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Comparison of six irradiation techniques for delivering hypofractionated whole-breast radiotherapy with a simultaneous integrated boost after breast-conserving surgery

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► ***Original article***

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ABSTRACT

Background: To compare the following techniques for hypofractionated whole-breast irradiation (WBI) with simultaneous integrated boost (SIB) after breast-conserving surgery (BCS): three-dimensional conformal radiation therapy plus electron boost (3DCRT-EB), intensity-modulated radiation therapy (IMRT) plus EB (IMRT-EB), field-in-field IMRT plus EB (FIF-IMRT-EB), FIF-IMRT plus IMRT boost (FIF-IMRT-IB), IMRT plus IMRT boost (IMRT-IB), and volumetric-modulated arc therapy (VMAT) plus VMAT boost (VMAT-VB). ***Materials and Methods***: Twenty patients with left breast cancer were enrolled. The prescribed dose was 40.05 Gy in 15 fractions to the whole breast and an SIB to the tumor bed of 3.2 Gy/fraction (total, 48 Gy). Target-volume coverage, dose-conformity index, homogeneity index (HI), doses to organs at risk (OAR), and costs were compared. ***Results:*** FIF-IMRT-EB performed the best, while FIF-IMRT-IB, IMRT-IB, and VMAT-VB performed the worst. The mean dose to the planning target volume for breast evaluation (PTV Eval-breast) was significantly lower for IMRT-EB and FIF-IMRT-EB than for the other plans. For both PTV Eval-breast and PTV Eval-boost, VMAT-VB had the lowest target-volume coverage for 95% of the prescription dose and the highest target-volume coverage for >105% of the prescription dose. Among the six plans, VMAT-VB had the best HI for PTV Eval-boost and the highest doses to all OAR, except the coronary artery. Plans with EBs had lower mean doses for the contralateral lung and contralateral breast than plans with IMRT boosts. FIF-IMRT-EB had a low cost; plans with IMRT boosts had the highest costs. ***Conclusion:*** FIF-IMRT-EB may be the most suitable irradiation technique for hypofractionated WBI with SIB after BCS.

Keywords: *Breast cancer, breast-conserving surgery, hypofractionated whole-breast radiotherapy, radiotherapy, simultaneous integrated b,moost.*

INTRODUCTION

Breast-conserving surgery (BCS) plus postoperative radiotherapy has been shown to yield equivalent outcomes as mastectomy, with better cosmetic results [(1)]. However, some patients choose to directly have a mastectomy, and some may not receive radiotherapy for 5–7 weeks after BCS due to the limitations of conventional breast irradiation [(2, 3)]. Accelerated hypofractionated irradiation can shorten the duration of radiotherapy to approximately 3 weeks. Randomized controlled trials have demonstrated similar local control rates, overall survival, and cosmetic outcomes between accelerated hypofractionated

irradiation and conventional fractionated irradiation [4–7]. However, the use of a tumor bed boost after whole-breast irradiation (WBI) has been shown to significantly improve outcomes (range, 0–74.5%) as compared to WBI without a tumor bed boost [8]. A randomized study has reported that among patients who received WBI with conventional fractionation, a tumor bed boost was associated with better local control rates than those in the non-boost group[9]. Currently, there is limited evidence from randomized trials regarding the efficacy and tolerability of hypofractionated WBI with a simultaneous integrated tumor bed boost for breast cancer. Several randomized trials to compare the benefits of simultaneous integrated boost (SIB) with hypofractionated and conventional fractionated WBI are ongoing [10–13].

A better SIB technique should be systematically developed to avoid adverse *cosmetic outcomes after* tumor bed boost [14]. Recently, several prospective studies have assessed modern radiotherapy techniques, including intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) [15–17]. However, there are no well-defined standards for using SIB as part of hypofractionated WBI after BCS. In this study, we compared six radiotherapy techniques in terms of the target volume coverage, dose conformity and homogeneity indexes, doses to organs at risk (OAR), and cost in order to determine the optimal technique for accelerated hypofractionated WBI with SIB.

MATERIALS AND METHODS

Patients

The study involved 20 patients with early-stage cancer of the left breast who underwent radiotherapy after BCS at the Sun Yat-Sen University Cancer Center (SYSUCC) between August 2014 and December 2014. The inclusion criteria were as follows: (1) female patient with a single-lesion cancer of the left breast after BCS and negative surgical margins; (2) negative axillary lymph node or sentinel lymph node; (3) T1–2N0M0 stage according to the American Joint Committee on Cancer staging system; (4) hormone receptor status and human epidermal growth factor receptor 2 (Her 2) status available; and (5) endocrine therapy and/or adjuvant chemotherapy performed according to treatment guidelines. The ethics committee of SYSUCC approved this study. Table 1 shows the characteristics of the patients.

Table 1. Clinicopathological characteristics of the 20 study patients

Characteristic	Value
Age (yr)	
Median	43
Mean (SD) (years)	42.5±10.4
Range	36-56
Menopausal status (*n*)	
Premenopausal	22
Postmenopausal	6
Tumor stage (*n*)	
T1	16
T2	13
Tumor location (*n*)	
UIQ	4
UOQ	12
LIQ	2
LOQ	2
Pathological type (*n*)	
Invasive ductal carcinoma	19
Mucinous adenocarcinoma	1
ER/PR status (*n*)	
Negative	6
Positive	14
Her-2 status (*n*)	
Negative	18
Positive	2
Sentinel nodes sampled (*n*)	
No	12
Yes	8
Axillary lymph node dissection (*n*)	
No	8
Yes	12

ER, estrogen receptor; Her-2, human epidermal growth factor receptor 2; LIQ, lower inner quadrant; LOQ, lower outer quadrant; PR, progesterone receptor; SD, standard deviation; UIQ, upper inner quadrant; UOQ, upper outer quadrant.

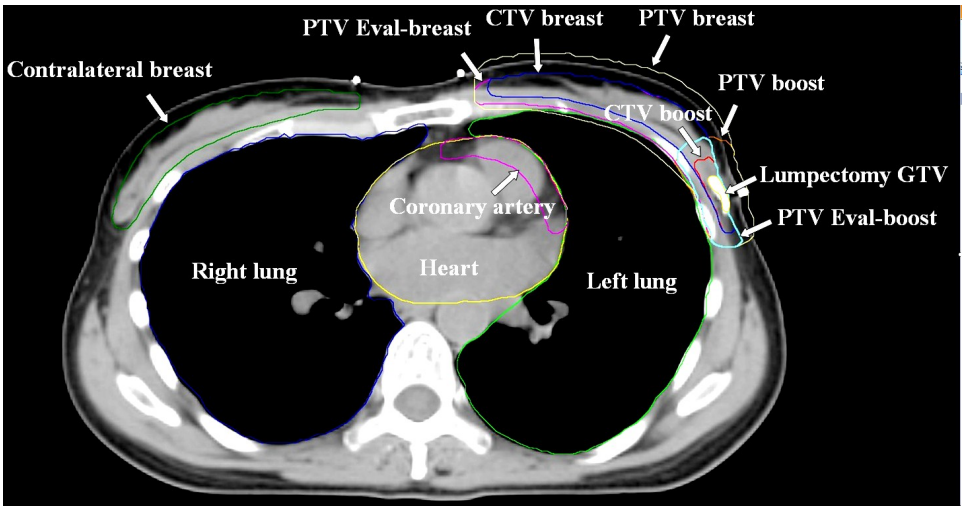

Figure 1. Delineation of the target volume and organs at risk.

Target volumes and OAR

The clinical target volume (CTV) was delineated in accordance with the guidelines of International Commission on Radiation Units Report 83[18]. The delineation of lumpectomy, planning target volume (PTV) of the breast, PTV for evaluation (PTV Eval-breast), and OAR was primarily based on our previous report (figure 1)[19]. We expanded the CTV isotropically with a 0.7-cm margin in all directions, except toward the skin surface, to generate the PTV. The coronary artery was identified as the area of left front one-fourth heart 1 cm subsurface [20]. The target volumes and the volumes of the OAR are shown in table 2.

Table 2. Target volume and volumes of organs at risk in the 20 study patients

	Volume		
	Mean ± SD (cm^3)	**Median (cm^3)**	**Range (cm^3)**
PTV-Whole breast	115.2±474.9	472.3	645.2-276.2
PTV-Boost	13.9±60.2	58.6	98.2-47.2
Ipsilateral lung	182.0±1088.0	1057.6	1599.8-812.8
Contralateral lung	262.7±1188.5	1195.3	1783.1-654.2
Heart	65.8±534.5	557.3	643.3-374.1
Contralateral breast	113.5±469.5	456.0	653.6-298.3
Coronary artery	3.4±60.1	60.3	64.8-52.8
Thyroid	3.7±10.2	10.3	19.8-5.6

PTV, planning target volume; SD, standard deviation

Radiotherapy plans

Six radiotherapy plans were generated for each patient, by using the Eclipse treatment planning system (version 11.0.1, Varian Medical Systems, Los Angeles, CA, USA). The prescribed dose was 40.05 Gy delivered in 15 fractions to the whole breast (2.67 Gy/fraction) and an SIB to the tumor bed of 3.2 Gy/fraction (total SIB dose, 48 Gy). The dose–volume criteria were assessed according to the Radiation Therapy Oncology Group 1005 protocol [13].

1. Three-dimensional conformal radiation therapy plus an electron boost (3DCRT-EB): A pair of opposed tangential fields were used to irradiate the whole breast. By applying a wedge plate or adjusting the collimator angle, the tangential field of the lung was kept close to the

minimum, the healthy breast was completely avoided, and the dose distribution was made more even. Single-field EB plans were used to cover the PTV for evaluation of the boost irradiation (PTV Eval-boost). EBs were planned with energies of 6–15 MeV, depending on the depth of the PTV Eval-boost, to ensure that the PTV Eval-boost covered the 95% isodose line.

2. Field-in-field IMRT plus an EB (FIF-IMRT-EB): In brief, the contribution of parallel opposed tangential photon beams without wedges and multiple subfields was used to achieve the desired homogeneity of the PTV Eval -breast. The dose distributions *were first calculated* and assessed using *open beams*. Additional subfields and a lung block were used to smooth out the hot areas and the lung shape to increase the homogeneity and reduce the dose to the lung. Subfields within 5 MU were removed. A single-field EB was used for each PTV Eval-boost.

3. IMRT plus an EB (IMRT-EB): A two-field opposed IMRT plan was used for WBI. The angle of the radiation field was consistent with that of the 3DCRT plans, and inverse optimization was applied. Single-field EB plans were used for each PTV Eval-boost.

4. IMRT plus an IMRT boost (IMRT-IB): A two-field opposed IMRT plan was used for WBI. In addition, five fields with opposed tangential directions were generated to deliver a highly homogeneous dose to the PTV Eval-boost by using a "step and shoot" IMRT plan. Two adjacent beams in the same direction were separated by 20° to 30°. The maximum number of segments was 50.

5. FIF-IMRT plus an IMRT boost (FIF-IMRT-IB): The FIF-IMRT plan was designed using the method described for FIF-IMRT-EB. The IMRT boost plan was designed using the method described for IMRT-IB.

6. VMAT plus a VMAT boost (VMAT-VB): Two 180° arcs were used for each VMAT plan. The first arc started from the body midline. The starting angle was kept away from the breast, and the ending angle was 180° plus the starting angle. The second arc had exactly opposite starting and ending angles relative to the first arc. The collimator angle was adjusted on the basis of the individual target size. The PTV Eval-breast and PTV Eval-boost plans were o ptimized simultaneously.

Conformity index and homogeneity index

The conformity index (CI) and homogeneity index (HI) were calculated using the following formulae:

CI = $V_{95\%}$/PTV, where $V_{95\%}$ is the total volume receiving 95% of the prescribed dose (PD).

HI = ($D_{2\%}$ – $D_{98\%}$)/$D_{50\%}$,, where $D_{2\%}$, $D_{98\%}$, and $D_{50\%}$ are the doses received by 2%, 98%, and 50% of the PTV.

The closer the HI and CI are to 1, the better is the plan [21].

Cost–benefit analysis

Our cost-benefit analysis included fees for initial consultation, computed tomography simulation, treatment planning, dosimetry calculation, quality assurance, and cost of radiotherapy. Because our study yielded multiparametric results, we implemented a quantitative scoring method to guide our evaluation and decisions regarding which was the superior technique. Under this method, 7 points were awarded to a plan if its performance for a given parameter was significantly better than that of all the other plans. When conducting pairwise comparisons of each parameter, points were subtracted from a plan's score if more than one plan performed significantly better than the rest of the plans, and the lowest value was taken from equivalent values. For example, if 3DCRT and IMRT-EB both performed significantly better than the other four plans, then the score for each of these two plans was 6. Otherwise, the score decreased to 1 gradually. The most cost-effective technique was the one that had the highest score on the cost–benefit analysis.

Statistical analysis

Data were analyzed using SPSS software (release 17.0, SPSS Inc., Chicago, IL, USA). We performed one-way analysis of variance to evaluate differences among the dosimetric parameters of the six radiotherapy techniques. All tests were two-sided, and $p<0.05$ was considered to indicate significant differences.

RESULTS

Target-volume coverage

Table 3 and figure 2 show the dosimetric parameters for target-volume coverage for the six plans. The dosimetric parameters for PTV Eval-breast and the CI and HI were significantly better for the VMAT-VB plan than for the other plans ($p < 0.05$). The CI of 3DCRT was significantly worse than that of the other plans (p ¬ 4.49). There were no signi[D]icant differences in CI and HI among the four IMRT plans ($p > 0.05$). The mean dose (Dmean) of the PTV Eval-breast was significantly lower in the IMRT-EB and FIF-IMRT-EB plans than in the other plans ($p < 0.05$). VMAT-VB had the lowest $V_{95\%}$ value and the highest $V_{105\%}$ value among all the plans. The $V_{95\%}$ values of the remaining five plans did not significantly differ from each other ($p > 0.05$). The $V_{105\%}$ value of FIF-IMRT-EB was significantly lower than those of the other plans ($p < 0.05$).

In the case of the PTV Eval-boost, the CIs of IMRT-EB, FIF-IMRT-EB, and VMAT-VB were significantly superior to those of the other plans ($p < 0.05$). VMAT-VB had the best HI of the six plans ($p < 0.05$). The Dmean of 3DCRT and VMAT-VB were greater than those of the other plans, while that of FIF-IMRT-EB was the lowest. VMAT-VB had the lowest $V_{95\%}$ and the highest $V_{105\%}$ among the six plans. The $V_{105\%}$ of IMRT-EB was significantly higher than that of FIF-IMRT-IB, but there were no significant differences in $V_{105\%}$ among FIF-IMRT-EB, FIF-IMRT-IB, and IMRT-IB.

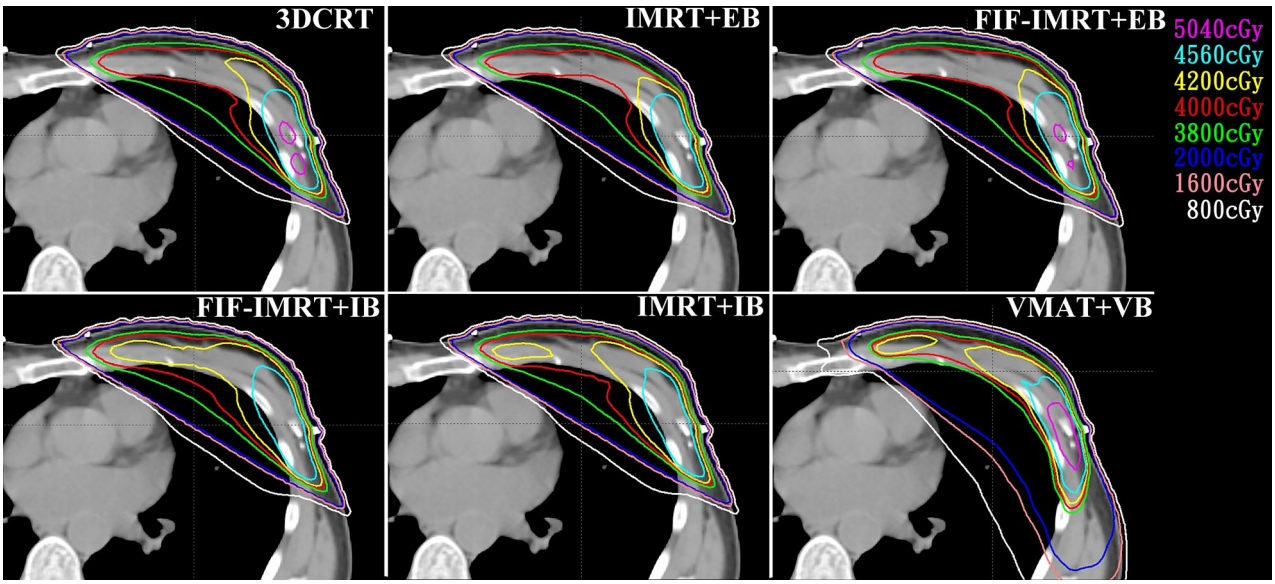

Figure 2. Transverse dose-distribution curves of target-volume coverage and doses to organs at risk for the six techniques in a representative patient.

Table 3. Comparison of planning target volume, organs at risk, and cost of treatment among the six radiotherapy techniques.

Dosimetric parameters	3DCRT	IMRT + EB	FIF-IMRT+EB	FIF-IMRT +IB	IMRT+IB	VMAT+VB
PTV-WBI						
CI	0.16 ± 1.64^{A}	0.14 ± 1.45^{B,a}	0.16 ± 1.51^{B,c}	0.17 ± 1.48^{b,e}	0.18 ± 1.48^{B,g}	0.07 ± 1.17^{B,b,d,f,h}
HI	0.03 ± 0.28^{A}	0.06 ± 0.30^{a}	0.02 ± 0.28^{c}	0.01 ± 0.27^{e}	0.05 ± 0.29^{g}	0.10 ± 0.37^{B,b,d,f,h}
Dmean (cGy)	48.1 ± 4290.0^{A}	55.6 ± 4228.3^{B,a}	43.6 ± 4210.0^{B,c}	50.3 ± 4270.1^{b,d}	62.2 ± 4283.0^{b,d}	43.9 ± 4278.4^{b,d}
$V_{95\ (\%)}$	0.9 ± 98.9^{A}	1.2 ± 97.9^{a}	0.8 ± 98.3^{c}	0.83 ± 98.6^{e}	1.2 ± 98.3^{g}	2.6 ± 96.0^{B,b,d,f,h}
$V_{105\ (\%)}$	10.2 ± 50.4^{A}	10.2 ± 33.8^{B,a}	6.7 ± 25.6^{B,b,c}	9.0 ± 38.5^{B,d,e}	9.7 ± 44.8^{B,b,d,f,g}	6.8 ± 55.6^{b,d,f,h}
PTV-boost						
CI	0.23 ± 1.62^{A}	0.21 ± 1.42^{B,a}	0.23 ± 1.40^{B,c}	0.33 ± 1.85^{B,b,d,e}	0.37 ± 1.97^{B,b,d,g}	0.32 ± 1.44^{f,h}
HI	0.02 ± 0.10^{A}	0.02 ± 0.10^{a}	0.20 ± 0.09^{c}	0.01 ± 0.07^{B,b,e}	0.03 ± 0.08^{b,g}	0.05 ± 0.16^{B,b,d,f,h}
Dmean (cGy)	63.6 ± 4936.3^{A}	69.4 ± 4890.2^{B}	47.4 ± 4875.7^{B,a}	35.9 ± 4886.3^{B}	54.4 ± 4901.0^{B}	55.9 ± 4919.5^{b}
$V_{95\ (\%)}$	1.4 ± 99.3^{A}	2.2 ± 98.2^{a}	2.1 ± 98.2^{c}	1.0 ± 99.5^{d,e}	1.31 ± 99.4^{f,g}	2.9 ± 96.4^{B,b,d,h}
$V_{105\ (\%)}$	17.2 ± 23.5^{A}	18.0 ± 13.0^{B,a}	9.8 ± 4.8$^{B,\ c}$	0.6 ± 0.2^{B,b,e}	14.4 ± 7.7^{B,g}	13.2 ± 28.4^{b,d,f,h}
Heart						
Dmean (cGy)	69.5 ± 216.1^{A}	55.7 ± 206.0^{a}	62.3 ± 217.1^{c}	67.3 ± 248.4^{e}	60.0 ± 237.9^{g}	17.7 ± 376.9^{B,b,d,f,h}
$V_{8Gy\ (\%)}$	1.9 ± 4.3^{A}	1.7 ± 4.4^{a}	1.8 ± 4.6^{c}	1.9 ± 4.5^{e}	1.7 ± 4.4^{g}	1.5 ± 6.7^{B,b,d,f,h}
$V_{16Gy\ (\%)}$	1.6 ± 3.1^{A}	1.3 ± 3.0	1.6 ± 3.3^{a}	1.6 ± 3.3^{c}	1.3 ± 3.0	0.9 ± 2.2^{B,b,d}
$V_{20Gy\ (\%)}$	1.5 ± 2.8^{A}	1.2 ± 2.6^{a}	1.5 ± 3.0^{c}	1.5 ± 3.0^{e}	1.2 ± 2.6^{g}	0.6 ± 1.3^{B,b,d,f,h}
CA						
Dmean (cGy)	570.4 ± 1208.3	470.0 ± 1146.1	514.9 ± 1211.8	515.7 ± 1232.3	468.9 ± 1167.1	180.3 ± 976.7
$V_{8Gy\ (\%)}$	18.0 ± 35.8	15.7 ± 36.2	16.6 ± 36.8	17.1 ± 36.7	17.4 ± 34.2	11.1 ± 44.0
$V_{16Gy\ (\%)}$	16.0 ± 27.3^{A}	13.5 ± 26.2	15.0 ± 28.4^{a}	15.1 ± 28.4^{c}	13.5 ± 26.3	8.4 ± 17.7^{B,b,d}
$V_{20Gy\ (\%)}$	15.3 ± 25.0^{A}	12.5 ± 22.8^{a}	14.4 ± 25.7^{c}	14.4 ± 25.8^{e}	12.5 ± 22.9^{g}	6.5 ± 10.7^{B,b,d,f,h}
Ipsilateral lung						
Dmean (cGy)	169.7 ± 590.9^{A}	152.1 ± 544.6^{a}	160.9 ± 577.1^{c}	158.3 ± 606.4^{e}	148.7 ± 573.4^{g}	72.7 ± 786.8^{B,b,d,f,h}
$V_{4Gy\ (\%)}$	7.0 ± 23.4^{A}	6.6 ± 22.6^{a}	6.6 ± 23.3^{c}	6.7 ± 25.0^{e}	6.7 ± 24.3^{g}	3.0 ± 48.0^{B,b,d,f,h}
$V_{8Gy\ (\%)}$	4.8 ± 16.1^{A}	4.5 ± 15.5^{a}	4.7 ± 16.1^{c}	4.7 ± 16.3^{e}	4.5 ± 15.6^{g}	2.8 ± 30.1^{B,b,d,f,h}
$V_{16Gy\ (\%)}$	3.8 ± 12.3^{A}	3.6 ± 11.5^{a}	3.8 ± 12.3^{c}	3.8 ± 12.4^{e}	3.5 ± 11.5^{g}	1.2 ± 16.1^{B,b,d,f,h}
Contralateral lung						
Dmean (cGy)	3.2 ± 6.6^{A}	1.4 ± 5.2^{a}	1.3 ± 5.0^{c}	6.2 ± 21.2^{B,b,d,e}	6.3 ± 21.3^{B,b,d,g}	34.4 ± 168.4^{B,b,d,f,h}
$V_{4Gy\ (\%)}$	0.1 ± 0.1^{A}	0 ± 0^{a}	0 ± 0^{c}	0 ± 0^{e}	0 ± 0^{g}	3.8 ± 5.7^{B,b,d,f,h}
Contralateral breast						
Dmax (cGy)	20.1 ± 94.9^{A}	13.0 ± 75.5^{B,a}	13.5 ± 92.5^{c}	32.2 ± 136.1^{B,b,d,e}	32.4 ± 120.3^{B,b,d,f,g}	39.7 ± 350.7^{B,b,d,h}
$V_{1.44Gy\ (\%)}$	0 ± 0^{A}	0 ± 0^{a}	0 ± 0^{c}	0.3 ± 0.1^{e}	0.2 ± 0.1^{g}	13.4 ± 19.1^{B,b,d,f,h}
Cost *	0.0 ± 11731.0^{A}	0.0 ± 21241.0^{B,a}	6171.6 ± 13621.0^{B,b,c}	0.0 ± 39841.0^{B,b,d,e}	0.0 ± 39841.0^{B,b,d,g}	0.0 ± 27211.0^{B,b,d,f,h}
MU	15.4 ± 389.2^{A}	54.4 ± 516.2^{B,a}	11.0 ± 372.0^{B,c}	33.9 ± 502.70^{b,e}	72.8 ± 644.5^{B,f,g}	51.0 ± 799.6^{B,bd,h}

3DCRT, three-dimensional conformal radiation therapy; CA, coronary artery; CI, conformity index; EB, electron boost; FIF, field-in-field; HI, homogeneity index; IB, IMRT boost; IMRT, intensity-modulated radiation therapy; PTV, planning target volume; VB, VMAT boost; VMAT, volumetric-modulated arc therapy; WBI, whole-breast irradiation.

*The exchange rate was 1 US dollar to 6.8 Renminbi (RMB) on 12 June 2017.

ASignificantly different from B ($p < 0.05$); asignificantly different from b ($p < 0.05$); csignificantly different from d ($p < 0.05$), esignificantly different from f ($p < 0.05$); gsignificantly different from h ($p < 0.05$). Otherwise, no significant differences were present between any two variables ($p > 0.05$).

Doses to OAR

The Dmean and V_{8Gy} of the heart were significantly higher and the V_{20Gy} was significantly lower for VMAT-VB than for the other five plans ($p < 0.05$). There were no significant differences among the non-VMAT plans in terms of Dmean, V_{8Gy}, V_{16Gy}, and V_{20Gy} of the heart ($p > 0.05$; table 3). For the coronary artery, the V_{16Gy} was significantly lower for VMAT-VB than for the remaining five plans ($p < 0.05$), but there were no significant differences in Dmean and V_{8Gy} among the six plans ($p > 0.05$; table 3).

Our analysis of the dose to the ipsilateral lung showed that VMAT-VB had the highest Dmean, V_{4Gy}, V_{8Gy}, and V_{16Gy} ($p < 0.05$) among all the

plans. The Dmean and V_{4Gy} of the contralateral lung were also higher for VMAT-VB than for the remaining five plans ($p < 0.05$). The 3DCRT-EB plan yielded a lower Dmean for the contralateral lung than did the plans with IMRT boosts ($p < 0.05$; table 3).

Among the six plans, VMAT-VB had the highest maximum dose (Dmax) and $V_{1.44Gy}$ for the contralateral breast ($p < 0.05$). Plans with the SIB delivered via an EB had a lower Dmax for the contralateral breast than did plans that used 3DCRT or an IMRT boost ($p < 0.05$; table 3).

Cost–benefit analysis and the ranking of the six techniques

The 3DCRT plan was associated with the lowest cost, followed by the FIF-IMRT-EB; plans with an IMRT boost had the highest costs ($p < 0.05$; table 4). Of the six plans, the FIF-IMRT-EB was the most cost-effective technique. Plans with SIBs administered via IMRT or VMAT scored the lowest on the cost–benefit analysis.

Table 3. Comparison of planning target volume, organs at risk, and cost of treatment among the six radiotherapy techniques.

Dosimetric parameters	3DCRT	IMRT +EB	FIF-IMRT+ EB	FIF-IMRT + IB	IMRT+IB	VMAT+VB
TV						
PTV-WBI CI	1	4	2	2	5	6
PTV-WBI HI	1	1	1	1	1	6
$V_{95\ (\%)}$	3	2	3	3	3	1
V_{48Gy}-breast PTVE	2	2	2	1	1	2
$V_{43.2Gy}$-breast PTVE	4	5	5	2	2	1
LUMP PTVE CI	3	5	5	1	1	4
LUMP PTVE HI	2	2	2	1	2	6
LUMP PTVE $V_{95\ (\%)}$	5	2	2	5	2	1
$V_{52.8Gy}$-LUMP PTVE	2	2	2	2	2	1
Dmax-LUMP PTVE	2	2	5	5	2	1
Total	25	27	29	23	21	29
OAR						
Heart Dmean (cGy)	2	2	2	2	2	1
Heart V_{8Gy} (%)	2	2	2	2	2	1
Heart V_{20Gy} (%)	2	1	1	1	1	2
Ipsilateral lung V_{4Gy} (%)	1	2	2	2	2	1
Ipsilateral lung V_{8Gy} (%)	2	2	2	2	2	1
Ipsilateral lung V_{16Gy} (%)	2	2	2	2	2	1
Contralateral lung V_{4Gy} (%)	2	2	2	2	2	1
Contralateral breast Dmax (cGy)	2	4	4	2	2	1
Thyroid $V_{1.44Gy}$ (%)	6	2	2	2	2	1
Total OAR	21	19	19	17	17	10
Cost	6	4	5	1	1	3
MU	5	2	6	2	2	1
Overall total	57	52	59	43	41	43

3DCRT, three-dimensional conformal radiation therapy; CI, conformity index; Dmax, maximum dose; Dmean, mean dose; EB, electron boost; FIF, field-in-field; HI, homogeneity index; IB, IMRT boost; IMRT, intensity-modulated radiation therapy; MU, monitor unit; OAR, organs at risk; PTVE, planning target volume evaluation; TV, target volume; VB, VMAT boost; VMAT, volumetric-modulated arc therapy; WBI, whole-breast irradiation.

DISCUSSION

Currently, there is no standard to guide the use of SIB during hypofractionated WBI after BCS. Therefore, an optimal irradiation technique based on contemporary treatment modes should be explored. In this study, we compared the advantages and disadvantages of six techniques for hypofractionated WBI with SIB by analyzing the target-volume coverage, doses to OAR, and cost-effectiveness of each plan.

A randomized trial has found that photon-beam irradiation is associated with adverse *cosmetic outcomes after* tumor bed boost with conventional dose fractionation [14], which may be attributable to the dosimetric characteristics of the photon beams and the use of *outdated radiotherapy techniques*. Recent studies have found that IMRT provides better whole-breast dose uniformity than 3DCRT [22, 23]. The CI and HI of target-volume coverage are important factors to evaluate the superiority of radiotherapy techniques may also be critical factors affecting cosmetic outcomes in breast cancer patients. A recent study [24] of tumor bed boost after WBI showed that a better CI could be obtained by using the arc technique. The study also determined that the V95% of two-field photon-beam boost plans was significantly better than that of plans with the EB technique (94.4% vs. 79.9%); however, the CI was worse (39 vs. 47)[24]. In contrast, Park et al. found that a photon boost was associated with better HI and CI values than an EB [25]. The present study showed that VMAT-VB had better CI and HI for WBI, while SIBs delivered using EBs had similar CIs as those of VMAT boosts. In addition, the HI was better with the EB than with the VMAT boost.

EB is a widely used technique to deliver tumor bed boost in breast cancer due to its dosimetric characteristics. However, an EB to a deep tumor bed may increase the risk of overdose to OAR. The six irradiation techniques in our study all met the requirements of target-volume coverage and dose to OAR. Our study showed that in Chinese female patients with relatively small breasts, an EB could achieve relatively satisfactory target-volume coverage that was similar to those of more precise techniques. Moreover, there was no significant increase in irradiation dose to OAR, including the heart and lungs.

China is a developing country, but the incidence of breast cancer in China is increasing rapidly [26]. Patients with breast cancer may have to undergo surgery, chemotherapy, and even targeted therapy and subsequent adjuvant radiotherapy, which poses a heavy economic burden that significantly affects the quality of life of the patients and their prognosis [27]. At SYSUCC, the cost of FIF-IMRT-EB treatment is only 20,000 Renminbi (RMB), which is more than that of 3DCRT but significantly lower than that of IMRT boosts or the VMAT technique. Moreover, our scoring model showed that FIF-IMRT-EB had the best performance. Therefore, we suggest that FIF-IMRT-EB is suitable for patients with relatively small breasts who have undergone BCS. In addition, precise radiotherapy techniques such as IMRT and VMAT tend to be influenced by respiration. Studies have found that respiration significantly affects the dose to the target volume and OAR [28–31]. Although the active breathing-control technique may reduce the impact of respiration, it increases the economic burden to the patients and decreases their quality of life.

Long-term follow-up studies have found that among breast cancer patients who received radiotherapy, the mortality rate due to ischemic heart disease and lung cancer increased significantly [32–34]. Therefore, the survival advantage after radiotherapy was probably offset by the increased risk of cardiovascular disease and lung cancer in early series. Long-term clinical studies in the era of modern radiotherapy have not found that low-dose hypofractionated radiotherapy increases the incidence of cardiac deaths [35]. New techniques, including VMAT and IMRT boosts, can expose nearby OAR to low-dose irradiation and thus further increase radiation injury [36, 37]. However, dosimetry studies have found that tangential-field IMRT, multi-directional IMRT, and VMAT can significantly decrease the risk of lung cancer [38]. It should be noted that high-dose irradiation to the lung could increase

the probability of radiation-induced lung cancer [39]. In our study, the Dmean to the ipsilateral lung was less than 10 Gy for each irradiation plan, but the irradiation doses to both the lungs were higher for VMAT-VB than for the other techniques. Although there have been few studies about the long-term outcomes of patients who undergo VMAT [15], our results showed that VMAT may not be an optimal technique in breast cancer patients.

CONCLUSION

Our results suggest that relevant parameters such as target-volume coverage, dose to OAR, and cost should be considered comprehensively when selecting a technique for *hypofractionated* WBI with SIB. FIF-IMRT-EB may be the optimal radiation technique for breast cancer patients who will undergo *hypofractionated* WBI with SIB after BCS.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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