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A Study of Volumetric Variation in the Excision Cavity during Hypofractionated Whole Breast Radiotherapy

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Abstract

Background: Based on the special pattern of recurrence in the excision cavity, secondary computed tomography (CT) can be introduced after hypofractionated whole breast radiotherapy with early breast cancer, aiming for accurate delineation of tumor bed boost and reduced toxicity. This study aimed to assess the volumetric changes in the lumpectomy cavity before and after hypofractionated whole breast radiation therapy (WBRT) and related clinical factors.

Method: This prospective study was designed and CT simulation was done for 45 patients from September 2019 to April 2020, two radiotherapy treatment planning were generated for each patient before and after hypofractionated WBRT. The tumor bed is defined using surgical clips, seroma, and postoperative alterations. Based on the original CT and tumor bed boost CT, statistically significant decrease was examined. The relationship between various factors and the volume decrease in the excision cavity was examined.

Results: The median value of reduction in the excision cavity was 15.4 cm^3 with the statistical significance ($P < 0.001$). In multivariate linear regression, the significant variable which predict the volume reduction was the presence of seroma ($B = 24.48$, confidence interval, 13.09 to 35.87, $P < 0.001$).

Conclusion: our results suggested significant benefit from re-simulation before boost planning especially for patients with clinical evident seroma.

Keywords: Breast neoplasms, Radiation dose hypofractionation, Lumpectomy cavity, Radiotherapy

Introduction

Breast cancer is a global health problem as it's the second leading cause of cancer death in women.[1] Advanced in the screening and increased awareness of breast cancer leaded to early diagnosis of breast cancer. Radiotherapy (RT) is an effective modality to decrease breast cancer recurrence after breast conservative surgery.[2] Breast conserving surgery (BCS) followed by whole breast irradiation is the current standard treatment for early breast cancer.[3, 4] Radiation therapy after BCS is delivered (whole breast radiation therapy (WBRT)) over a period of 5-6 weeks, with or without boost to the tumor bed.[5, 6, 7]

Hypofractionated whole breast irradiation exhibited the same local control and toxicity outcomes as standard fractionation, which was supported by prospective randomized studies. 3, 8, 9 But the addition of boost radiation (10–16 Gy) to the tumor bed greatly lowers the probability of local recurrence, particularly in patients at high risk due to factors like young age, a big tumor, a high grade, a considerable intraductal component, and a near or positive margin. While improving local control, delivery of higher total doses with the tumor bed boost may increase the risk of radiation induced toxicity which may negatively affect patient psychology and quality-of-life which is an important concern for the patients with high life expectancy.[10, 13] Accurate contouring of the excision cavity is necessary, as it prevents the geometric miss of the excision cavity and reduce the unnecessary radiation to normal tissue.[14] Target volume contouring of the excision cavities on computed tomography CT image is performed by the guidance of surgical clips secured in the excision cavity wall, seroma, breast tissue changes apparent on CT images, mammography or observation of presurgical magnetic resonance imaging (MRI) and pathology reports.[1] Therefore, the delineation of tumor bed may be less precise and important organs may get extra radiation if the initial CT planning is utilized to plan the boost irradiation patients with a significantly changes in the lumpectomy cavity throughout the course of hypofractionated WBRT.[15,16] This study aimed to assess the rate of change in the size of excision cavity volume (ECV) during hypofractionated whole breast irradiation and determine the factors that may cause a large volumetric change in ECV. This reduction might reduce the received dose by critical organs (lung, heart) and the remaining breast tissue.

Material and Methods

45 patients with invasive breast cancer who had had breast conserving surgery and, if necessary, adjuvant chemotherapy were the subjects of a prospective research from September 2019 to April 2020. The South Egypt Cancer Institute (SECI) ethics committee authorized the trial (ethics code: 480), and all patients provided written informed permission. Our sample size was calculated with its power based on G power software version 3.1.3 using t test for comparison difference between (ECV pre and post radiation), alpha error probe 0.05, power (1-beta error probe) 0.8. The minimum required sample was 41 patients, and we raised them to 45 patients.

To evaluate volumetric changes during hypofractionated WBRT, two RT treatment planning procedures were carried out for each patient based on the baseline CT simulation and tumor bed boost CT simulation. The first CT planning was completed just before hypofractionated WBRT began, and the second was completed two days before the conclusion of 40.05 Gy hypofractionated WBRT.

Three-dimensional treatment planning with 6- 15 mega voltage (MV) photons energy using linear accelerators Electa Synergy Platte Form was applied in all patients based on the guidelines the breast cancer contouring atlas of the North American-based Radiation Therapy Oncology Group (RTOG). [17]

With the guidance of surgical clips, seroma, and other surgical changes the lumpectomy cavity CTV was delineated based on CT-1 and CT-2. To create the PTV, the ECVs were enlarged with a 2 cm margin on both sets of designs. A boost dosage of 10 Gy over 5 fractions utilizing an electron beam with electron applicators of various sizes and energies was given after the WBRT dose of 40.05 Gy over 15 fractions, or 2.67 Gy/fraction. At least 90% isodose line coverage of ECV was required for acceptable plans.

Statistical analysis

Data analysis was undertaken using SPSS version 20. Categorical data were presented in form of frequencies and percentages, quantitative variables were expressed as median (range). Non-parametric tests were run after ensuring that the data were normal. Wilcoxon and Sign test, Mann Whitney U test, and Kruskal Wallis test evaluate median ECV changes across two groups or more, respectively. Wilcoxon and Sign test was used to assess breast volume between before and after irradiation. Spearman's correlation was used to explore the correlation among ECV changes from pre to post irradiation and different variables. Significant variables in bivariate analysis beside age were entered in multivariable linear regression to identify predictors of ECV changes. The level of significance was considered at P value < 0.05.

Results

The patient and tumor characteristics are shown in Table 1. Median age was 46 years (range, 34 to 53 years). The range of body weights were of 54 to 80 kg with a median weight of 70 kg. Twenty patients were T1 tumors and 25 had T2 tumors. 20 patients were N0, 20 patients had N1 and 5 patients were N2. The upper inner quadrant was the most frequent site. 20 patients (44.4%) had seromas at the initial CT scans. 22 patients (48.9%) started WBRT between 4 and 6 months, from surgery and 23 patients (51.1%) after 6 months (Table 1). The shrinkage of the excision cavity was observed in 100% (45/45). The median interval between the start of WBRT and boost was 23 days (range, 22-25 days). The median volume of the excision cavity before and after hypofractionated WBRT were 38.40 cm^3 (range, 17 to 99.7 cm3) and 24 cm^3 (range, 10.6 to 80 cm^3), respectively. The median reduction of the excision cavity was 15.4 cm^3 (range, 2.0 to 61.2 %) ($P < 0.001$). The median reduction of the preirradiated breast volumes was 1154.4 cm^3 and its median reduction after WBRT was 773 cm^3. Representing a median change of 127 cm^3 (range, 15.41 to 1041.2) ($P < 0.001$) (Table 2).

Four variables: T stage, N stage, grade and location of tumor were not predictive for volumetric reduction and lost significance (Table 3).

The median time between surgery and radiation treatment was 7 months (range, 4-9 months), and in the univariate analysis, the presence of seroma and the duration between lumpectomy and radiation therapy had a significant influence on volumetric decrease. ($R = -0.71$ $P = 0.001$) (Figure 1). Moreover, there was a strong positive correlation between preirradiated lumpectomy cavity and post radiation volume reduction ($r = 0.8$ $P < 0.001$) (Table 4).

The reduction in the tumor bed volume was inversely correlated with the age and body weight but there was no statistical significance ($r = -0.03, -0.05$ $P = 0.827$ and 0.0717 respectively) (Table 4).

Significant variables in univariate analysis beside age were entered in multivariate linear regression and the significant variable that predict volume reduction was the presence of seroma ($B = 24.48$, confidence interval (CI), 13.09 to 35.87, $P < 0.001$). (Table 5).

Discussion

Our study's findings showed that hypofractionated RT reduced the lumpectomy cavity, with the decrease being more pronounced in the seroma. These findings may have a significant impact on the accuracy and precision of breast cancer radiation.

In the present series, there was 100% reduction in the ECV (45/45 patients, representing15.4% median reduction (range, 2 to 61.2) ($P < 0.001$). Hepel et al.[19] conveyed that there was decreasing in the execision cavity volume during WBRT with mean value 52% due to a decrease in postoperative seroma size. Many other studies; [15, 19–22] however, demonstrated a significant reduction in tumor bed cavity during hypofractionated WBRT in patients without seroma due to healing processes in the tumor bed that were responsible for its reduction. Granulation tissue formation may have evolved into fibrous tissue during radiation due to decreased blood perfusion in the irradiated tissue with progressive decrease in tissue oxygenation, which may be a contributing factor in volume reduction.Although different mechanisms (e.g., fluid leakage or inflammation) can generate in lumpectomy cavity[23] Therefore, we exclude patients with increasing cavity size from subsequent analysis.

Dynamic mechanisms of tissue remolding within the lumpectomy cavity are occurring during the course of hypofractionated RT. These changes are responsible for significant reduction of the excision cavity, which may lead to the less optimal dosimetry coverage or unnecessary radiation to critical organs and the remaining breast tissue if the initial CT scan is used for the boost irradiation. [15,17,22,24]

In our study, there was no significant reduction in the breast volume during hypofractionated WBRT ($P = 0.785$) conflicting to the change in the volume of excision cavity. This was comparable to earlier studies[12,15,25] that demonstrated the loss of significance of the link between breast volume and lumpectomy cavity reduction. Tersteeg et al. [20] reported a linear relationship between absolute volume of the excision cavity and the absolute volume reduction. There was statistically significant relationship between the initial cavity volume and its reduction ($r = 0.8$ $P < 0.001$). Hepel et al. [19] reported significant decrease in the lumpectomy cavity if the initial ECV is >15 cm^3 Flannery et al.[21] concluded that a separate boost CT simulation is essential in the patients with excision cavities (>30 cm^3).

Seroma development and change may be influenced by biological processes and outside stimuli.[23] Oh et al.[18] observed that bodyweight was negatively linked with volumetric changes, which is consistent with our findings. The quantity of breast tissue around the seroma may have had an impact on external forces acting on the seroma that caused this association. Other investigators[15,19] reported no significant association between body weight and volumetric changes.

Prendergast et al.[15] reported that time interval between surgery and the start of RT was inversely correlated with the reduction in the tumor bed this was similar to our study in univariate analysis , as the median interval between surgery and RT was 7 months which is sufficient to reveal any effect of radiation on the lumpectomy cavity. However, in the clinic, seroma was still observed in some patients after several months following surgery.

Using a second CT simulation prior to delineating the tumor bed, seroma and tumor bed shrinkage during hypofractionated WBRT may be taken advantage of to reduce the exposure of normal tissue and boost the therapeutic ratio (Figure 2). According to our study, the median reduction in seroma volume during hypofractionated WBRT was 35.90 cm^3 % in terms of the Seroma fluid absorption. There may be benefit of replanning the boost with repeated CT simulation to ensure adequate coverage. Hepel et al.[19] and Flannery et al.[21] suggested that repeating CT scan before irradiation of the tumor bed is necessary for accurate contouring of the at-risk volume.

Limitations

This study aimed to investigate volumetric change after hypofractionated WBRT and related clinical factors with absence of dosimetric data, assessment of local control or evaluation of toxicity. Another limitation was that the contouring of breast was done by more than one radiotherapist, which result in inter-observer variability in measuring the breast volume. Whereas breast parenchyma may prevent the clear visualization of postsurgical cavities in the conserved breast. In comparison to CT, MRI scans may aid in a better resolution of postoperative seroma cavities with accurate delineation. Given the paucity of contrast shown on CT images, tumor beds may be more easily detected using MRI's strong soft tissue contrast, making it a potentially useful technique in the future for breast RT definition. Therefore, further prospective research is advised.

Conclusion

The results of our study by hypofractionated schedules were comparable to the results reported by standard fractionation as there were a significant shrinkage of the lumpectomy cavity after hypofractionated WBRT. The lumpectomy cavity volume dramatically reduced as the amount of time passed between the operation and the start of hypofractionated WBRT increased. There was a considerable volumetric decrease in those with clinically obvious seroma. To improve the dosimetric parameters and to increase the therapeutic ratio, a second CT simulation before boost planning is strongly considered.

Conflict of Interest

None declared.

References

1. Coughlin SS, Ekwueme DU. Breast cancer as a global health concern. *Cancer Epidemiol.* 2009;33(5):315-8. doi: 10.1016/j.canep.2009.10.003.
2. Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol.* 2007;25(22):3259-65. doi: 10.1200/JCO.2007.11.4991.
3. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347(16):1233-41. doi: 10.1056/NEJMoa022152.
4. VanDongen JA, Voogd AC, Fenman IS, Legrand C, Sylvester JR, Tong D. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organizaon for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000;92:1143-50. doi: 10.1093/jnci/92.14.1143.
5. Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med.* 2001;345(19):1378-87. doi: 10.1056/NEJMoa010874.
6. Freedman GM, Anderson PR, Hanlon AL, Eisenberg DF, Nicolaou N. Pattern of local recurrence after conservative surgery and whole-breast irradiation. *Int J Radiat Oncol Biol Phys.* 2005;61(5):1328-36. doi: 10.1016/j.ijrobp.2004.08.026.
7. Cho H and Kim C. Volumetric changes in the lumpectomy cavity during whole breast irradiation after breast conserving surgery. *J Radiat Oncol,* 2011;29(4):277-82. doi: 10.3857/roj.2011.29.4.27.
8. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al: Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362(6):513-20. doi: 10.1056/NEJMoa0906260.
9. Haviland JS, Owen JR, Dewar JA, Barrett-Lee JP, Dobbs JH, Hopwood P, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. *Lancet Oncol.* 2013;14(11):1086-94. doi: 10.1016/S1470-2045(13)70386-3.

10. Kindts I, Laenen A, Depuydt T, Weltens C**.** Tumor bed boost radiotherapy for women after breast-conserving surgery. *Cochrane Database Syst Rev.* 2017;11(11):CD011987. doi: 10.1002/14651858.
11. Poortmans PM, Collette L, Horiot JC, Bogaert WF, Fourquet A, Kuten A, et al. Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomized EORTC boost trial. *Radiother Oncol*. 2009;90:80-5. doi: 10.1016/j.radonc.2008.07.011.
12. Poortmans PM, Collette L, Bartelink H, Struikmans H, Bogaert WF, Fourquet A, et al. The addition of a boost dose on the primary tumor bed after lumpectomy in breast conserving treatment for breast cancer. A summary of the results of EORTC 22881-10882 “boost versus no boost” trial. *Cancer Radiothery*. 2008;12:565-70. doi: 10.1016/j.canrad.2008.07.014.
13. Vrieling C, Collette L, Fourquet A, Hoogenraad JW, Horiot CJ, Jager JJ, et al. The influence of the boost in breast-conserving therapy on cosmetic outcome in the EORTC “boost versus no boost” trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. European Organization for Research and Treatment of Cancer. *Int J Radiat Oncol Biol Phys*. 1999;45:677-85. doi: 10.1016/s0360-3016(99)00211-4.
14. Benda RK, Yasuda G, Sethi A, Gabram HS, Hinerman WR, Mendenhall PN. Breast boost: Are we missing the target? *Cancer.* 2003;97:905-9. doi: 10.1002/cncr.11142.
15. Prendergast B, Indelicato DJ, Grobmyer SR, Saito AI, Lightsey JL, Snead FE, et al. The dynamic tumor bed: volumetric changes in the lumpectomy cavity during breast-conserving therapy. *Int J Radiat Oncol Biol Phys.* 2009;74:695-701. doi: 10.1016/j.ijrobp.2008.08.044.
16. Sharma R, Spierer M, Mutyala S, Thawani N, Cohen HW, Hong L, et al. Change in seroma volume during whole-breast radiation therapy. *Int J Radiat Oncol Biol Phys* 2009;75:89-93. doi: 10.1016/j.ijrobp.2008.10.037.
17. Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Sola AB, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol.* 2015;114:3-10. doi: 10.1016/j.radonc.2014.11.030.
18. Oh KS, Kong FM, Griffith KA, Yanke B, Pierce LJ. Planning the breast tumor bed boost: changes in the excision cavity volume and surgical scar location after breast-conserving surgery and whole-breast irradiation. *Int J Radiat Oncol Biol Phys.* 2006;66:680-6. doi: 10.1016/j.ijrobp.2006.04.042.
19. Hepel JT, Evans SB, Hiatt JR, Price LL, DiPetrillo T, Wazer DE, et al. planning the breast boost: comparison of three techniques and evolution of tumor bed during treatment. *Int J Radiat Oncol Biol Phys.* 2009;74:458-63. doi: 10.1016/j.ijrobp.2008.08.051.
20. Tersteeg RJ, Roesink JM, Albregts M, Warlam-Rodenhuis CC, van Asselen B. Changes in excision cavity volume: prediction of the reduction in absolute volume during breast. *Int J Radiat Oncol Biol Phys.* 2009;74:1181-5. doi: 10.1016/j.ijrobp.2008.09.056.
21. Flannery TW, Nichols EM, Cheston SB, Marter KM, Naqvi SA, Markham KM, et al. Repeat computed tomography simulation to assess lumpectomy cavity volume during whole-breast irradiation. *Int J Radiat Oncol Biol Phys.* 2009;75:751-6. 24. doi: 10.1016/j.ijrobp.2008.11.024.
22. Weed DW, Yan D, Martinez AA, Vicini FA, Wilkinson TJ, Wong J. The validity of surgical clips as a radiographic surrogate for the lumpectomy cavity in image-guided accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys.* 2004;60(2):484-92. doi: 10.1016/j.ijrobp.2004.03.012.
23. Whipp EC, Halliwell M. Magnetic resonance imaging appearance in the postoperative breast: The clinical target volume-tumor and its relationship to the chest wall. *Int J Radiat Oncol Biol Phys.* 2008;72(1):49-57. doi:

10.1016/j.ijrobp.2007.12.021.

24. Huh SJ, Han Y, Park W, Yang JH. Interfractional dose variation due to seromas in radiotherapy of breast cancer. *Med Dosim.* 2005;30:8-11. doi: 10.1016/j.meddos.2004.10.002.
25. Zhou ZR, Mei X, Chen XX, Yang ZZ, Hou J, Zhang L, et al. Systematic review and meta-analysis comparing hypofractionated with conventional fraction radiotherapy in treatment of early breast cancer. *Surg Oncol.* 2015;24(3):200-11. doi: 10.1016/j.suronc.2015.06.005.

Table 1. The characteristics of studied patients

Variables	**n=45**	**(%)**
Age (y), median (range)	46.00 (34-53)	
Weight (kg), median (range)	70.00 (54-80)	
Quadrant		
Upper outer	10	22.2
Upper inner	25	55.6
Lower outer	10	22.2
Seroma		
Yes	20	44.4
No	25	55.6
T stage		
T1	20	44.4
T2	25	55.6
N stage		
0	20	44.4
1	20	44.4
2	5	11.1
Grade		
2	33	73.3
3	12	26.7
Surgery to radiotherapy time in months		
4-6	22	48.9
>6	23	51.1
Median (range)	7.00 (4-9)	
WBRT to boost time in days	23(22-25)	

Data expressed as frequency (%) or median (range); WBRT: Whole breast radiotherapy

Table 2. ECV changes and breast volume after whole breast irradiation

Variables	**Pre-irradiation**	**Post-irradiation**	**Difference (pre-post irradiation)**	***P*-value***
ECV	38.40 (17.0-99.7)	24.00 (10.6-80.0)	15.4 (2.0-61.2)	**<0.001**
Breast volume	1154.40 (538.0-1455.4)	773.00 (113.2-1440.0)	127 (15.4-1041.2)	**<0.001**

Data expressed as median (range); * Wilcoxon and sign test; ECV: Excision cavity volume

Table 3. Factors affecting the changes in ECV from pre to post irradiation

Variables	**ECV difference**	***P*-value***
Seroma		
Yes	35.90 (15.4-61.2)	**<0.001**
No	3.40 (2.0-19.7)	
T stage		
T1	15.4 (2.0-61.0)	0.136
T2	19.70 (3.4-61.2)	
n stage		
0	10.1 (2.0-38.0)	0.525
1	15.4 (2.0-61.2)	
2	19.7 (4.7-61.2)	
Quadrant		
Upper outer	20.4 (2.0-38.8)	0.912
Upper inner	15.4 (3.4-33.0)	
Lower outer	31.6 (2.0-61.2)	
Grade		
2	15.4 (2.0-61.2)	0.476
3	24.2 (2.0-61.2)	

Data expressed as median (range) *Mann-Whitney U Test, Kruskal Wallis test; ECV: Excision cavity volume

Table 4. Correlation between ECV difference and some variables

Variables	**ECV difference**	
	r	***P***
Age	-0.03	0.827
Weight	-0.05	0.717
Breast volume difference	0.04	0.785
Surgery to radiotherapy time in months	-0.71	**<0.001**
Pre radiation lumpectomy cavity volume	0.8	**<0.001**

ECV: Excision cavity volume

Table 5. Predictors of ECV changes from pre to post irradiation

Variables	**Multivariate analysis**	
	***B* (95% CI)**	***P*-value***
Age	-0.14 (-81 – 0.53)	0.676
Presence of Seroma	**24.48 (13.09-35.87)**	**<0.001**
Surgery to radiotherapy time	-2.94 (-6.83- 0.93)	0.133

CI: Confidence interval; *multivariate regression analysis, dependent variable is ECV changes from pre- to post-irradiation; ECV: Excision cavity volume

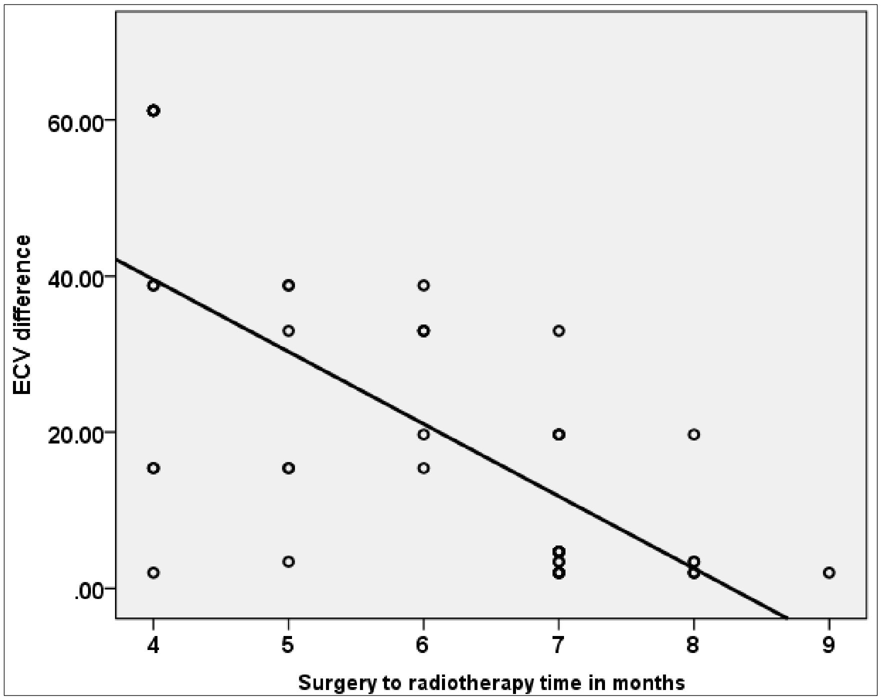
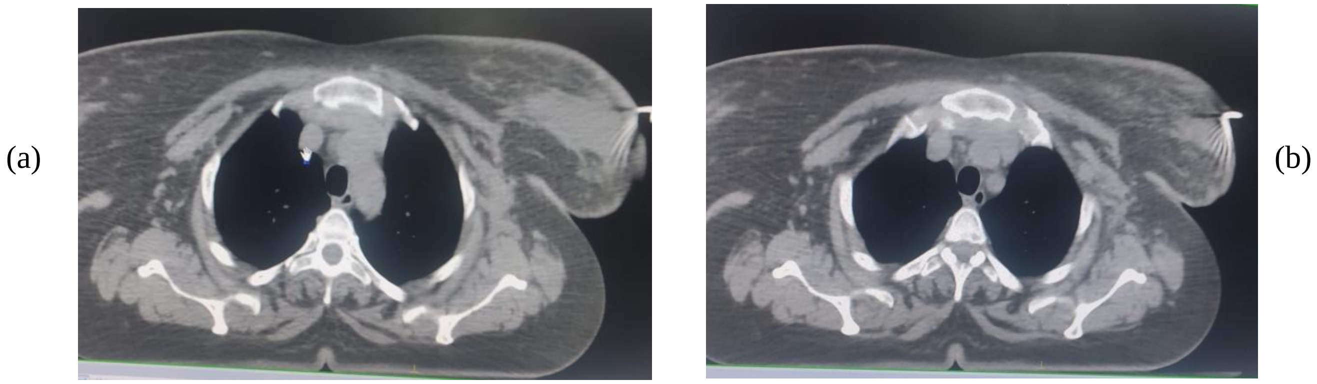


Figure 1. This figure shows the correlation among the months elapsed between surgery and radiotherapy and ECV, excision cavity volume changes from pre to post irradiation. Each point represents a single lumpectomy cavity. The relative reduction in excion cavity volume demonstrates an inversely proportional trend when compared with time elapsed since surgery (R = -0.71, *P*=0.001).

ECV: Excision cavity volume; RT: Radiation therapy



(2a) (2b)

Figure 2. This figure shows the changes of seroma in the excision cavity before (2a) and after (2b) hypofractionated whole breast irradiation.