8	4.1 ± 7.9	0.001	25.1 ± 26.0	3.9 ± 7.8	0.003

fIMRT = forward intensity-modulated radiotherapy, SD = standard deviation, LAD = left anterior descending coronary artery, V47.5, V40 and V5 = percentage of volume receiving 47.5, 40 and 5 Gy, respectively. \*Significance tested using paired Student t-test.

observed in 14 patients (88% of patients treated in prone position). No RTOG Grade 2 or worse acute or late toxicity occurred. At a median follow-up of 26.8 months (range, 11.0–36.9 months), no patient experienced locoregional or distant recurrence or died of the disease.

## DISCUSSION

To our knowledge, this is the first study in Asia of prone fIMRT for adjuvant breast radiotherapy. Recently there has

been growing evidence for prone breast irradiation improving target dose homogeneity and conformity, non-target dose sparing, treatment feasibility and long-term clinical outcomes [20, 21]. Prone position allows for exclusion of lung and axilla from the treatment fields, thus could reduce late radiation toxicities. In women with pendulous or large breasts, prone position is more beneficial compared with the supine position because it allows the breast tissue to fall away from the chest wall, thus possibly preventing acute skin toxicity, especially along the inframammary fold.

**Table 4.** Subgroup analysis of mean differences ( $\Delta$ ) in cardiac doses (supine minus prone) by forward intensity-modulated radiotherapy (positive values represent prone position better for cardiac radiation sparing)

	Patients ( <i>n</i> )	$\Delta$ Heart mean dose (Gy) $\pm$ SD	$\Delta$ LAD mean dose (Gy) $\pm$ SD
Age	*	$P=0.152$	$P=0.132$
<50 years	10	$-0.9 \pm 2.9$	$-2.7 \pm 14.2$
>50 years	11	$0.6 \pm 1.7$	$5.2 \pm 12.3$
Body mass index	*	$P=0.387$	$P=0.349$
<25	11	$-0.9 \pm 3.0$	$-1.9 \pm 5.1$
>25	10	$0.6 \pm 1.4$	$5.1 \pm 7.9$
Clinical target volume	*	$P=0.177$	$P=0.047$
<450 cm <sup>3</sup>	9	$-1.3 \pm 3.0$	$-6.0 \pm 15.4$
>450 cm <sup>3</sup>	12	$0.7 \pm 1.4$	$7.0 \pm 8.8$
Breast depth in prone position	*	$P=0.023$	$P=0.033$
<7 cm	9	$-1.5 \pm 2.9$	$-6.5 \pm 14.9$
>7 cm	12	$0.8 \pm 1.4$	$7.4 \pm 9.0$
Breast depth $\Delta$ (Prone – supine)	*	$P=0.011$	$P=0.020$
<3 cm	10	$-1.4 \pm 2.8$	$-5.8 \pm 14.2$
>3 cm	11	$1.0 \pm 1.4$	$8.1 \pm 9.2$
Breast width $\Delta$ (Supine - prone)	*	$P=0.082$	$P=0.036$
<4 cm	13	$-0.9 \pm 2.5$	$-3.0 \pm 14.0$
>4 cm	8	$1.0 \pm 1.8$	$8.6 \pm 11.1$
Tumor bed location	*	$P=0.654$	$P=0.263$
Upper breast	14	$-0.5 \pm 2.8$	$-0.8 \pm 14.7$
Lower breast	7	$0.5 \pm 1.6$	$6.0 \pm 10.2$
Tumor bed location	*	$P=0.673$	$P=0.622$
Inner breast	10	$0.4 \pm 2.8$	$6.1 \pm 14.7$
Outer breast	11	$0.5 \pm 2.2$	$5.3 \pm 13.1$

SD = standard deviation, LAD = left anterior descending coronary artery. \*Significance tested using non-parametric Mann-Whitney test.

The dose conformity implies high target volume dose coverage and minimal unnecessary irradiation of surrounding tissues. In our series, dose conformity was more affected by the patient position than by the planning techniques. The shape of the breast tissue changed under different positions. The wedged tangents or fIMRT generated directional gradients or intensity maps on opposed tangential fluences. However, the treatment techniques owned limited role when the basic tangential fields anatomically included

**Table 5.** Number of segments or beams, monitor units, and treatment time estimates for forward intensity-modulated radiotherapy for 16 prone and 5 supine patients

Patient	No. of segments	Monitor Units	Treatment time (min)
Prone			
1	8	234.0	2.8
2	9	228.7	3.0
3	8	222.0	2.8
4	8	233.0	2.8
5	6	221.0	2.2
6	8	235.0	3.1
7	8	234.0	2.8
8	8	230.0	2.8
9	6	220.0	2.2
10	8	230.8	2.8
11	8	236.0	2.8
12	9	249.0	3.1
13	8	229.5	2.8
14	8	235.0	2.8
15	9	233.7	3.1
16	6	227.0	1.7
Mean $\pm$ SD	$8 \pm 1$	$231.4 \pm 7.2$	$2.8 \pm 0.3$
Supine			
1	8	235.0	2.2
2	6	241.0	2.3
3	8	238.0	2.8
4	6	221.0	2.2
5	6	225.0	2.2
Mean $\pm$ SD	$6 \pm 1$	$231.2 \pm 8.0$	$2.2 \pm 0.4$
<i>P</i> *	0.082	0.353	0.057

fIMRT = forward intensity-modulated radiotherapy, MV = megavoltage, SD = standard deviation. \*Significance tested using unpaired Student t-test.

the surrounding tissues, which was the case in the supine position. The prone position essentially isolated the breast tissue from the surrounding tissues by gravity, which was beneficial in determining the dose conformity.

The left lung volume was essentially greater in prone position. It has been proven that the left lung is located directly under the left breast in supine position, subjecting it to compressive force from the weight of the breast; the prone position prevents this compression, leading to better expansion of the lung. Conventional breast radiotherapy has been shown to increase the risk of ipsilateral lung



carcinoma with an excess relative risk of 0.11 [12]. Prone breast radiotherapy could protect the ipsilateral lung through reducing radiation doses and achieving better expansion, thus possibly reducing the risk of radiation-associated lung toxicities.

Cardiac toxicity has been recognized as an issue in breast radiotherapy, particularly in patients treated for left-sided early-stage breast cancer. Radiation dose has been shown to increase the risk of coronary artery disease, ischemic heart disease, pericarditis and valvular disease in women with irradiated left breast cancer [22, 23]. Nevertheless, reports on heart doses in prone position are not concordant [5, 6, 15]. In this study we explored the selection criteria for patients who would have better cardiac sparing with prone position radiotherapy, and found that patients with large breast depth in prone position might be beneficial for prone position radiotherapy. However, due to the limited number of patients studied, further investigation is needed, e.g. on the value of the additional indicator of breast depth to breast volume.

In our series, we discovered that for patients with tumor beds in the upper outer or inner quadrant of the breast, the seromas were sometimes drawn toward the axillary regions or the chest walls, leading to less separation of the breast tissue from the chest wall or axilla in prone position, resulting in wider breast width and tilted tangents in order to fully cover the tumor bed, which would be accompanied by more cardiac or axillary doses, thus possibly making these patients less suitable for prone breast radiotherapy.

Concerns about reproducibility and efficacy of the prone position exist among investigators. In our results, we did not find any statistical difference in positioning reproducibility between the prone and supine positions. Though random and systemic errors in setup precision was not accordant between prone and supine position, prone positioning has shown the advantage of reducing chest-wall movements during respiration [24, 25]. The safety and efficacy of prone setup has also been demonstrated by large series studies [26].

In early-stage breast cancer patients who undergo breast-conserving therapy and adjuvant radiotherapy, locoregional failures occur mainly in the tumor bed and the ipsilateral breast. Prone irradiation was linked with concern that locoregional control rates may be reduced because of the omission of low axillary lymph node regions from the tangential fields, but in subsequent studies the disease control in prone position has been shown to be equivalent to that in supine position [2, 26]. For women with large breasts and low risk of harboring disease in the axilla, prone breast radiotherapy may be advantageous.

Our study has several limitations. Our sample size was relatively small. The group included for analysis was heterogeneous with respect to breast volume, breast physical variables, and multimodality treatments. Our findings

should be interpreted with caution given the possible selection bias introduced by patient selection. The median follow-up of 26.8 months would modestly support the safety and feasibility of the regimen. Studies assessing prone fIMRT in prospective randomized fashion are needed. More detailed subgrouping strategies are also required for Asian women who may benefit from prone breast radiotherapy.

## CONFLICT OF INTEREST

The authors have no potential conflicts of interest.

## ACKNOWLEDGEMENTS

These findings have been presented in part at the 16th Taiwan Joint Cancer Conference, 30 April–1 May 2011, Taipei, Taiwan, and also at the 97th Annual Meeting of the Radiological Society of North America (RSNA), 27 November–2 December 2011, Chicago, USA.

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