

Original Article

Dosimetric impact of tumor bed delineation variability based on 4DCT scan for external-beam partial breast irradiation

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Abstract: This study sought to evaluate the dosimetric impact of tumor bed delineation variability (based on clips, seroma or both clips and seroma) during external-beam partial breast irradiation (EB-PBI) planned utilizing four-dimensional computed tomography (4DCT) scans. 4DCT scans of 20 patients with a seroma clarity score (SCS) 3~5 and ≥ 5 surgical clips were included in this study. The combined volume of the tumor bed formed using clips, seroma, or both clips and seroma on the 10 phases of 4DCT was defined as the internal gross target volume (termed IGTV_c, IGTV_s and IGTV_{c+s}, respectively). A 1.5-cm margin was added by defining the planning target volume (termed PTV_c, PTV_s and PTV_{c+s}, respectively). Three treatment plans were established using the 4DCT images (termed EB-PBI_c, EB-PBI_s, EB-PBI_{c+s}, respectively). The results showed that the volume of IGTV_{c+s} was significantly larger than that of IGTV_c and IGTV_s. Similarly, the volume of PTV_{c+s} was markedly larger than that of PTV_c and PTV_s. However, the PTV coverage for EB-PBI_{c+s} was similar to that of EB-PBI_c and EB-PBI_s, and there were no significant differences in the homogeneity index or conformity index between the three treatment plans ($P=0.878$, 0.086). The EB-PBI_s plan resulted in the lowest ipsilateral normal breast and ipsilateral lung doses compared with the EB-PBI_c and EB-PBI_{c+s} plans. To conclude, the volume variability delineated based on clips, seroma or both clips and seroma resulted in dosimetric variability for organs at risk, but did not show a marked influence on the dosimetric distribution.

Keywords: Breast cancer, external beam partial breast irradiation, four-dimensional computed tomography, clips, seroma

Introduction

Radiotherapy following breast-conserving surgery has been proven to be effective for improving local control and long-term survival [1]. Traditionally, patients who undergo breast-conserving therapy receive whole-breast irradiation (WBI). Post-lumpectomy radiation therapy consists of 4-5 weeks of WBI for a total dose of 45-50 Gy in 23-25 fractions, usually followed by a boost of 10-16 Gy in 5-8 fractions to the tumor bed. However, pathologic and clinical data suggest that the vast majority of ipsilateral breast recurrences occur in the vicinity of the tumor bed, and remote recurrences are uncommon regardless of whether WBI is delivered [2]. Therefore, partial breast irradiation may be a better choice for treatment.

The earliest studies of accelerated partial breast irradiation (APBI) used brachytherapy [3,

4]. However, in recent years, interest in administering APBI via conformal external-beam radiation has grown as a result of improvements in targeting and dosimetric planning. External-beam partial breast irradiation (EB-PBI) is non-invasive, allows treatment after full pathologic information is available without subjecting the patient to a second surgical procedure, and may be less operator-dependent. Several reports of EB-PBI have shown promising early outcomes with few local recurrences, minimal toxicity, and excellent cosmetic outcomes [5-7]. However, compared with brachytherapy, there remain several inherent challenges with this approach, including a significantly increased integral normal tissue dose, especially for ipsilateral breast tissue [8]. This increased dose is caused by the requirement for a larger planning target volume (PTV) stemming from concerns about target delineation, target motion caused

by respiration, and daily setup variability. Alternate immobilization techniques, such as four-dimensional computed tomography (4DCT) scanning, have been shown to minimize respiratory motion while potentially displacing normal structures [9]. Furthermore, studies have demonstrated that the presence of clips or seroma can improve delineation accuracy and consistency [10, 11]. Kirby et al. [10] reported that the number of implanted markers influences the accuracy of target delineation and that five to six surgical clips are preferable for tumor bed delineation for PBI. Landis et al. [11] indicated that the shift of the center of mass decreases and the percent volume overlap increases significantly as the seroma clarity score (SCS) increases. Therefore, to improve the accuracy and consistency of delineation, all of the enrolled patients in the current study had SCS 3~5 and ≥ 5 surgical clips to mark the boundaries of the lumpectomy cavity.

Although EB-PBI has recently been recommended by European and American radiation oncology societies, several unanswered questions remain, such as the optimal patient eligibility criteria, gross target volume (GTV), planning target volume (PTV), breast definition, technique of dose delivery, dose fractionation, and dosimetric constraints associated with fewer late side effects. The dosimetric impact of tumor bed delineation variability utilizing clips and seroma based on 4DCT scanning for EB-PBI is also not clearly established. Therefore, to investigate the impact of different reference markers for treatment plans based on 4DCT scanning for EB-PBI, we compared and analysed three different treatment plans for patients based on clips, seroma or both clips and seroma.

Materials and methods

Patients

Twenty patients who underwent wide local excision of breast cancer with full-thickness unstitching of the excision cavity (10 left-sided and 10 right-sided lesions) followed by EB-PBI between June 2009 and November 2013 were included in this study. All of the enrolled patients had SCS 3~5 and ≥ 5 surgical clips to mark the boundaries of the lumpectomy cavity. For every patient, ≥ 5 roundish surgical clips

with a diameter of 2 mm were implanted. The surgical clips were fixed to the cranial, caudal, medial, lateral and dorsal walls of the surgical cavity, respectively. The average interval from lumpectomy to 4DCT scan was 10 weeks (range, 3-16 weeks). All of the patients were free from chronic lung diseases, and their ventilation functions were normal. With the approval of the Institutional Review Board (Shandong Tumor Hospital Ethics Committee), written informed consent was obtained from all patients.

Four-dimensional CT image acquisition

All twenty patients were immobilized in the supine position on a breast board using an arm support (with both arms above the head to adequately expose the breast). 4DCT images and respiratory signals were acquired with a thickness of 3 mm at the conclusion of the standard CT simulation using a 16-slice Brilliance Big Bore CT scanner (Philips Medical Systems, Inc., Cleveland, OH, USA). The signals were sent to the scanner to label each CT image with a time tag. GE Advantage 4D software (General Electric Healthcare, Waukesha, WI, USA) was used to sort the reconstructed 4DCT images into 10 respiratory phases based on these tags, with 0% corresponding to end inhalation (EI) and 50% corresponding to end exhalation (EE). Then, the constructed 4DCT image sets were transferred to the Eclipse treatment planning system (Eclipse™8.6; Varian Medical Systems, Palo Alto, CA) for structure delineation.

Tumor bed delineation

The 10%~90% phases of the 4DCT images were registered on the 0% phase images, which served as the basic phase image. On the ten sets of 4DCT images, the tumor bed was delineated based on the clips, the seroma, or both the clips and seroma (defined as GTV_c , GTV_s , GTV_{c+s} , respectively). All tumor beds were delineated by the same radiation oncologist on the 4DCT images using the same window and level setting. The combined volume of the GTV on the 10 4DCT phases was defined as the internal gross target volume (denoted as $IGTV_c$, $IGTV_s$ and $IGTV_{c+s}$). For each patient, the $IGTV_c$, $IGTV_s$ and $IGTV_{c+s}$ volumes were recorded.

Table 1. Target volume and PTV/IPSB based on the three reference markers (median, cc, %)

Parameter	Clips	Seroma	Clips and seroma
IGTV	18.4 (9.9-81.9)	12.2 (3.5-91.3)	25.7 (13.9-103.2)
PTV	130.0 (76.7-294.9)	93.3 (58.0-300.9)	140.6 (84.2-321.3)
Ipsilateral breast	568.1 (329.1-1116.1)	568.1 (329.1-1116.1)	568.1 (329.1-1116.1)
PTV/IPSB	22.7 (13.0-37.0)	17.9 (9.0-37.0)	25.2 (13.0-42.0)

Abbreviations: PTV/IPSB, the ratio of planning target volume to the ipsilateral whole breast volume (%).

Treatment planning and dosimetric evaluation

The PTV was specified as the IGTV (IGTV_c, IGTV_s, IGTV_{c+s}) plus a 1.5 cm margin (denoted as PTV_c, PTV_s and PTV_{c+s}). The PTV was limited to 5 mm from the skin surface and lung-chest wall interface. For each patient, the volumes of the PTV_c, PTV_s and PTV_{c+s} were recorded. The ipsilateral breast (IPSB) was delineated based on the 4DCT images, and the ratio of PTV (PTV_c, PTV_s, PTV_{c+s}) to the IPSB volume was calculated (termed PTV_c/IPSB, PTV_s/IPSB, PTV_{c+s}/IPSB). The ipsilateral normal breast was the IPSB excluding the PTV margin. In addition, we contoured the ipsilateral lung (IPSL) and heart (left-sided lesions).

In all cases, three-dimensional conformal radiotherapy (3D-CRT) technique using 6-MV photons with 4-field non-coplanar beam arrangement was developed. Three treatment plans were established from the 4DCT images (EI phase) based on PTV_c, PTV_s and PTV_{c+s} (defined as EB-PBI_c, EB-PBI_s, EB-PBI_{c+s}, respectively). The initial prescription dose, defined as 90% of the isodose line, was 3.4 Gy administered twice daily, totalling a dose of 34 Gy delivered over 5 days. The criterion of the 3D-CRT EB-PBI treatment plan was to ensure that at least 95% of the PTV volume received the prescribed dose.

The dose distribution was calculated separately in all three treatment plans, and dose-volume histogram parameters for the PTV, IPSL and heart were calculated for each treatment plan in all patients. Parameters such as the mean dose (D_{mean}), homogeneity index (HI), and conformal index (CI) were evaluated in PTV. HI was defined as follows:

$$HI = \frac{D_2 - D_{98}}{D_T}$$

In this equation, D_2 and D_{98} represent the doses covering 2% and 98% of the target volume, and

D_T is the prescribed dose [12]. CI was defined as follows:

$$CI = \frac{PTV_{ref}}{V_{PTV}} \times \frac{PTV_{ref}}{V_{ref}}$$

In this equation, PTV_{ref} represents the volume of PTV that is covered by the prescribed dose; V_{PTV} is defined as the planning target volume; and V_{ref} represents the volume enclosed by the prescribed isodose [13, 14]. The ipsilateral lungs and heart were evaluated using the D_{mean} and the volumes receiving ≥ 5 , 10, or 20 Gy (V_5 , V_{10} , and V_{20} , respectively). The ipsilateral normal breast was evaluated using the D_{mean} and the volumes receiving ≥ 20 or 30 Gy (V_{20} and V_{30} , respectively).

Statistical analysis

SPSS 19.0 software was used for statistical analysis. In view of observed deviations from the normal distribution, non-parametric statistics were utilized. As the variables did not follow a normal distribution, the data were summarized with medians (minimum-maximum). Friedman tests were performed to establish the variability of each dosimetric parameter, PTV/IPSB and the IGTV and PTV volumes based on the clips, seroma or both clips and seroma. All significant effects were investigated post-hoc using Wilcoxon-signed-ranks tests. For all tests, the conventional significance level of $P < 0.05$ was adopted.

Results

Target volume

The average duration from lumpectomy to 4DCT scan was 10 weeks (range, 3-16). The volume of IGTV_c was similar to that of IGTV_s for six patients during weeks 4-8, the IGTV_c was less than IGTV_s in two patients during weeks 0-3, and the IGTV_c was larger than IGTV_s for twelve patients during weeks 8-16. The volume of IGTV_{c+s} was significantly larger than that of

Table 2. Planning target volume parameters for the three different treatment plans (median)

Parameter	EB-PBI _c	EB-PBI _s	EB-PBI _{c+s}	Z	P
HI	0.12 (0.09-0.17)	0.12 (0.09-0.14)	0.12 (0.09-0.15)	0.26	0.878
CI	0.64 (0.50-0.75)	0.65 (0.52-0.75)	0.66 (0.51-0.76)	4.9	0.086
V _{90%}	98.2 (95.4-99.8)	98.1 (95.1-100.0)	97.8 (95.5-99.9)	1.29	0.525
D _{mean}	36.12 (35.54-36.52)	36.13 (35.79-36.63)	36.06 (35.68-36.67)	0.30	0.861

Abbreviations: HI, homogeneity index; CI, conformity index; V_{90%}, percentage of the planning target volume for evaluation receiving the prescribed dose (%); D_{mean}, mean dose (Gy).

IGTV_c and IGTV_s ($P < 0.001$). Similarly, the volume of PTV_{c+s} was significantly larger than that of PTV_c and PTV_s ($P < 0.001$). However, the volumes of IGTV_s and PTV_s were significantly smaller than those of IGTV_c and PTV_c ($P = 0.019$, 0.004 , respectively). The PTV_{c+s}/IPSB ratio was significantly larger than that of PTV_c/IPSB and PTV_s/IPSB ($P < 0.001$), and the PTV_c/IPSB ratio was also significantly larger than that of PTV_s/IPSB ($P = 0.003$) (**Table 1**).

Planning target volume parameters

The HI and CI results of the PTV are listed in **Table 2**. There was no significant difference between the HI values of EB-PBI_c, EB-PBI_s and EB-PBI_{c+s} ($P = 0.878$). We also observed no significant difference in CI between EB-PBI_c, EB-PBI_s and EB-PBI_{c+s} ($P = 0.086$). The median PTV coverage of EB-PBI_c, EB-PBI_s and EB-PBI_{c+s} was 98.2, 98.1 and 97.8, respectively. The three different treatment plans showed similar coverage of the PTV ($P = 0.525$), and there was no significant difference in the mean dose received between the three methods ($P = 0.861$) (**Table 2**).

Dose to organs at risk

For the ipsilateral normal breast, the mean dose, V₂₀ and V₃₀ received from the EB-PBI_s treatment plan were significantly lower than those from the EB-PBI_c and EB-PBI_{c+s} treatment plans ($P = 0.008$, 0.020 , 0.017 , respectively), whereas there was no significant difference in the dose received between the EB-PBI_c and EB-PBI_{c+s} treatment plans ($P = 0.550$, 0.520 , 0.370 , respectively) (**Table 3**).

Similarly, for the ipsilateral lung, the mean dose, V₅, V₁₀ and V₂₀ received from the EB-PBI_s treatment plan were significantly lower than those from the EB-PBI_c and EB-PBI_{c+s} treatment plans ($P < 0.001$), although there was no signifi-

cant difference between the doses received from the EB-PBI_c and EB-PBI_{c+s} treatment plans ($P = 0.135$, 0.184 , 0.211 , 0.367 , respectively) (**Table 3**).

There was no significant difference between the three different treatment plans with regard to the mean doses, V₅ or V₁₀ received by the heart in case of left-sided lesions ($P = 0.148$, 0.073 , 0.183 , respectively) (**Table 3**). Overall, all of the techniques allowed organs at risk (OARs) to be spared with low doses.

Discussion

Accurate delineation of the tumor bed is one of the most critical aspects of 3D-CRT EB-PBI treatment planning because the irradiated volume is restricted to a small breast volume. Different surrogates have been used to define the lumpectomy cavity for the tumor boost, including the scar on the breast, surgical clips, seroma and imaging by ultrasound or CT scan. Yang et al. [15] reported that the definition of the target volume was based either on surgical clips if present or on the seroma if clearly visible. In our study, the tumor beds were delineated from the ten sets of 4DCT images based on the clips, the seroma, and both the clips and seroma.

By confining treatment to a limited volume of breast tissue adjacent to the lumpectomy cavity, it is possible to deliver a larger dose per fraction, thereby reducing the overall treatment time to approximately 1 week while maintaining good tumor control and cosmetic results. Our primary goal is to achieve accurate radiotherapy. The 4DCT dataset contains spatial information for the target volume during the entire respiration cycle. The IGTV included the volume and displacement information during the whole respiration cycle, and it was created by merging

Table 3. Dosimetric evaluation for the three different treatment plans (median, %)

Parameter	EB-PBI _c	EB-PBI _s	EB-PBI _{c+s}
Ipsilateral normal breast			
V ₂₀	27.7 (17.3-43.0)	23.6 (14.8-41.7)	27.9 (16.4-38.8)
V ₃₀	15.8 (8.6-31.2)	13.9 (6.7-28.8)	17.2 (7.7-26.6)
D _{mean} (Gy)	12.2 (8.2-20.2)	10.9 (7.3-18.9)	12.5 (8.2-19.6)
Ipsilateral lung			
V ₅	9.0 (3.1-17.3)	6.8 (1.4-16.8)	9.3 (2.7-17.8)
V ₁₀	4.9 (1.6-11.3)	3.8 (0.6-11.5)	5.2 (1.4-12.4)
V ₂₀	1.8 (0.3-3.6)	1.1 (0-3.7)	1.8 (0.5-4.6)
D _{mean} (Gy)	1.7 (0.1-3.5)	1.4 (0.5-3.6)	2.0 (0.8-3.6)
Heart (left-sided lesions)			
V ₅	0.3 (0-13.9)	0 (0-9.8)	0.7 (0-14.2)
V ₁₀	0.1 (0-9.7)	0 (0-5.4)	0 (0-9.6)
V ₂₀	0	0	0
D _{mean} (Gy)	0.4 (0.2-2.3)	0.4 (0.2-1.6)	0.4 (0.2-2.5)

Abbreviations: EB-PBI_c, treatment plan established based on clips; EB-PBI_s, treatment plan established based on seroma; EB-PBI_{c+s}, treatment plan established based on both clips and seroma; D_{mean}, mean dose.

all the volume derived from each of the 10 respiratory phases of the 4DCT dataset [16, 17].

Our previous publication [18] was first to investigate the volume and localization of IGTV utilizing the seroma and surgical clips based on 4DCT scan for EB-PBI, and these results showed that the volume of IGTV_{c+s} was significantly larger than that of IGTV_c and IGTV_s (similar to the results presented here). In the present study, we also investigated the volume of PTV based on different markers, and we found that PTV_{c+s} was remarkably larger than PTV_c and PTV_s (similar to PTV/IPSB). These results may be due to decreased seroma clarity and volume in the lumpectomy cavity from the time of lumpectomy to the 4DCT scan, or to the irregular distribution of the clips. For example, the limited soft-tissue contrast on CT makes it an unreliable modality for detecting a layer of an image lacking surgical clips. It is worth noting, however, that further studies should be conducted to determine whether this variability could result in suboptimal dose coverage of the PTV or variability of the cosmetic results from clips or seroma.

The present study confirmed that EB-PBI delivered with the 3D-CRT treatment protocol described by Chafe et al. [19] is simple, repro-

ducible and safe. While achieving appropriate PTV coverage, EB-PBI offered significant dosimetric sparing of normal tissues and acceptable late toxicity. Gatti et al. [20] reported that 3D-CRT EB-PBI can be safely and effectively delivered to breast cancer patients at a low risk of relapse submitted to breast conserving surgery with excellent patient compliance and low toxicity. Lei et al. [21] also investigated sixteen stage 0/1 breast cancer patients with prior breast augmentation treated with EB-PBI, and these authors reported that the cosmetic outcome at the final follow-up was judged as excellent/good by 81.2% of patients, and as excellent/

good by 93.8% of physicians. These favourable results support the consideration of breast-conserving surgery followed by radiotherapy, and specifically EB-PBI. The dosimetric analysis of this study also revealed that EB-PBI using clips or seroma was technically feasible with low dosimetrics. However, the PTV coverage for the EB-PBI_{c+s} treatment plan was similar to that of the EB-PBI_c and EB-PBI_s treatment plans. In addition, we also observed no significant differences in HI or CI between the three treatment plans, which suggests from another aspect that the volume variability delineated based on different reference markers did not have a remarkable influence on the dosimetric distribution during free breathing.

An additional theoretical advantage of EB-PBI is a decreased dose to normal tissue. With a smaller target volume, it may be expected that adjacent organs such as the heart and lungs will receive less radiation. Patel et al. [22] revealed that 3D-CRT EB-PBI delivers a low dose to the ipsilateral lung and heart, and the average doses for the ipsilateral lung and heart were 3.7 Gy (range 1.0-7.1) and 0.5 Gy (range 0.0-2.9), respectively. In this study, the mean doses for EB-PBI_s were 10.9 Gy and 1.7 Gy for ipsilateral normal breast and ipsilateral lung, respectively, and the EB-PBI_s treatment plan delivered significantly lower doses to OARs

compared to the EB-PBI_c and EB-PBI_{c+s} plans. This difference is likely due to differing target volumes, especially the seroma volume. A reduction of seroma volume is normally observed in patients during the first weeks of adjuvant radiotherapy [23]. Kader et al. [23] reported that given the magnitude and timing of seroma volume and clarity loss, the optimal time to obtain the planning CT scan for PBI is within 8 weeks after surgery. In our study, the average interval from lumpectomy to 4DCT scan was 10 weeks (range, 3-16). The volume of IGTV_c approached the volume of IGTV_s for six patients during weeks 4-8, and the IGTV_c<IGTV_s in two patients during weeks 0-3. However, after 8 weeks, the volume of IGTV_c was larger than that of IGTV_s for 12 patients. The seroma volume might be impacted by the time between surgery and planning CT scan. Therefore, the time from lumpectomy to 4DCT simulation scan could be appropriately chosen when delineation of the tumor bed was based on seroma. Given the magnitude and time trends of seroma volume and clarity loss, the optimal time to obtain the planning CT scan for PBI is within 4-8 weeks after surgery.

Conclusion

The results of our study suggest that significant volumetric variability delineated based on clips, seroma or both the clips and seroma could result in dosimetric variability for OARs. The EB-PBI_s treatment plan results in a significant reduction of dose to normal tissues when compared to the EB-PBI_c and EB-PBI_{c+s} treatment plans. However, the volume variability delineated based on different reference markers did not have a marked influence on the dosimetric distribution. Furthermore, additional patients and studies will be needed to validate the accuracy of this margin, and longer follow-up will be needed to assess acute and chronic toxicity, tumor control, and cosmetic results for the three EB-PBI treatment plans based on clips, seroma or both clips and seroma.

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Disclosure of conflict of interest

None.

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