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Sequential or simultaneous-integrated boost in early-stage breast cancer patients: trade-offs between skin toxicity and risk of compromised coverage

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Abstract

Purpose To determine the dosimetric effects of set-up errors on boost coverage, and compares skin toxicity of sequential and simultaneous boost techniques for left-sided breast cancer.

Materials and methods This retrospective study included 23 early-stage breast cancer cases. Single isocenter HFWBI-SIB(s-SIB), single isocenter HFWBI-SB(s-SB) and dual isocenter HFWBI-SB(d-SB) were planing. Rotations of 0.5°, 1°, and 2° coupled with translationals of 0.5 mm, 1.0 mm, and 2.0 mm were applied along three orthogonal axes. The dose to 95% of the PTV (D95) and the volume covered by 95% of the prescribed dose (V95) were evaluated using GEE univariate analysis to determine how PTV coverage was related to $1/CI_{RTOG}$, PTVboost volume, PTVboost separation to isocenter. The relationship between the high-dose regions within the PTVbreast and Ratio_V was evaluated using univariate analysis.

Results The s-SIB had optimal target coverage and lower high-dose volume, but it increased the risk of compromised coverage to tumor bed. For the s-SB technique, V95 exceeded 95% under all setup errors. At 2.0° coupled with 2.0 mm, s-SIB and d-SB exhibited V95 values below 95% in 34.8% and 8.7% of cases, respectively. At other setup errors, both s-SIB and d-SB demonstrated V95 values greater than 95%. Notably, high-dose regions such as V105%, V107%, and V110% within the PTVbreast across the three techniques displayed a significant correlation with Ratio_V.

Conclusion Simultaneous-integrated boost for early-stage breast cancer can reduce skin toxicity compared to sequential techniques but with the risk of compromising tumor bed coverage.

Keywords Sequential, Simultaneous-integrated, Skin toxicity, Tumor bed coverage, Predictive models

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Introduction

Breast cancer was the second most common malignant tumor globally, following lung cancer, according to the 2022 Global Cancer Statistics Report published by the World Health Organization's International Agency for Research on Cancer [1]. For patients with early invasive breast cancer, the integration of adjuvant radiotherapy after breast-conserving surgery has supplanted mastectomy as the preferred treatment approach, primarily due to its capacity to elevate 10- and 15-year survival rates. Presently, two forms of adjuvant radiotherapy are utilized post-breast-conserving surgery: hypofractionated whole breast irradiation (HF-WBI) and conventional fractionated whole breast irradiation (CF-WBI) [2–5]. HF-WBI have advantages of a shortened treatment duration, decreased radiation dose to normal tissues, lower treatment costs, and improved patient compliance [6–8].

The majority of ipsilateral breast tumor relapses (IBTR) occur near the site of the original tumor excision-specifically, the tumor bed, according to previous clinical studies and data from pathological breast specimens [9–11]. Tumor bed boost therapy has been shown in numerous randomized trials, both with and without whole-breast radiation following breast-conserving surgery, to potentially reduce the risk of breast tumor recurrence by as much as half [12, 13]. Dose escalation to the tumour-bed by a sequential (SB) significantly increase the risk of severe fibrosis in the breast [14–18]. Alternatively, the approach of delivering a simultaneous integrated boost for whole-breast hypofractionated radiotherapy(SIB) inherently encompass three advantages:(1) Dosimetric superiority [19, 20], including optimal target coverage(especially regarding dose conformity of the boost volume) and a reduction in high-dose volume for PTV breast, arises from the simultaneous optimization of both targets, enabling more effective fluence modulation; (2) Practical benefits, such as shortening the duration of radiation therapy and reducing costs, which help alleviate the time and financial burden on patients, improve compliance with postoperative adjuvant radiation therapy, and decrease the workload for healthcare professionals [21]; and (3) Potential biological advantages, stemming from the low α/β ratio of breast cancer tissue, which is akin to that of late-responding tissues, making it more sensitive to fractionated doses [22]. The latest multicenter, phase III, open-label, randomized controlled trial by Coles, Charlotte E., et al. indicates that the control group (40 Gy/15Fr to whole breast + 16 Gy/8Fr sequential dose escalation) had the lowest cumulative 5-year incidence of IBTR at 1.9%, while trial group 1 reported 2.2% (36 Gy/15Fr to whole breast, 40 Gy/15Fr to partial breast, and 48 Gy/15Fr concomitant photon boost to tumour-bed volume) and trial group 2 reported 3.2% (36 Gy/15Fr to whole breast, 40 Gy/15Fr to partial breast, and 53 Gy/15Fr concomitant photon boost to tumour-bed volume) [23]. Regarding safety, the cumulative 5-year incidence of moderate or severe breast induration reported by clinicians was lowest in trial group 1 at 10.6% ($p = 0.40$ compared to the control group), while the control group had 11.5% and trial group 2 had 15.5% ($p = 0.015$ compared to the control group). Additionally, when the target volume for the escalated radiation therapy was smaller, the incidence of moderate or severe adverse events at 5 years was decreased [23].

As of now, a consensus remains elusive regarding whether the tumor bed boost should be delivered sequentially or simultaneously. The impact of setup errors on the accuracy of radiation therapy dose delivery is an important factor to consider [24, 25]. Research by Heikkilä, Annele et al. indicated that in the presence of rotational setup errors, the dose distribution of deep inspiration breath hold VMAT and tangential field-in-field are sufficiently robust, but still exhibit some poor outcomes (PTV Dmin reduced by up to −6.48 Gy in VMAT and −11.87 Gy in FiF after 3° rotations) [26]. The study by Zhao, Yanqun et al. suggests that translational setup errors of 5–10 mm had a significant effect on the CTV coverage [27]. In the design of radiation therapy plans for breast cancer, isocenters of beam were often positioned at the geometric center or centroid of the target. Nevertheless, it is frequently observed that the tumor bed is located away from the isocenter, due to a large separation between the medial and lateral aspects, with the boost positioned either medially or laterally. Moreover, the SIB plan features a radiation dose that rapidly decreases from the tumor-bed volume to the surrounding breast tissue, and this rapid decrease in dose outside the tumor-bed is somewhat similar to that in SRS. Roper, Justin et al. indicated that a reduction in target volume, an increase in rotational errors, and large distance between targets all contribute to an increased risk of compromised coverage [28]. This means that in breast cancer radiation therapy, the distance from the tumor bed to the isocenter, the volume of the tumor bed, and the degree of conformality in dose coverage may all impact tumor bed dose coverage under setup errors during treatment sessions.

The purpose of this study was to compare the differences between sequential and simultaneous integrated boost techniques for early-stage left-sided breast cancer after breast-conserving surgery at organs at risk (OARs), high-dose regions in non-boost of the whole-breast, and dose homogeneity of the targets. Furthermore, our investigation delved into the assessment of potential risks associated with tumor bed dose coverage, particularly under simulated scenarios involving setup errors that encompass both rotational and translational

components. A retrospective univariate analysis was conducted on a cohort of 23 patients to elucidate the relationship between PTVboost coverage, PTVboost volume, and the distance from the PTVboost to the isocenter, and endeavor to development of a target coverage model based on these findings. In parallel, a univariate analysis was performed to investigate the relationships among the volumes of the PTVbreast, PTV boost, and the high-dose volume in the PTVbreast. This analysis facilitated the development of a predictive model for high-dosevolume in the PTVbreast. The harmonious integration of these two models may be provide valuable insights for determining the optimal dose-escalated strategy of boost for individual patients.

Materials and methods

Patients and target delineation

Twenty-three female patients diagnosed with early-stage left-sided breast cancer, who were treated with hypofractionated whole-breast radiotherapy (HFWBI) and tumour-bed dose escalation between January 2023 and March 2024, were retrospectively sequentially selected in this study. All patients were anonymized and with approval from the institutional review board. CT scans were acquired using a GE Discovery RT590 CT simulator with a 5 mm slice thickness,with patients positioned supine and supported by a custom cushion, while a wing board for arm positioning above the head. The CT data were then imported into Eclipse TPS (Version 15.5) for planning.

All OARs, including the ipsilateral lung, contralateral lung, heart and contralateral breast were automatically segmented by AccuContour (Manteia Medical Technologies Co. Ltd., Xiamen, China) and reviewed by a senior oncologist. The whole-breast clinical target volume (WB-CTV) and the boost clinical target volume (CTVboost) were delineated by an experienced radiation oncologist according to the international guidelines RTOG 1005 [29]. For CTVboost, it is essential to enhance the accuracy of delineation by considering various factors such as the patient's scar tissue, radiological changes in the breast tissue pre and post-operative, the surgical report, and/or the presence of surgical clips. A uniform 5 mm margin were added to this WB-CTV and CTVboost to create the whole breast planning target volume (WB-PTV) and the boost planning target volume (PTVboost), respectively. Subsequently, all PTVs were constrained to 5 mm under the patient's body. The WB-PTV, subtracting the PTV-boost, was considered as the non-boost breast planning target volume (PTVbreast).

Treatment plans and evaluation

For each patient, all dynamic IMRT plans were created for Varian Truebeam accelerator with a dose rate of 600 MU/min and using the photon optimization (PO) algorithm and the analytical anisotropic algorithm(AAA) (Eclipse v15.5,Varian,USA). The calculation grid size was $2.5 \times 2.5 \times 2.5$ mm.Within the context of our research, each patient was assigned three distinct high-fractionated whole breast irradiation (HFWBI) plans. The original clinical plan generated sequential dose escalation to the tumour-bed with single isocentre (s-SB). The other two distinct IMRT plans was sequential dose escalation to the tumour-bed with dual isocentre (d-SB) and simultaneous integrated boost to the tumour-bed dose with a single isocentre (s-SIB), respectively. For the s-SB and d-SB plans, the prescribed dose for the WB-PTV was 42.5 Gy/16Fr, followed by a sequential boost dose of 8.7 Gy/3Fr. For the s-SIB plan, the dose to the breast PTV was 42.5 Gy/16Fr, along with a simultaneously integrated boost of 48.5 Gy/16Fr. The biologically effective doses (BED) with an α/β ratio of 4 Gy for the WB-PTV and PTVbreast were 70.8 Gy. The BED for the boost planning target volume (PTVboost) was 85.24 Gy in the s-SIB plan and 85.77 Gy in the HFWBI-SB plan [30]. The dose-volume constraints to the targets and critical OARs were set based on the RTOG 1005 protocol.

For the s-SB and d-SB techniques, the beam configurations and optimisation conditions for the whole breast were consistent with the 7 tangential fields, which align with clinical plans. To enhance dose uniformity within the target volume while minimize high-dose areas, both plans utilised the manual field secondary placement multiple sub-PTV strategy from our previous research [31]. The s-SB technique maintains a constant isocenter for the boost irradiation, which is always positioned at the centroid of the WB-PTV. Conversely, for the d-SB technique, the isocentre for boosts is located at the centroid of the PTVboost, thereby reducing the impact of rotational setup errors on the dose coverage of the targets. The number of irradiation beams for the boost in the s-SB and d-SB plans consists of five, with four evenly distributed on the medial and lateral sides of the target, and the remaining one being perpendicular to the target. In the case of the s-SIB technique, the isocentre is also set at the WB-PTV centroid, with beam and angles aligned with the s-SB whole breast irradiation.

Plans evaluation were conducted using cumulative dose volume histograms (DVHs). Metrics including V95, V105, Dmean, D98%, D2%, homogeneity index (HI), and conformity index (CI) values for both the PTVboost and PTVbreast were compared. The CI and HI for the planning target volumes of the breast and boost were calculated for each plan.

$$CI_{RTOG} = PIV/TV \quad (1)$$

$$CI_{paddick} = (TV_{PIV*}TV_{PIV})/(TV * PIV) \quad (2)$$

$$HI = (D2 - D98)/D50 \quad (3)$$

where TV refers to the target volume, PIV denotes the volume surrounding the PTV prescribed dose, and TV_{PIV} represents the overlap between TV and PIV [32]. The CI value closer to 1 indicating improved conformity of the dose to the planning target volume (PTV). For the HI, D2%, D98%, and D50% represent the doses received by 2%, 98%, and 50% of the target volume, respectively [32]; higher HI values indicate poorer uniformity in dose distribution.

The doses delivered to OARs, particularly the ipsilateral lung and heart, were meticulously evaluated. Furthermore, the doses to the contralateral breast and lung were analyzed. The parameters compared included Dmean, V5, V20, and V30 for the ipsilateral lung and heart, alongside Dmean and V5 for the contralateral breast. For the contralateral lung, only V5 was taken into consideration.

Setup error and dose correlation study

The simulation of setup errors was conducted in the plan isocenter, utilizing a Cartesian coordinate system. All adjustments are performed exclusively via the Eclipse TPS at the isocenter. Translationals of 0.5 mm, 1.0 mm, and 2.0 mm coupled with rotations of 0.5°, 1°, and 2°(only 0.5 mm combined with 0.5°, 1.0 mm combined with 1°, and 2.0 mm combined with 2°) were applied along three orthogonal axes after Cartesian coordinate transformation. For the d-SB plans, the setup errors of the two isocenters were the same. The specific calculation methods have been described in detail in our previous research [33]. PTV dose metrics were derived from sampling these plans with translational-coupled rotational errors. Therefore, except the initial 69 plans, set-up errors plans were created for each combination of the rotation and translationals, resulting in a total of 207 set-up errors plans. To evaluate the impact of setup errors on PTVboost dose coverage, the Average reduction (Avg. Red) and Maximum reduction (Max. Red) in V95 and D95 were compared compared across different planning strategies.

The values of D95 and V95 derived from the Eclipse TPS were subjected to statistical analysis utilizing Generalized Estimating Equations (GEE). The analysis of coverage rates was performed in accordance with the respective $1/CI_{RTOG}$. The correlations of intrapatient were accounted by GEEs. The effects of $1/CI_{RTOG}$ on D95, at rotations of 0.5°, 1.0°, and 2.0° coupled with translationals of 0.5 mm, 1.0 mm, and 2.0 mm, were characterised by univariate linear regression:

$$D95 = a * (1/CI_{RTOG}) + c \quad (4)$$

Parameter estimates were calculated in relation to *P* values and confidence intervals. The identity link of the normally distributed outcome data (i.e., linear model) was assessed using the Kolmogorov–Smirnov supremum test, which simulates the cumulative sum of residuals as a goodness-of-fit measure. The PTVboost volume and the separation of PTVboost to the isocenter for the D95 of PTVboost under setup errors were also analyzed using Eq. (4).

The V95 data were classified into categories below and above 95%. For rotations of 0.5°, 1.0°, and 2.0°, coupled with translationals of 0.5 mm, 1.0 mm, and 2.0 mm, univariate logistic regression models were constructed using GEE. These models, incorporating $1/CI_{RTOG}$, estimate the probability of V95 coverage under 95%:

$$Log(p/(1-p)) = A * (1/CI_{RTOG}) + C \quad (5)$$

P values, 95% confidence intervals (CIs), and odds ratios were presented to assess the relationship between $1/CI_{RTOG}$ and V95.

PTVbreast' high-dose regions analysis

The ratio of PTVbreast volume to PTVboost volume (Ratio_V) was subjected to univariate analysis and correlated with the high-dose regions of V105%, V107%, and V110% within the PTVbreast. As the volume proportion of PTVboost within the PTVbreast increases, the dose fall-off area surrounding the boost becomes larger. This dose fall-off area is the main factor in forming the high-dose region of PTVbreast. The effects of Ratio_V for high-dose were characterised using univariate linear regression:

$$V(Rx\%) = R * Ratio\_V + C \quad (6)$$

where Rx represents values of 105, 107, or 110. *P*-values and 95% confidence intervals (CIs) were calculated to assess the relationship between Ratio_V and V(Rx%).

Dosimetric effects and skin toxicity were observed as short-term outcomes. To comprehensively evaluate the long-term tumor control and patient survival rates associated with different techniques, we also assessed the tumor control probability (TCP) of the PTVboost. A Poisson Linear-Quadratic (PLQ) model was constructed to determine the TCP, along with the dose–response characteristics, utilizing the logistic function as follows [34]:

$$TCP = [\exp(-\exp[e\gamma - (EQD_2/D50) * (e\gamma - \ln(\ln(2)))])] \quad (7)$$

$$EQD_2 = D(1 + d/(\alpha/\beta))/(1 + 2(\alpha/\beta)) \quad (8)$$

where e represents the natural constant, γ is the normalized dose–response slope, and D50 refers to the dose required to achieve 50% TCP for a specific endpoint. For the breast radiotherapy model, the parameters are set as D50 = 30.89 Gy, γ = 1.3 and α/β = 4 [35, 36]. EQD2 stands for the equivalent dose delivered in 2-Gy fractions and is calculated using Eq. 3 [37]. Here, D denotes the cumulative dose, d represents the dose per fraction, and α/β is the correction factor.

Statistics

For setup errors, the descriptive statistics of the data are presented as mean ± standard deviation (SD) and median [range], applicable to PTVboost and PTVbreast. The D95 and V95 analyses under setup errors are only performed for PTVboost. Parameter estimates, P values, and confidence intervals were calculated. Analyses were performed with IBM SPSS 21 software (SPSS, Chicago, USA), employing the Wilcoxon signed-rank test for statistical evaluation, with P values below 0.05 considered statistically significant.

Results

Patient characteristics

Across the 23 cases, the tumour grade varied from I to III, with six cases not specified. The median tumour diameter was 1.7 cm, ranging from 0.6 to 3.5 cm. The median volume of the PTVboost was measured at 129.2 cc (range: 47.3–357.5 cc), while the median volume of the PTVbreast was 348.7 cc, falling within a range of 122.8–792.6 cc. The ratio of PTVbreast to PTVboost averaged 2.83 displaying a range from 0.78 to 7.55. Additionally, the ratio of the tumor bed clinical target volume to the whole-breast planning target volume (Ratio_G/P) ranged from 0.08 to 0.39. The characteristics of the patients are shown in Table 1.

Table 1 Patient characteristics

Characteristic		n (%)*
Patients		23
Treated breasts		23
Age (y)		
	Median (range)	48[34–61]
PTVbreast Volume [cm^3]		
	Median [range]	348.7[122.8–792.6]
	Mean ± SD	371.3 ± 162.6
PTVboost Volume [cm^3]		
	Median [range]	129.2[47.3–357.5]
	Mean ± SD	154.8 ± 79.3
CTVboost Volume [cm^3]		
	Median [range]	82.9[31.7–232.0]
	Mean ± SD	98.6 ± 11.5
Ratio_V		
	Median [range]	2.29[0.78–7.55]
	Mean ± SD	2.83 ± 1.6
Ratio_G/P		
	Median [range]	0.19[0.08–0.39]
	Mean ± SD	0.19 ± 0.02
Tumor size(cm)		
	Median [range]	1.7[0.6–3.5]
	Mean ± SD	1.85 ± 0.76
	The tumour size for the two cases was not stated	
Tumor grade		
	I	4
	II	10
	III	3
	Not stated	6

PTVboost Boost planning target volume *PTVbreast* Whole breast volume subtracting the PTVboost *Ratio_V* PTVbreast volume/PTVboost volume *Ratio_G/P* Tumor-bed clinical target volume/whole-breast planning target volume *SD* Standard deviation

Quality comparison of planning

The dosimetric parameters of PTVboost and PTVbreast for the three plans—s-SB, d-SB and s-SIB—along with the statistical analysis, are detailed in Supplementary Table 1 and Supplementary Table 2, respectively. A dose constraint of 95% prescription dose covering 95% of the PTV was established, and except for one case, all plans met the clinical criteria for PTV coverage.

For PTVboost, the s-SIB technique exhibited the lowest D98%, D50%, D2% and TCP values when compared to both the s-SB and d-SB techniques. s-SIB provided the highest CI, while s-SB had the lowest HI. In high-dose region, the V105 and V107 values for s-SIB were significantly higher than that of s-SIB and d-SB technique. Additionally, the V105 and V107 values for d-SB were lower than s-SB ($p = 0.002$, $p = 0.431$, respectively). For PTVbreast, the s-SIB technique demonstrated significantly lower D98% and D2% values compared to both the s-SB and d-SB techniques. Additionally, the s-SIB technique exhibited lower V95 values than the other techniques (s-SIB, $p = 0.003$; d-SB, $p = 0.065$). The s-SIB technique was significantly better than other two techniques regarding PTVbreast V105, V107, V110, CI and HI. Moreover, the d-SB technique was significantly better than s-SB for PTV breast V105, V107, V110, and CI, but not for HI ($p = 0.115$).

Supplementary Table 3 presents the dosimetric parameters for all organs at risk (OARs). For the mean dose to the heart, s-SIB was significantly lower than both s-SB and d-SB ($p = 0.019$, $p = 0.001$, respectively). There were no significant differences among V5, V20,

and V30; however, s-SIB demonstrated lower values, while d-SB had lower V5 and V20 but higher V30. For the ipsilateral lung, with the s-SIB technology, the mean dose, V5, V20, and V30 were significantly lower compared to the other two techniques, and there were no significant differences between s-SB and d-SB. While the d-SB technique revealed the lowest V5 for the contralateral lung, there were no significant differences among the techniques. The values of Dmean and V5 for the contralateral breast between s-SB and d-SB showed no significant differences. However, these values were notably lower when compared to those obtained from s-SIB.

Analysis of PTVboost dose coverage under set-up error

The D95 and V95 values of three technique are plotted as a function of the $1/CI_{RTOG}$ in Figs. 1 and 2. The reduction in V95, D95 and TCP (Avg and Max) values of PTVboost were compared across three different planning strategies, as shown in Supplementary Table 4 and Supplementary Fig. 3. From the graph, we can observe that the average reductions of V95, D95, and TCP appear to increase with larger setup errors, and the variation in TCP is more significant.

At a 0.5°coupled with 0.5 mm set-up, all targets had V95 values > 95%, and the target coverage was comparable to the ideal case of no set-up errors across the three techniques. The average decrease in V95 was within 0.34 percentage points, with the largest individual decrease of 0.9 percentage points occurring in the s-SIB plan. When setup errors were within 1.0° coupled with 1.0 mm, both the s-SB and d-SB plans maintained excellent target coverage, with the average decrease in V95 remaining under 0.38 percentage points and the maximum individual decrease being 1.1 percentage points. Under the same setup error conditions, although the V95 values for the s-SIB plan were all greater than 95%, the average only showed a modest decrease of 1.06 percentage points, while the maximum individual decrease reached 3.3 percentage points. Coverage worsened substantially for s-SIB plans when the set-up error increased to 2.0° coupled with 2.0 mm, resulting in only 65.2% of targets

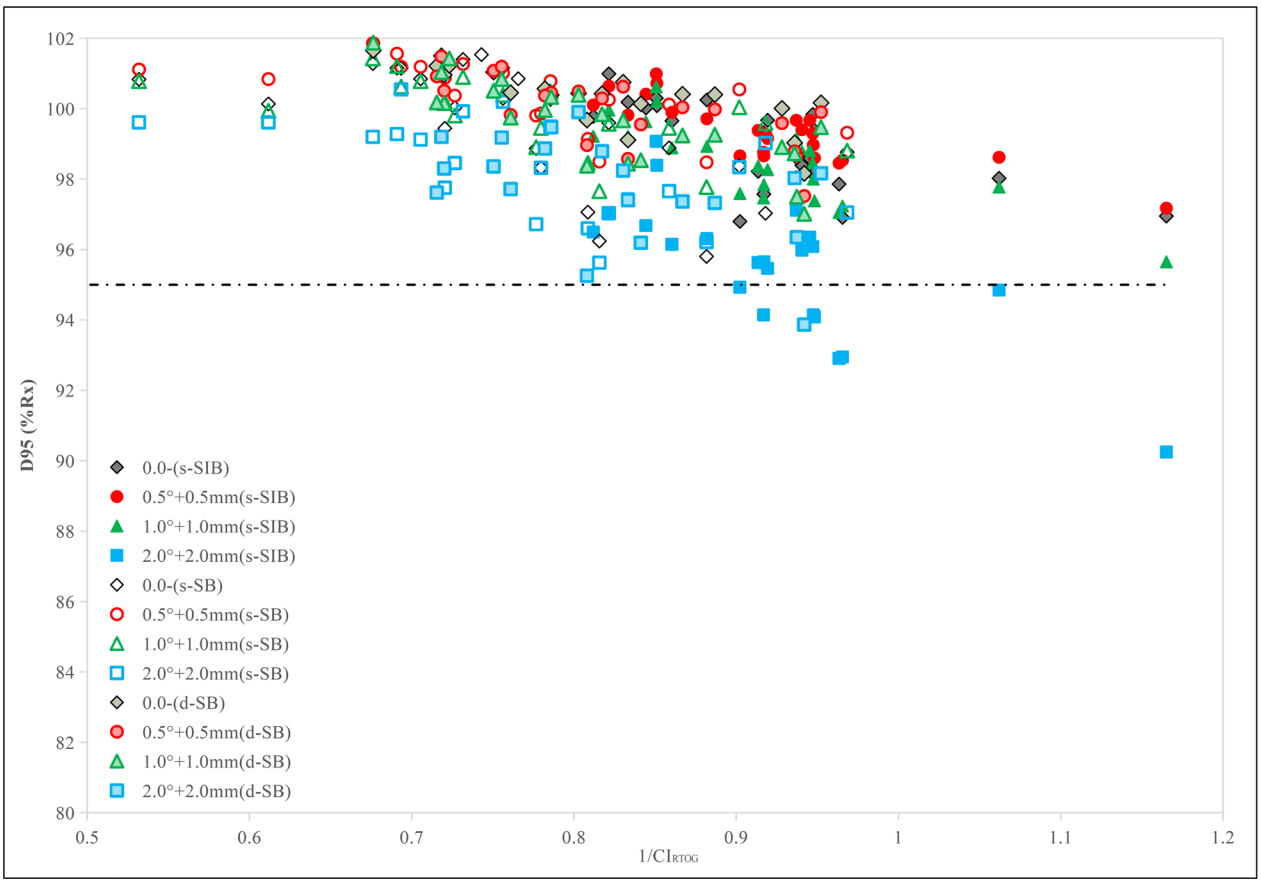

Fig. 1 D95 is plotted as a function of 1/CI and stratified based on setup error, specifically focusing on the combined effect of rotational and translational factors across the three techniques. Abbrev: D95 = The dose to 95% of the PTV, CI = CI_{RTOG} = PIV/TV, Where TV refers to the target volume, PIV denotes the prescription isodose volume.

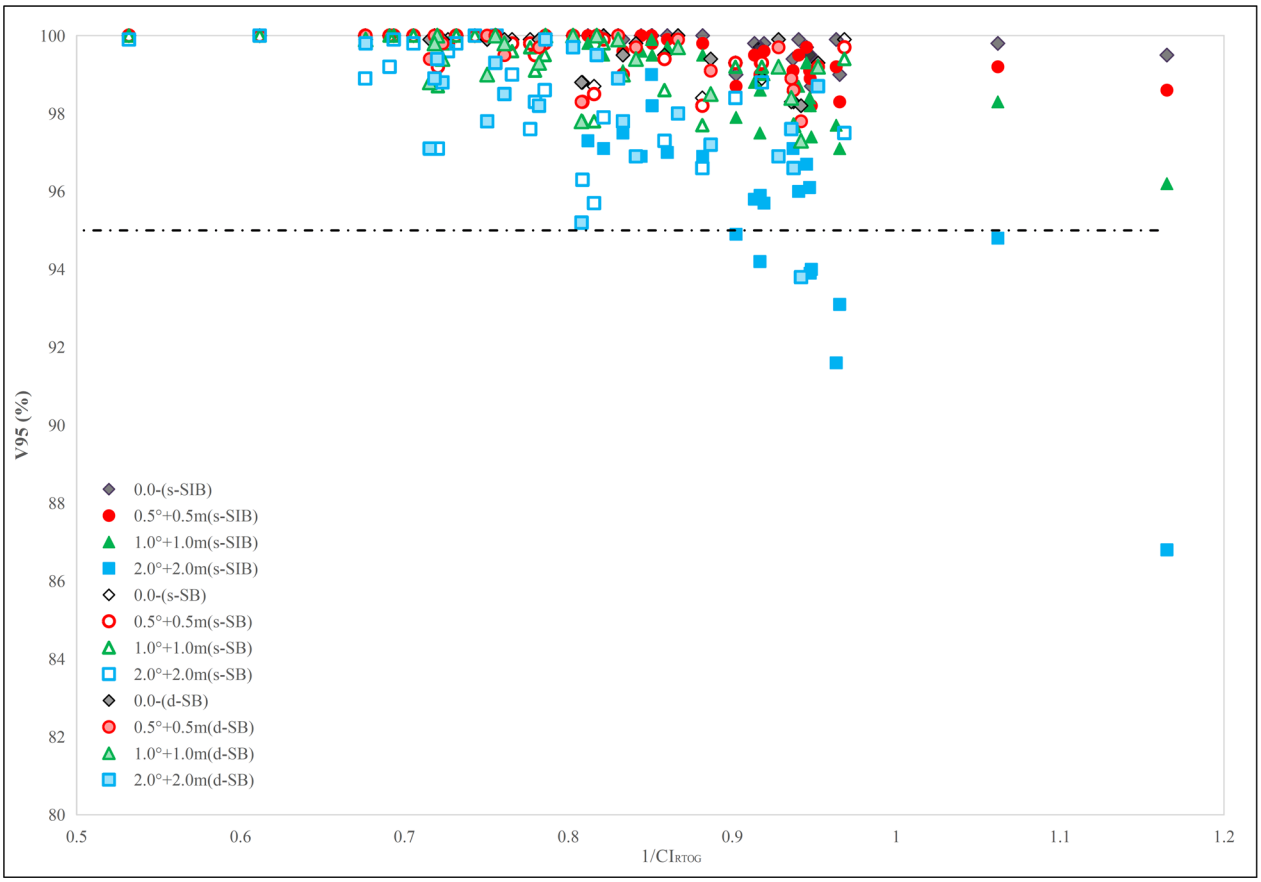

Fig. 2 V95 is plotted as a function of 1/CI and stratified by setup error, with a particular emphasis on the combined influence of rotational and translational across the three techniques. Abbrev: V95 = Volume covered by 95% of the prescribed dose, CI = CI_{RTOG} = PIV/TV, Where TV refers to the target volume, PIV denotes the prescription isodose volume.

achieving V95 values greater than 95%; one cases had coverage values was < 90% with a decrease of 12.7 percentage points,while the average values of V95 decreased by 4.2 percentage points. The s-SB plans maintained coverage values were > 95%, and d-SB plans had two cases coverage values were < 95%.

For D95 values, when setup errors were within 1.0° coupled with 1.0 mm, all targets had D95 values greater than 95%. Additionally, when the setup error was 0.5°coupled with 0.5 mm, the D95 values for the s-SIB plan showed a slight increase, while in the case of the s-SB plan, all D95 values increased when the setup error was within 1.0° coupled with 1.0 mm. However, when the setup error increased to 2.0°coupled with 2.0 mm, only 65.2% of targets had D95 values greater than 95% for the s-SIB plan, and these cases were the same as those with V95 values greater than 95%. In the case of the d-SB plan, only one patient's D95 value was less than 95%, while all target D95 values for the s-SB plan were greater than 95%.

The univariate GEE linear regression showed that the $1/CI_{RTOG}$ of the target is a statistically significant predictor of D95, with statistical significance found in all set-up error scenarios. Parameter estimates, confidence intervals, and *p*-values are shown in Table 2. For the GEE linear models under the three setup errors, the QICC values indicate a good fit. As Supplementary Fig. 1 shows, regardless of the technique used, the relative effects of $1/CI_{RTOG}$ on coverage increases with larger setup errors, with the s-SIB plan being the most affected. In the univariate logistic regression model, as shown in Supplementary Fig. 2, for the s-SIB and d-SB plans, $1/CI_{RTOG}$ is significantly associated with V95 coverage < 95% under a 2° coupled with 2.0 mm setup error (see Table 3). In other setups, since the case coverage for all plans exceeds 95%, the model could not be estimated.

We additionally employed logistic regression and linear regression methodologies to assess the influence of tumor bed volume on target coverage, and the influence of the distance between the tumor bed and the isocenter on target coverage. Univariate analysis has unveiled that neither the volume of the boost nor the distance serve as predictive indicators for D95 and V95 values pertaining

Table 2 GEE univariate linear regression model (Eq. 1) for predicting D95 of PTVboost as a percentage of the prescription dose

Planning strategies	Rotation		Parameter estimate	95% CI	QICC	*P* value
s-SB						
	0.5°	a	−8.15	−12.12,−4.13	65.10	< 0.0001
		c	106.15			
	1.0°	a	−8.83	−12.92, −4.76	72.76	< 0.0001
		c	106.56			
	2.0°	a	−9.62	−13.72, −5.53	108.02	< 0.0001
		c	106.51			
d-SB						
	0.5°	a	−9.47	−12.67, −6.27	21.61	< 0.0001
		c	107.95			
	1.0°	a	−10.09	−13.43, −6.73	82.66	< 0.0001
		c	108.21			
	2.0°	a	−11.56	−16.65, −6.46	117.32	< 0.0001
		c	108.65			
s-SIB						
	0.5°	a	−10.12	−12.71, −7.53	29.36	< 0.0001
		c	108.43			
	1.0°	a	−11.20	−14.08, −8.31	34.54	< 0.0001
		c	108.98			
	2.0°	a	−14.97	−18.71, −11.23	186.31	< 0.0001
		c	111.00			

CI Confidence interval *QICC* Corrected Quasi-likelihood Information Criterion *D95* Dose to 95% of planning target volume *GEE* generalized estimating equations

The model is parameterized at rotation errors of 0.5°, 1.0°and 2.0°. D95 GEE linear regression model as show in Eq. 4

Table 3 GEE univariate logistic regression model (Eq. 5) for predicting the probability (*p*) that V95 of PTVboost under 95%

Planning strategies	Rotation		Parameter estimate	Odds ratio	OR 95% CI	QICC	*P* value
s-SB							
	0.5°	Not estimable:V95 > 95% in all case					
	1.0°	Not estimable:V95 > 95% in all case					
	2.0°	Not estimable:V95 > 95% in all case					
d-SB							
	0.5°	Not estimable:V95 > 95% in all case					
	1.0°	Not estimable:V95 > 95% in all case					
	2.0°	A	9.45	12,697	6389,2.56E + 04	19.38	< 0.0001
		C	−11.08				
s-SIB							
	0.5°	Not estimable:V95 > 95% in all case					
	1.0°	Not estimable:V95 > 95% in all case					
	2.0°	A	11.68	118,695	144.5,9.75E + 07	40.57	< 0.0001
		C	−12.52				

OR Odds ratio *CI* confidence interval *QICC* Corrected Quasi-likelihood Information Criterion *GEE* generalized estimating equations *V95* Volume covered by 95% of prescribed dose.

The model parameterizes of rotation errors. The volume of the planned target PTVboost, distance from the PTVPTVboost centroid to the isocenter and the Volume of 95% isodose line/Volume of prescription isodose line are variables. Parameter estimates related to volume (A), distance (B) and $GI_{R95\%}$(G) are reported using their respective odds ratio (OR) and OR 95% confidence intervals and *p*-values.V95 GEE logistic model as show in Eq. 5

to PTV boost. The variation in V95 values was depicted against the distance to the isocenter, stratified by volume, in Fig. 3. The variations in the effects of distance and volume on coverage were contingent upon rotational error. Specifically, at a given distance, V95 values inclined to be greater for larger targets and lesser for smaller targets, with the discrepancy becoming more evident at larger rotations. The three instances enclosed within the black rectangular box may potentially influence this trend, with a plausible rationale being that the CI_{RTOG} values associated with the PTV boost for these instances are notably elevated (1.17, 1.18, and 1.23), indicating that the prescription isodose volume significantly exceeds the volume of the PTV boost. In this situation, the impact of CI_{RTOG} on target coverage is decisive, as the target of $1/CI_{RTOG}$ emerges as a statistically robust predictor for target coverage.

PTVbreast' high-dose regions analysis

High-dose regions of V105%, V107%, and V110% within the PTVbreast across three techniques were found to be significantly associated with the Ratio_V. Parameter estimates, confidence intervals, and *p*-values are presented in Table 4. The values for V105%, V107%, and V110% for the three techniques are plotted in Fig. 4. For all techniques, high-dose regions decreased as the Ratio_V increased, with the s-SIB showing the least reduction in V105%, V107%, and V110% for each unit increase in the Ratio_V, while the s-SB exhibited the greatest decrease. Table 5 compares the high-dose regions of PTVbreast among the different techniques. The values of V105%, V107%, and V110% for s-SIB were significantly lower than those of the other two techniques, with an average V110% of 8.2 and a maximum of only 15.5. For d-SB, the high-dose region were significantly lower than those for s-SB. The s-SB technique exhibited the poorest high-dose regions with the average V105% reaching 52.7 and a maximum of 68.9.

As an setup errors illustrative case, Fig. 5 shows the initial dose distributions for all three techniques and the dosimetric effects of a 2.0° and 2.0 mm error combination when PTVboost is located on the left lateral side of the breast. In s-SIB, over 44.5% of the PTV was not encompassed by the prescribed dose. Similarly, in d-SB, more than 23% of the PTV failed to receive the prescribed dose, while in s-SB, this figure exceeded 18.9%. The expansion from GTVboost to PTVboost was 5 mm.

Discussion

The safety and efficacy of whole-breast hypofractionated boost therapy is currently a focal point of interest, aimed at achieving optimal local control with minimal acute and late toxicity for patients with early-stage left-sided breast cancer. In this study, we compared target volume coverage and doses to OARs in early-stage breast cancer patients undergoing breast-conserving surgery using hypofractionated techniques combined with SB (single- and dual- isocenter) and SIB techniques. Additionally, we determine the dosimetric effects to the tumor bed under simulated varying degrees of setup error across the three techniques. These findings may help determine whether an individual patient is a good candidate for SB or SIB techniques. The sample size (data from 23 patients) is relatively small, which may affect the generalizability and statistical significance of the results. A larger sample size may be needed to further improve the robustness of the results.

Early studies have explored the dosimetric advantages of SIB in breast treatment [22, 38, 39]. We confirmed these findings while comparing SIB with two different sequential boosts. This can be simply explained by the fact that more efficiently shaped boost beams result in smaller irradiated volumes, including lower doses outside the tumor bed used and smaller field openings. Compared to s-SB, d-SB shows similar coverage of the target volume and organ-at-risk dose constraints; however, the proportion of high-dose regions within the PTV-breast is significantly reduced with Ratio_V < 6.888, theoretically lowering the risk of fibrosis or late skin reactions. This is due to d-SB having more efficiently shaped boost beams, resulting in a smaller volume of non-boost tissue being irradiated. Of course, placing an additional isocenter will increases the workload for the technicians.

The analysis results of the high-dose regions in the PTVbreast show that the Ratio_V is a statistically significant predictor of 105%, V107%, and V110% across the three techniques. The difference in high-dose regions between s-SB and d-SB gradually diminishes compared to s-SIB as the Ratio_V value increases. According to Formula 6, when the Ratio_V value is approximately 9.725, s-SB and d-SB tend to converge. When the Ratio_V value exceeds 6.888, the V107% of d-SB will be greater than that of s-SB, and when the Ratio_V value exceeds 7.252, the V110% of d-SB will also be greater than that of s-SB. The volume parameters for PTVbreast and PTV_boost are easily obtainable from treatment planning systems, which facilitates the construction of predictive models for PTVbreast high-dose regions specific to each institution (this model can be implemented in 3DCRT, IMRT, and VMAT). This allows for early decision-making regarding the treatment technique during the planning process. In the IMPORT HIGH trial, the median tumor-bed clinical target volume was 12.8 cm^3, and the ratio of this volume to the whole-breast planning target volume was 0.015 [23]. In our experiment, the corresponding median volume and ratio were 82.9 cm^3 and 0.19, recpectively.

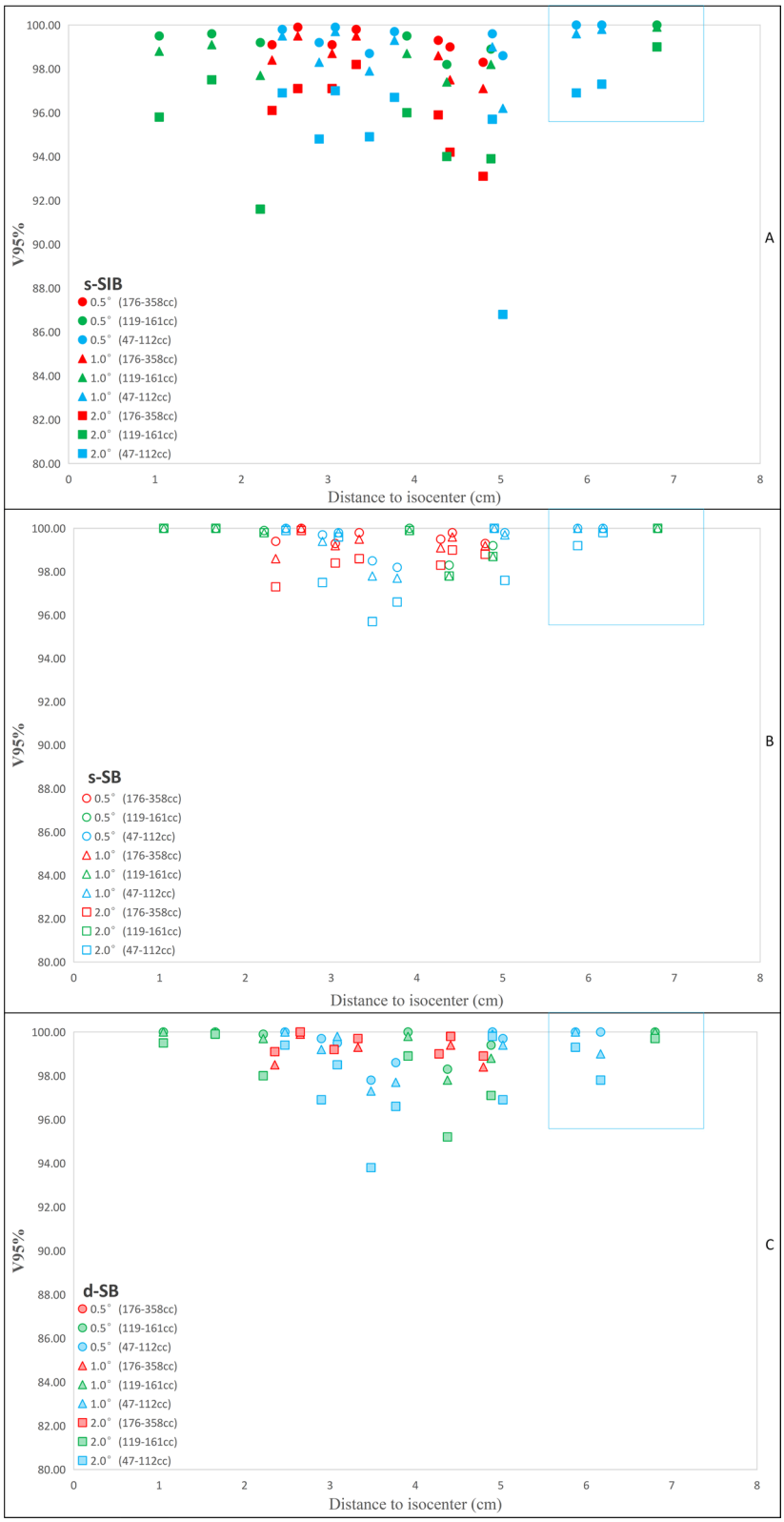

Fig. 3 Under three distinct methodologies, the V95 values are plotted as a function of the PTV boost distance to isocenter and stratified by PTV volume, at rotations of 0.5°coupled with 0.5 mm, 1.0°coupled with 1.0 mm and 2.0° coupled with 2.0 mm.The CI_{RTOG} values for the PTV boost in the three instances contained within the light blue rectangular box are relatively high, measuring 1.17, 1.18, and 1.23, respectively. Abbrev: V95 = Volume covered by 95% of the prescribed dose.

Table 4 Univariate analysis predictive factors for V105,V107,V110 of PTVbreast in different planning strategies

Strategies	Variables		Parameter estimate	95% CI	Univariate analysis (*P* value)
s-SB	V105				
	Ratio_V	R	−5.64	−7.92, −3.36	< 0.0001
		C	68.66		
d-SB	V105				
	Ratio_V	R	−5.24	−7.41, −3.07	< 0.0001
		C	64.74		
s-SIB	V105				
	Ratio_V	R	−2.48	−4.72, −0.25	0.029
		C	33.08		
s-SB	V107				
	Ratio_V	R	−5.72	−7.90, −3.54	< 0.0001
		C	58.92		
d-SB	V107				
	Ratio_V	R	−4.60	−6.51, −2.70	< 0.0001
		C	51.20		
s-SIB	V107				
	Ratio_V	R	−1.92	−2.93, −0.91	0.001
		C	19.33		
s-SB	V110				
	Ratio_V	R	−5.09	−7.29, −2.89	< 0.0001
		C	49.48		
d-SB	V110				
	Ratio_V	R	−3.59	−5.77, −1.41	0.003
		C	38.56		
s-SIB	V110				
	Ratio_V	R	−1.211	−1.92, −0.51	0.002
		C	11.67		

V105 Volume covered by 105% of prescribed dose *Ratio_V* PTVbreast/PTVboost (PTVboost = Boost planning target volume *PTVbreast* Whole breast volume subtracting the PTVboost) *CI* confidence interval.

The model employed univariate linear regression analysis, with a significance threshold set at $P < 0.05$, indicating statistical significance for the predictor variables

According to our predictive model, when the median volume and ratio are close to or equivalent to those in the IMPORT HIGH trial, the high-dose regions of HFWBI-SB are only slightly higher than those of HFWBI-SIB. This may help explain why the 5-year cumulative incidence of moderate or marked breast induration in test group 1 of the IMPORT HIGH trial was lower than that of the control group, but not significantly.

For the PTV boost dose coverage under setup error, the results indicate that the $1/CI_{RTOG}$ of the target is a statistically significant predictor of boost coverage. Additionally, the decrease in boost coverage values tends to increase with larger setup errors. This finding may help explain the IMPORT HIGH trial's observation of a slightly higher IBTR rate in test group 2, as there was a modest dose reduction away from the index quadrant for high prescriptions, which necessitates better CI_{RTOG} values. This slightly differs from some previous studies on multiple-target SRS [28, 31]. The impact of CI_{RTOG} on PTVboost coverage is as we expected, in that plans with $CI_{RTOG} > 1$ essentially indicate suboptimal PTV coverage, making them more sensitive to setup errors. Therefore, under the condition of fixed PTVboost volume and fixed distance from PTVboost to the planned isocenter, ensuring adequate dose coverage for the target requires considering appropriate CI_{RTOG} values based on different ranges of setup errors. This will be the focus of our future research.TCP.

In our study, the PTVboost volume and distance to isocenter were not statistically significant predictors of target coverage. However, as the boost volume decreases or the distance to the isocenter increases, the target coverage values also gradually decline. Two potential reasons could explain this phenomenon: first, a large boost volume has minimal impact on target coverage. In our trial, patient selection was sequential, with a median boost volume of 129.2 [47.3–357.5]; second, the distance from the boost to the isocenter was relatively small, with a median of 3.77 [1.05–6.80]. Considering these three factors, when a case has a small boost volume, a larger distance to the isocenter, and a good CI_{RTOG}, there is a risk of compromised target coverage. Based on these, we plan to select patients at high risk for compromised target coverage in our future trials using specific criteria, and we will construct a multifactorial predictive model for target coverage through multivariate linear regression analysis. This will help estimate the dosimetric consequences of any setup errors and may contribute to reducing the IBTR rate.

In this study, we executed rotational errors coupled translational errors of the same magnitude seamlessly intergrated a Cartesian coordinate system at the isocenter. Although this study assumes that the positioning errors follow a uniform distribution, in actual clinical practice, the errors may be more complex, which potentially leading to discrepancies between simulation results and reality. However, our findings have preliminarily demonstrated the feasibility of quantifying the potential impact of errors at different levels on target coverage based on the error data obtained under this setup. The selection of the levels of rotational and translational errors was grounded in previous research pertaining to setup inaccuracies in both rotational and translational domains. Betgen, Anja et al. noted in their assessment of setup variability during deep inspiration breath hold radiotherapy for breast cancer patients that the random

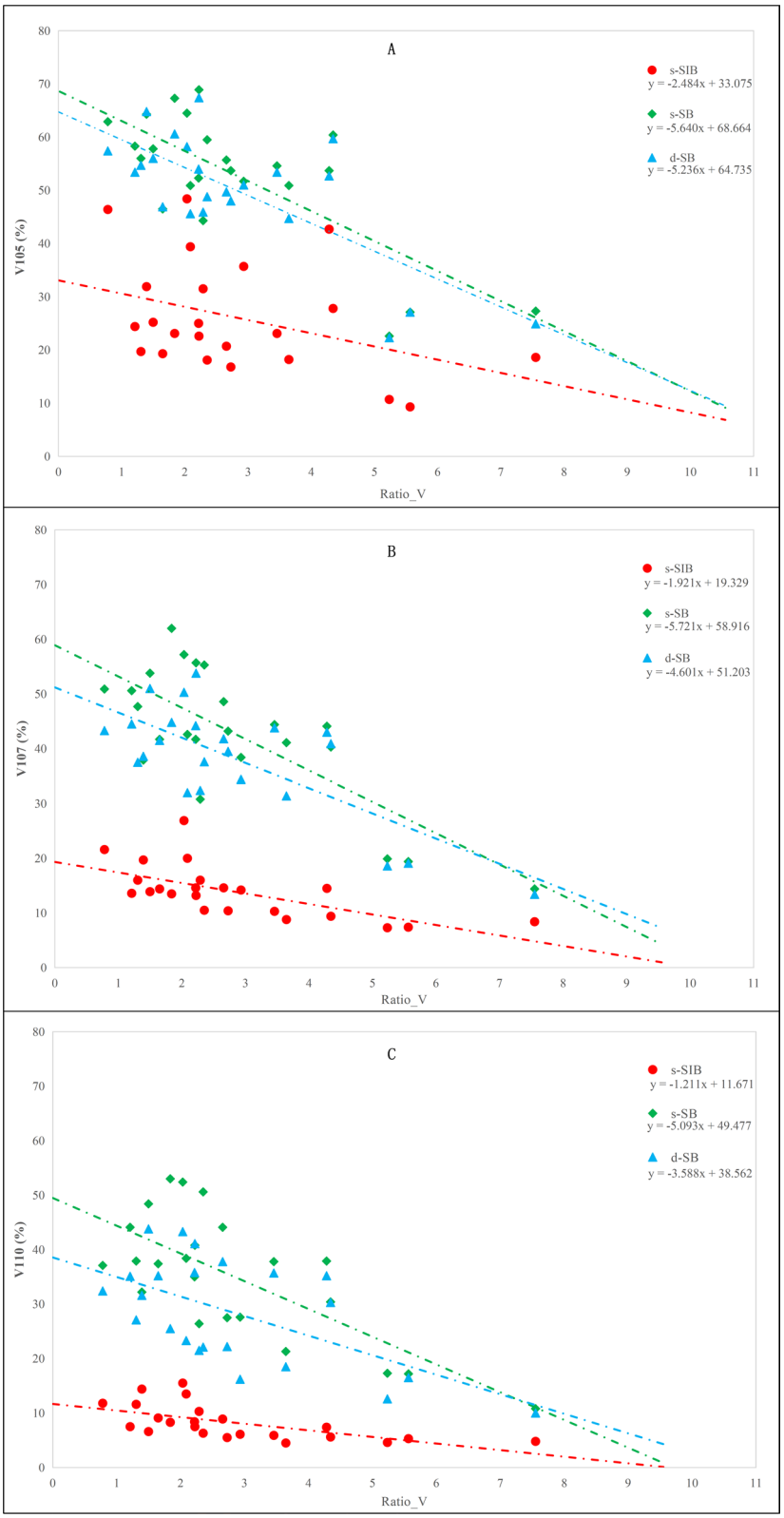

Fig. 4 The values for V105%, V107%, and V110% were plotted as a function of Ratio_V. The distinct fitted dashed lines correlate to the respective univariate linear regression equations, which are shown in the upper right corner.Abbrev: V95 = Volume covered by 95% of the prescribed dose, Ratio_V = The ratio of PTVbreast volume to PTVboost volume (Ratio_V)

Table 5 The PTVbreast high-dose region coverage comparison analysis for all studied techniques with mean ± SD and Median [range]

Structures	Parameter	s-SB	d-SB	s-SIB	*P*-value
PTVbreast					
	V105[%]				
	Median [range]	52.7[22.6–68.9]	51.2[22.3–67.4]	23.1[9.3–48.4]	i = 0.001;ii < 0.0001;iii < 0.0001
	Mean ± SD	52.7 ± 2.6	49.9 ± 2.4	26.0 ± 2.2	
	V107[%]				
	Median [range]	43.2[14.4–62]	40.9[13.4–53.8]	13.9[7.3–26.9]	i = 0.001;ii < 0.0001;iii < 0.0001
	Mean ± SD	42.7 ± 2.5	38.1 ± 2.1	13.8 ± 1.0	
	V110[%]				
	Median [range]	37.4[10.8–53.0]	30.3[10.0–43.8]	7.5[4.5–15.5]	i < 0.0001; ii < 0.0001; < 0.0001
	Mean ± SD	35.0 ± 2.4	28.4 ± 2.0	8.2 ± 0.7	

PTVbreast = *PTVbreast* Whole breast volume subtracting the PTVboost *s-SB* Sequential dose escalation of the tumour-bed with single isocentre *d-SB* Sequential dose escalation of the tumour-bed with dual isocentre *s-SIB* Simultaneous integrated boost of the tumour-bed dose with a single isocentre *SD* Standard deviation *i* s-SB vs d-SB *ii* s-SB vs. s-SIB *iii* d-SB vs.s-SIB $P < 0.05$ indicates a statistical significance

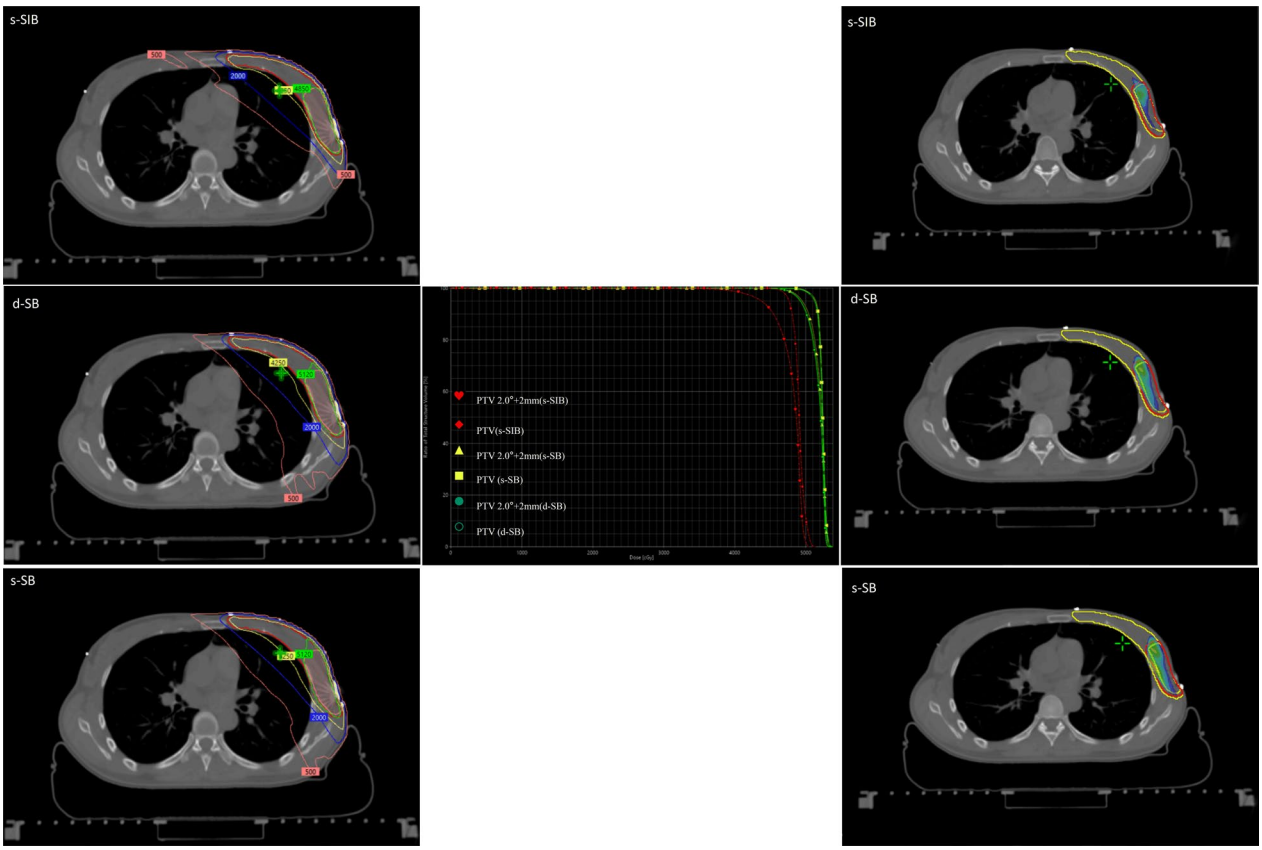

Fig. 5 An illustrative case showed the initial dose distributions for all three techniques and the dosimetric effects of a 2.0° and 2.0 mm error combination Abbrev:Substantial loss in target coverage for an 85.1-cc planning target volume (PTV) at 5.1 cm from isocenter when setup by 2.0° coupled with 2.0 mm. A green cross denotes the transaxial position of the isocenter. Dose-volume histogram data are reported for the PTV at no setup errors and coupled with a 2.0° and 2.0 mm across the three techniques.

(σ) translational error between fractions ranged from 0.09 to 0.22 cm, while the rotational Σ and σ errors varied between 0.08 and 1.56°. The σ errors within fractions were ≤ 0.14 cm and ≤ 0.47° [40]. For institutions equipped with real-time tracking capabilities using the surface guided radiation therapy system that can correct for

six-dimensional errors, the majority of patients demonstrated residual rotational inaccuracies of under 0.6 degrees [41]. Thus, our setup errors align consistently with those previously reported in the majority of studies, and we refrained from delving into more extreme scenarios. Additionally, we anticipated that intrafraction motion would be larger for free-breathing (FB) compared to deep inspiration breath hold (DIBH) techniques. In hypofractionated breast cancer treatments, opportunities for correction are limited, and though rare, extreme setup errors have the potential to significantly affect the target coverage of the tumor bed. Therefore, to ensure safe and accurate treatment, conservative measures must be taken; future experiments will account for at least some of the extreme setup errors observed in clinical practice.

Conclusion

In conclusion, simultaneous-integrated boost is a promising approach to in early-stage breast cancer that can reduce skin toxicity while minimizing the high-dose volume compared to other SB techniques. However, the setup errors observed in patient studies can compromise target coverage, particularly as PTVboost exhibited a larger $1/CI_{RTOG}$. The smaller volume of PTVboost and its significant distance from the isocenter also have detrimental effects on PTVboost coverage. In the PTV-breast, the Ratio_V is a statistically significant predictor of the high-dose regions volume. The predictive model for target coverage, in conjunction with the high-dose region volume estimation model, may be used to guide treatment planning or assess the adequacy of the selected patient-specific technique for therapeutic purposes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-025-02584-0.

Additional file1
Additional file2
Additional file3
Additional file4
Additional file5
Additional file6
Additional file7

Author contributions

Changyou Zhong: Data curation, methodology, project administration, writing – original draft. Minfeng Huang: Data curation, methodology, project administration Haidong Yu: Formal analysis, investigation Jun Yuan: Investigation, project administration Ruilian Xie: Data curation, formal analysis Zhenzhen Lai: Data curation, and investigation. Shanzhou Niu: Conceptualization, formal analysis, writing – review, and editing. Chunbo Tang: Conceptualization, formal analysis, writing – review, and editing.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

This retrospective study was reviewed and approved by the Institutional Review Boards of Meizhou People's Hospital(2024-C-159), and the requirement for individual informed consent was waived.

Human ethics declarations

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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