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Tumor bed volumetric changes during breast irradiation for the patients with breast cancer

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Purpose: The aim of this study was to evaluate changes in breast tumor bed volume during whole breast irradiation (WBI).

Materials and Methods: From September 2011 to November 2012, thirty patients who underwent breast-conserving surgery (BCS) followed by WBI using computed tomography (CT) simulation were enrolled. Simulation CT scans were performed before WBI (CT1) and five weeks after the breast irradiation (CT2). The tumor bed was contoured based on surgical clips, seroma, and postoperative change. We retrospectively analyzed the factors associated with tumor bed volumetric change.

Results: The median tumor bed volume on CT1 and CT2 was 29.72 and 28.6 mL, respectively. The tumor bed volume increased in 9 of 30 patients (30%) and decreased in 21 of 30 patients (70%). The median percent change in tumor bed volume between initial and boost CT was -5%. Seroma status (p = 0.010) was a significant factor in tumor bed volume reduction of 5% or greater. However, patient age, body mass index, palpability, T stage, axillary lymph node dissection, and tumor location were not significant factors for tumor bed volumetric change.

Conclusion: In this study, volumetric change of tumor bed cavity was frequent. Patients with seroma after BCS had a significant volume reduction of 5% or greater in tumor bed during breast irradiation. Thus, resimulation using CT is indicated for exquisite boost treatment in breast cancer patients with seroma after surgery.

Keywords: Breast neoplasms, Radiation, Lumpectomy cavity

Introduction

Over the years, numerous studies have reported that breast-conserving surgery (BCS) followed by whole breast irradiation (WBI) can replace modified radical mastectomy (MRM) as the primary treatment for early-stage breast cancer.

We know, again, that BCS and WBI are very effective in reducing morbidity and mortality compared with MRM [1]. Recent advances in surgery, radiation therapy (RT), and chemotherapy, and hormonal therapy have contributed to the improvement in the contemporary management of breast cancer. These advances have made improvement in local control, distant control, and overall survival rate possible [2,3].

Although recent treatment techniques have advanced, most local recurrences still occur within the tumor bed or in adjacent areas [4-6]. So the width and status of the surgical margin is considered the most important risk factor for local recurrence [7], and boost irradiation has been shown to increase the local control rate. Romestaing et al. [8] reported that patients treated with 10-Gy boost have a higher

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probability of local control. The relative risk was significantly lower for the boost group (0.3; range, 0.12 to 0.95). Therefore, in modern RT, WBI, and tumor bed boost are recommended.

With development of the technology, computed tomography (CT)–based planning has become more common in practice during the past few years. Our policy is to obtain CT scans just before the start of WBI and the boost, as the CT scans may give useful information about tumor bed volumetric changes. The breast anatomy at the time of the start of RT could differ from the breast anatomy at the time of the boost treatment. When change in the seroma volume occurs during WBI, it sometimes causes transition of the surgical clip coordinates. Numerous studies have noted the potential for the tumor bed volume to decrease during WBI [9-12].

The aim of this study is to analyze the factors associated with volumetric change in the tumor bed to improve accurate delivery of boost RT in breast cancer patients.

Materials and Methods

1. Patient population

From September 2011 to November 2012, six patients with carcinoma in situ and 24 patients with T1-2N0-3 breast cancer who underwent BCS followed by WBI at St. Vincent's Hospital were enrolled. We reviewed all medical records including radiology, pathology, operation, and radiation records. Institutional Review Board approval was obtained before the chart review.

2. Treatment

BCS was performed by one surgeon who specialized in breast cancer. During the operation, the tumor resection site was marked with radio-opaque metal clips to localize the boost radiation procedure. After the BCS, the T1b-2N0-3 patients were given doxorubicin-based combination chemotherapy. RT-planning CT scans were carried out twice, with the first CT scan (CT1) taken before the start of WBI and the boost CT scan (CT2) at 45 Gy for the boost radiation procedure. For each scan, all patients were immobilized with both arms abducted and underwent CT scans for 3-mm slice thickness.

Because tumor bed contouring can be subjective, only one radiation oncologist drew the surgical clip, postoperative breast tissue change and seroma, according to the contouring guidelines [13,14]. Thus, we tried to minimize interobserver difference in our study. We measured the tumor bed cavity using a surgical clip, as well as the postoperative changes and seroma coordinates and obtained a 3-dimensional tumor bed cavity by adding a consistent margin of 1 cm around all the coordinates. There was no lesion over the surface of skin, while some lesion invading of chest wall. All of these cases, tumor bed cavities were included in tangential portal. The process was the same for the CT2. The CT planning and volumetric calculations were performed using Eclipse (ver. 7.3.10; Varian Medical Systems, Palo Alto, CA, USA). All patients were treated through the opposite tangential portal with 50.4 Gy in 28

Table 1. Patients and tumor characteristics

Characteristic	Value
Age (yr)	54 (43–77)
Weight (kg)	62 (47–81)
BMI (kg/m^2)	25.7 (20.4–32.9)
Adjuvant chemotherapy	
Yes	19 (63.3)
No	11 (36.7)
T stage	
Tis	6 (20.0)
T1	17 (56.7)
T2	7 (23.3)
N stage	
N0	22 (73.3)
N1	7 (23.3)
N2	0 (0)
N3	1 (3.3)
Histology	
DCIS	5 (16.7)
LCIS	1 (3.3)
IDC	24 (80.0)
Side	
Right	15 (50.0)
Left	15 (50.0)
Quadrant	
Upper-outer	19 (63.3)
Upper-inner	5 (16.7)
Lower-outer	4 (13.3)
Lower-inner	2 (6.7)
Axillary staging	
No	5 (16.7)
ALND	21 (70.0)
SLNS	4 (13.3)
Seroma	
Yes	7 (23.3)
No	23 (76.7)

Values are presented as median (range) or number (%).
BMI, body mass index; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; LCIS, lobular carcinoma *in situ*; ALND, axillary lymph node dissection; SLNS, sentinel lymph node sampling.

fractions using 6 to 15 MV photons, followed by a boost dose of 9 Gy to the tumor bed, achieving a total dose of 59.4 Gy. All dose schedules were given five days per week.

3. Statistical analysis

Statistical analysis was done using the SAS software (SAS Institute, Cary, NC, USA). Univariate analysis using chi-square or Fisher exact test was used to determine possible associations between tumor bed volumetric changes and several clinical factors, including initial tumor bed volume, body mass index (BMI), status of seroma, and extent of axillary lymph node sampling.

Results

Patients' characteristics are listed in Table 1. The median age was 54 years (range, 43 to 77 years) and median BMI was 25.7 kg/m^2 (range, 20.4 to 32.9 kg/m^2). Nineteen patients (63.3%) received chemotherapy after the BCS. Six patients (20%) enrolled were diagnosed with ductal or lobular carcinoma in situ, 17 (56.7%) had T1 tumors and 7 (23.3%) had T2 tumors. There were 15 right breast lesions and 15 left breast lesions, respectively. Nineteen lesions (63.3%) were discovered in the upper outer quadrant, 5 lesions (16.7%) in the upper inner quadrant, 4 lesions (13.3%) in the lower outer quadrant, and 2

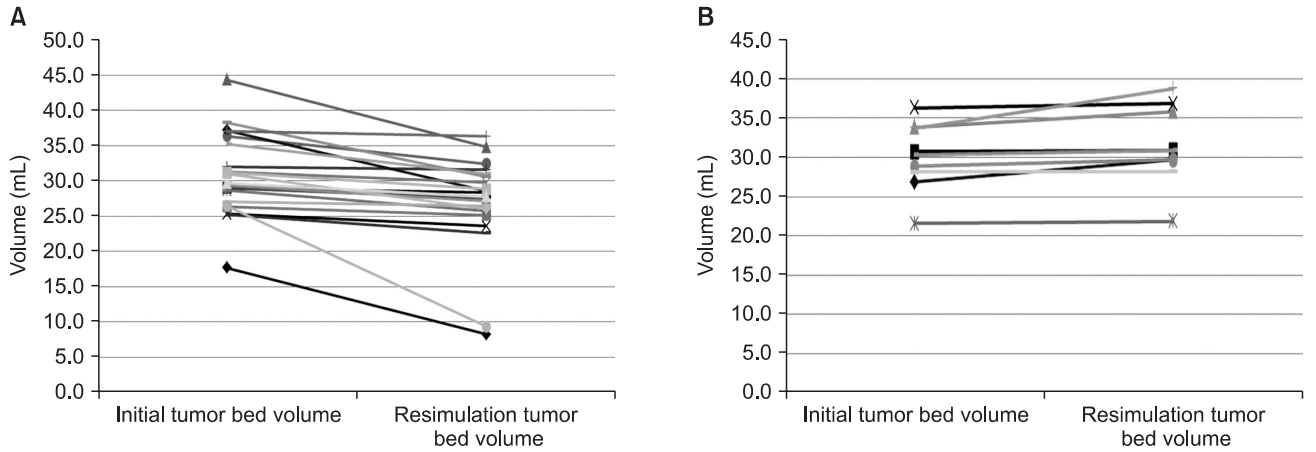

Fig. 1. (A) Decreasing tumor bed volume between initial and resimulation computed tomography (n = 21). (B) Increasing tumor bed volume between initial and resimulation computed tomography (n = 9).

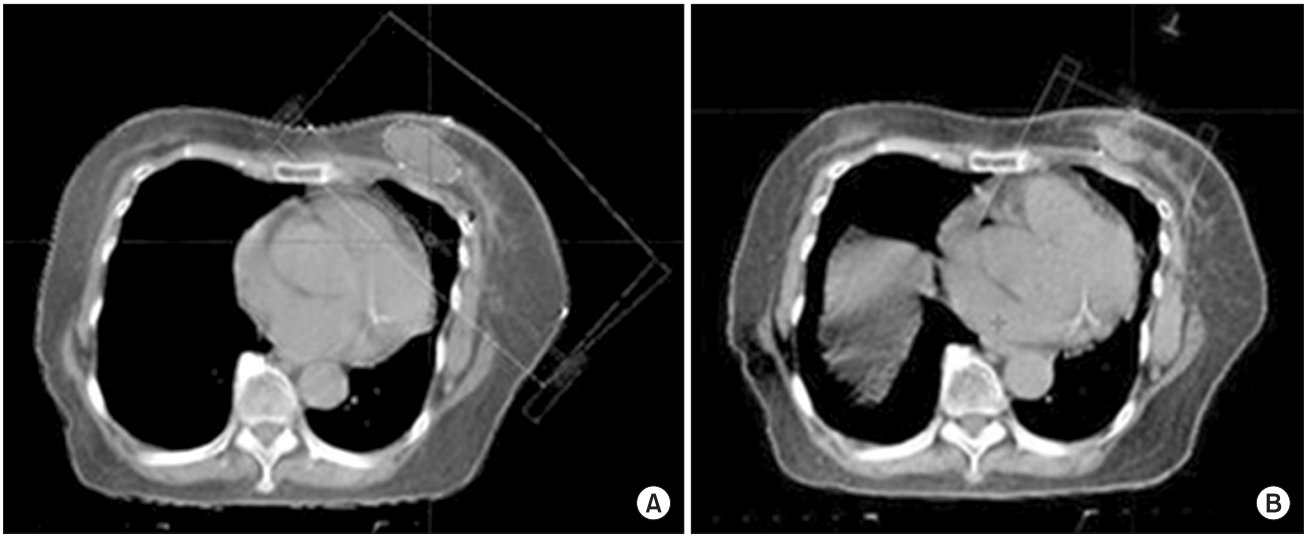

Fig. 2. Representation of tumor bed cavity (A) before breast irradiation and (B) five weeks after start of breast irradiation for the same patient.tomography (n = 9).

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lesions (6.7%) in the lower inner quadrant.

Twenty-one patients (70%) underwent axillary lymph node dissection and 4 patients (13.3%) had sentinel lymph node sampling. We reviewed the CT1 and CT2 of all patients and seroma was observed in 7 patients (23.3%) in the initial CT scans.

The median time from BCS to CT1 was 5 months (range, 1 to 8 months) and the median time from BCS to CT2 was 7 months (range, 2 to 9 months).

The median tumor bed volume based on the CT1 and CT2 was 29.72 mL (range, 17.70 to 44.40 mL) and 28.60 mL (range, 8.20 to 38.78 mL), respectively. The median percent change in tumor bed volume between CT1 and CT2 was -5% (p = 0.005; range, -65% to 15%). In the presence of seroma, the median seroma volume on the CT1 and CT2 was 30.84 mL (range, 17.31 to 205.33 mL) and 20.5 mL (range, 6.19 to 170.98 mL). The tumor bed volume increased in 9 of 30 patients (30%) and decreased in 21 of 30 patients (70%) (Fig. 1). The largest amount of increase and decrease in volume was +5.04 and -17.14 mL, respectively (Fig. 2).

The correlation analysis between patient characteristics and tumor bed volumetric change is summarized in Table 2. In the univaraite analysis, seroma status (p = 0.010) was a significant factor for tumor bed volume reduction of 5% or greater. However, age, BMI, T stage, lump size, axillary lymph node dissection, tumor location, and adjuvant chemotherapy were not statistically associated with tumor bed volumetric change.

Table 2. Univariate analysis between patient characteristics and tumor bed volume reduction of 5% or greater

Characteristic	Tumor bed volume		p-value
	<5%	≥5%	
Age (yr)			0.462
43–55	8 (53.3)	7 (46.7)	
>55	5 (33.3)	10 (66.7)	
Weight (kg)			0.269
47–62	5 (31.3)	11 (68.8)	
>62	8 (57.1)	6 (42.9)	
BMI (kg/m^2)			0.302
0–25	3 (37.5)	5 (62.5)	
>25	10 (45.5)	12 (54.4)	
T stage			0.672
Tis	2 (33.3)	4 (66.7)	
T1–T2	11 (45.8)	13 (54.2)	
Lump size (cm^3)			0.462
20.5–70	5 (33.3)	10 (66.7)	
>70	8 (53.3)	7 (46.7)	
No. of dissected axillary lymph node			0.484
0–11	5 (35.7)	9 (64.3)	
≥12	8 (50.0)	8 (50.0)	
Seroma			0.010
Yes	0 (0.0)	7 (100.0)	
No	13 (56.5)	10 (43.5)	
Tumor location (left-right)			0.462
Right	8 (53.3)	7 (46.7)	
Left	5 (33.3)	10 (66.7)	
Tumor location (quadrant)			0.292
Upper-outer	8 (42.1)	11 (57.9)	
Others	5 (45.5)	6 (54.5)	
Adjuvant chemotherapy			0.259
Yes	10 (52.6)	9 (47.4)	
No	3 (27.3)	8 (72.7)	

Values are presented as number (%).
BMI, body mass index.

Discussion and Conclusion

During RT, tumor bed volumetric change is an influential factor because the physician has to consider making readjustments to the boost radiation field. Factors found to have ability of detecting tumor bed volumetric change can be used to perform more precise RT planning, especially in early stage breast cancer patients having a large amount of tumor bed volumetric change [15].

We hypothesized that several factors, for example, BMI, the extent of axillary lymph node sampling, and status of seroma, are the most likely causes of tumor bed volumetric changes and designed this study to measure the relationship between tumor bed volumetric change and these factors and to assess the clinical efficacy of these factors retrospectively in this study. In our series, seroma was a significant factor associated with tumor bed volume reduction of 5% or greater during breast irradiation.

Oh et al. [16] stated that a significant reduction in the volume of the excision cavity during WBI. But when comparing plans generated from simulation CT vs. boost CT, there were no statistically significant difference in coverage. In this paper, though presence of seroma also lead to significant tumor bed volume reduction of 5% or greater, the median distance of tumor bed between CT1 and CT2 was 6.3 mm (range, 0 to 11.0 mm) and the excess of 10 mm was seen only 1 of 30 patients. Considering this outcome, tumor bed dose coverage between CT1 and CT2 was expected to be little difference. However tumor bed volume reduction can bring to excessive normal breast tissue irradiation and high dose inhomogeneity

according to the study of Huh et al. [17].

There are three reports which analyzed tumor bed volumetric change. Flannery et al. [10] reported that 44 patients with early-stage breast cancer underwent BCS and breast radiation therapy. They wanted to characterize how the lumpectomy cavity volume (LCV) changed and what factors influenced the changes. In that trial, CT simulation (CT1) was done within 60 days of the surgery, and a second CT simulation (CT2) was obtained after 21 to 23 fractions. The time from surgery to CT1, to the start of RT, or to CT2 did not have a statistically significant impact in LCV change. The LCV decreased in 38 of 44 patients (86%). Researchers also found that there was a significant correlation between initial LCV and decrease in volume ($p = 0.001$) and initial LCV and percentage decrease in volume ($p < 0.001$).

Similarly, Prendergast et al. [9] compared two CT scans of 36 patients receiving BCS and RT for early stage breast cancer. CT scans were obtained before the start of RT and before the boost, and the tumor bed volume decreased by a median value of 57.6% (range, -92% to 31%). On univariate analysis, the investigators did not find significant factors associated with tumor bed change. The results of this study were similar to those of previous studies. We also found that a large percentage (70%) of patients had a reduction in tumor bed volume at the time of the CT2.

And Cho and Kim [18] reported that the LCV reduced significantly after WBI. They wanted to evaluate the change in the LCV before and after WBI and to identify factors associated with the change of volume. The mean and median volume reduction in the lumpectomy cavity after WBI were 17.6 and 16.1 cm^3, respectively with the statistical significance ($p < 0.001$). The presence of seroma was significantly associated with a volumetric change in the lumpectomy cavity after WBI ($p = 0.011$). They suggested that to ensure appropriate coverage and to limit normal tissue exposure during boost irradiation in the patients who have seroma at the time of starting WBI, needed to repeat CT simulation at boost planning. Their opinions chimed in with the assessment of this study.

Seroma commonly forms around the tumor bed following BCS. A seroma is an accumulation of serous fluid in the dead space, and the amount of drainage and the surgeon's skill can affect the amount of seroma that develops [19]. The presence or absence of seroma might also influence tumor bed volumetric change. In our study the surgeon may have had excellent technical skills in performing BCS, which could have resulted in the relatively lower seroma rate (23.3%) than was found previously in other studies [20].

Another concern of ours was that the extent of axillary lymph node retrieval might alter lymphatic drainage, and as a result, not only arm edema but also breast edema may occur leading to tumor bed volumetric changes [21]. After lymph node dissection, an inflammatory response occurs, and inflammatory cells come out from the bloodstream and move into the inflammatory focus. Furthermore, there is extravasation of proteins and water, which results in increased vascular permeability that leads to breast edema. But in our study, breast edema was insignificant. There was lymph node retrieval of over 12 lymph nodes in 16 of 30 patients (53.3%), and the median number of lymph nodes dissected was 12 (range, 0 to 37), and therefore in this study, the extent of the lymph node sampling did not aggressively alter lymphatic drainage [22,23].

Our study had the limitations of having a small sample size and being a retrospective analysis. Therefore, changes in the volume of the tumor bed in this retrospective study should be interpreted with caution.

In conclusion, patients who underwent BCS for breast cancer and carcinoma *in situ* had meaningful change in their tumor bed volume during WBI. Patients with seroma after BCS had a significant tumor bed volume reduction of 5% or greater during radiotherapy. Thus, these patients need resimulation before boost treatment to determine the exact irradiation to give to the tumor bed. To prove significant association between seroma and volumetric change, a prospective cohort study is indicated.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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