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Technical note

# Post-chemotherapy target volumes are safe as boost volume for intact breast radiotherapy in locally advanced breast cancer*

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ABSTRACT

*Purpose:* The purpose of our study is to evaluate the challenges in identification of postoperative complexes (POC), the utility of clips in delineation of clinical target volume for boost in LABC downstaged with neoadjuvant chemotherapy (NACT) and to correlate this with patterns of recurrence.
*Methods and materials:* LABC patients who underwent NACT followed by BCS and radiotherapy (2007–2014) were the subject of our analysis. The data on visibility and characteristics of postoperative cavity (POC), concordance of its volume with clip volume on radiation planning scan were retrieved. A 1 cm margin beyond POC was delineated as a clinical target volume (CTV). Postoperative whole breast and supraclavicular radiotherapy (50 Gy/25fractions/5wk or 42.4 Gy/16#/3 wk) followed by boost (10–16 Gy/5-8#/1–1.5wk) were delivered. Patterns of recurrence were evaluated.
*Results:* Out of 60 patients, 28.3% patients had stage II disease and 71.7% had stage III disease. 25% patients achieved pathological CR (complete response). The median POC volume was 30 cc and the median clip volume was 40 cc. The concordance of POC volume with clip volume was seen in 80%. Clips served as a good surrogate for POC in 80% of patients. At a median follow-up of 65 months (IQ range 32–84 months), and a lost to follow-up rate of 11.6 %, 3.3% (n = 2) patients had local recurrence (LR) and 8.3% (n = 5) had regional recurrence (LRR) in the supraclavicular region.
*Conclusions:* Delineation of post NACT excision cavity as POC for boost radiotherapy is safe. Clips serve as a good surrogate for CTV delineation in 75% patients.
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## 1. Introduction

NACT increases the proportion of patients who undergo breast-conserving surgery (BCS) with no significant increase in the local recurrence rates.[1] BCT is possible in 17–50% patients with LABC, in those who are adequately downsized with negative resection margins. By down-staging involved axillary lymph-nodes, NACT also decreases the extent and morbidity of axillary surgery by expanding the use of sentinel lymph node biopsy (SLNB), provided that SLNB is feasible and accurate in centres that do it regularly.[2] Post-operative loco-regional radiotherapy after appropriate surgery is the standard of care.

Local (LR) or loco-regional recurrences (LRR) after NACT and BCS and loco-regional radiotherapy are seen in patients with adverse prognostic factors, like clinical N2 or N3 disease, lympho-vascular space invasion, a multifocal pattern of residual disease, and residual primary tumour larger than 2 cm.[3,4] More than 90% of ipsilateral breast tumor recurrences will occur in the original primary site, where true recurrences are most likely to occur. Those recurrences outside the tumor bed are usually labelled as new primaries, which arise >5 years after surgery, are clonally distinct, and have a better prognosis.[5] Optimal local control involves radiation to the whole breast and regional lymphatics, followed by a boost to the excision cavity. The clinical target volume (CTV) for boost should be entirely encompassed not only by boost fields but also by whole breast radiotherapy fields (WBI). Clinical target volume for boost is a three-dimensional (3D) clinic-pathologic concept most likely to contain the highest concentration of residual cancer cells after excision of the tumor.[6] CTV boost is a uniform expansion of a selected thickness (usually 5 mm) of apparently normal breast tissue around the postoperative cavity (POC) which contains the majority of any postsurgical malignant residual tissue. Delineation of CTV involves identification of the POC, an entity that has been shown to change radically over time elapsed since surgery and during WBI, which

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may also lead to changes in surgical clip position.[7–9] The term POC has been proposed by Whipp to define the seroma and is a purely visual perception of changes seen on MRI thought to represent tissue changes consequent upon excision.[5] They reported that the size of cavity was inversely related to the time elapsed since surgery and the POC directly touched the chest wall in 53% of cases and 89% lay within 10 mm of the chest wall. Computed tomography together with surgical clips is accepted as the gold standard for localizing and defining a CTV in early breast cancer.[10] However, the same is not known about LABC. The other issue of concern is whether to irradiate the tumor bed pre or post chemotherapy. Irradiating pre-chemotherapy volume would result in irradiation of a large volume, which would result in poor cosmesis and, hence, this issue needs to be addressed.[11] Since POC is likely to be large, proximity to the chest wall and skin, which can have implications for treatment planning. Involvement of the chest wall implies inclusion of chest-wall and ribs in PTV, which would lead to irradiation of a large volume of the underlying lung and heart (in left breast tumors) which, in turn, might lead to higher incidence of pneumonitis and cardiac morbidity. Administration of chemotherapy after excision (prior to publication of guidelines for NACT in LABC) has been reported to cause contraction of the POC. It is important to characterize the POC, evaluate its proximity to chest-wall and skin and determine the safety of delineating the post NACT POC.[12] Hence, we undertook this study to evaluate the safety of delineation of post NACT excision cavity as POC for postoperative radiotherapy, describe and measure the POC and clip volume, to evaluate the proximity of POC to the chest wall and skin on radiation treatment planning scan, in patients with LABC who underwent breast conservation after NACT.

## 2. Materials and methods

Patients with LABC (non-inflammatory breast cancer) who underwent NACT followed by BCS and whole breast radiotherapy during the period January 2007 to December 2014 were the subjects of this retrospective analysis. Clinical features and staging recorded at diagnosis, operative notes, and histopathology and cytopathology reports were retrieved. Patients were staged using the TNM-AJCC staging system, 7th edition (2010). All patients received standardized multidisciplinary treatment according to institute protocols, which included preoperative evaluation with a mammogram and core-needle biopsy.

NACT comprised either 6 cycles of a combination of 5-Fluorouracil, epirubicin/adriamycin, cyclophosphamide (FEC/FAC) or sequential 4 cycles of FEC/FAC followed by 4 cycles of single agent taxanes. No patient received Trastuzumab. NACT was either entirely preoperative or sandwiched with surgery. Breast conservation was offered to patients who achieved complete or partial response after NACT and were technically suitable for breast conservation. Where surgery was sandwiched, chemotherapy was initiated within a month of surgery. All patients underwent BCS in the form of wide local excision (WLE) or segmental/partial mastectomy, without oncoplastic reconstruction, and intra-operative margin assessment with frozen section histology of margins, followed by standard paraffin section histopathology of the whole surgical specimen. Any infiltrated margins (invasive or in-situ) were re-excised. Excision was circumferential (around the post-chemotherapy tumor or fibrosis) in all patients and the excision cavity was closed by full thickness closure. Clips were placed in medial, lateral, base, superior, inferior and anterior margins. All patients underwent axillary lymph node dissection.

Histopathological data was classified into two categories of pathological response: complete response (CR) and less than complete response (PR). CR were those without invasive cancer and in-situ in tumor as well as axillary lymph nodes i.e. ypT0 yp N0. Intrinsic subtype categorization into Luminal A, Luminal B, Her-2 type and triple negative was based on immunohistochemistry of biopsy samples acquired prior to initiation of NACT.

All patients were then planned for postoperative radiotherapy. A non-contrast enhanced radiation treatment planning CT scan was acquired at 3 mm slice intervals (Somatom Sensation Open CT scanner, M/s Siemens Medical System, Germany). Target delineation of CTV involved identification of POC. This comprised identification of seroma in the cavity or visual architectural changes thought to represent tissue changes around the excised tumor cavity. The cavity visualization score (CVS) of POC was used for defining the visibility of POC as described by Smitt et al. (Table 2)[13] Only the homogeneous background of POC was outlined, irregularities and surgical disturbances, such as breast tissue protrusions around the excision cavity were excluded. When clips were available they had to be inside the contoured volume. Assuming that clips represent the cavity wall they had to be surrounded by the contour with close contact. The volume of breast encompassed by clips was also delineated separately to evaluate the concordance of its volume with POC. The texture (homogenous or heterogeneous) and shape of the deepest aspect of the POC in relation to the chest wall were recorded and divided into the categories defined by Whipp, i.e. irregular, oval and irregular ellipsoid type.[5] The minimum distances between the POC and the chest wall, between the POC and skin and the craniocaudal extent of the chest wall and skin involvement by POC wall were also recorded. Because the deep aspect of extreme lateral and medial tumors is most commonly missed by bitangential fields, laterality of the POC was recorded in five segments: medial, medio-central, central, latero-central and lateral.

The POC was usually expanded by 1 cm to form the CTV (Clinical target volume). Another 1 cm margin was given beyond CTV to form the PTV (for boost). All patients were treated with the 3D-CRT technique. Whole breast and ipsilateral supraclavicular region were treated by a single isocentric technique. Whole breast was treated by bi-tangential fields and the supraclavicular region (including level 3 axillary lymphnodes) by a direct anterior field. Axilla was irradiated only in patients with extra-nodal extension on histopathology. Internal mammary chain was not electively irradiated in any patient. Conventional fractionation (50 Gy in 25 fractions in 5 weeks followed by a boost of 10 Gy in 5 fractions in one week to PTV) was used for patients treated by 2011 and thereafter hypofractionation (40 Gy in 15 fractions in 3 weeks followed by 10 Gy boost in 5 fraction) was adopted in our department for all patients with breast cancer. After completion of radiotherapy, patients with hormone receptor positivity received appropriate hormone therapy.

The data on pathological response to chemotherapy and patterns of recurrence were also collated. Patients were deemed to have LR, if they had recurrent breast tumour in ipsilateral breast on clinical and/or mammographic evaluation in follow-up and were confirmed to have a recurrent malignant lesion on cytopathology or histopathology. Statistical analysis was done using SPSS version 15.0 software (IBM SPSS Statistics for Windows, Version 15.0).

## 3. Results

Among 250 consecutive patients of LABC registered in our department for postoperative radiotherapy during 2007–2014, 60 patients had undergone BCS. The demographic characteristics of patients are given in Table 1. 42% of patients were less than 40 years age. 70% of patients had T3 and T4 tumors and 83% of patients had node positive disease. Pathological complete response (CR) was achieved in 15% patients and the rest achieved partial response or stable disease (PR). The median time interval from BCS to radiation was 3 months.

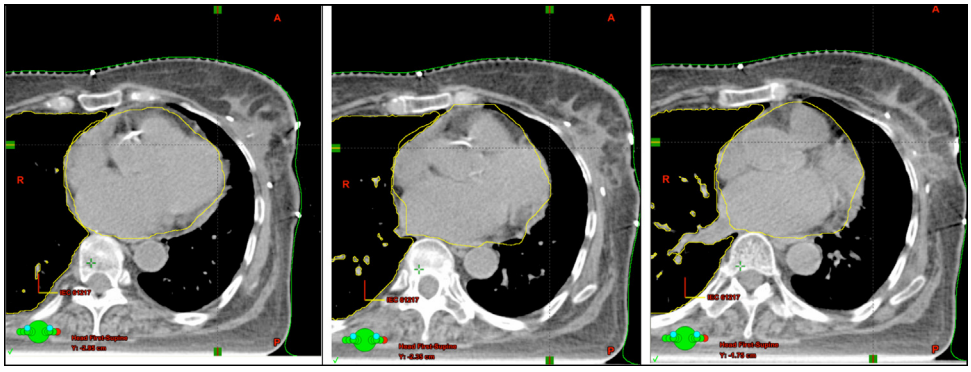

**Fig. 1.** Treatment planning scan showing proximity of post-operative complex (POC) to chest-wall and skin.
Treatment planning scan of left breast (at, superior, middle and inferior levels) showing POC with ill-defined wall margins with involvement of chest wall and skin. Clips form a good surrogate for POC localization.

**Table 1**
Demographic characteristics.

| Characteristic | Percentage |
|---|---|
| Median age | 45 years (range 24–70) |
| Premenopausal | 50 |
| Postmenopausal | 50 |
| T2:T3:T4 | 30:47:23 |
| N0:N1:N2:N3 | 16:53:27:4 |
| Stage II | 28.3 |
| Stage III | 71.7 |
| Intrinsic subtype | |
| Luminal A | 22 |
| Luminal B | 24 |
| Her-2-type | 15 |
| Triple negative | 39 |
| Type of chemotherapy | |
| Anthracycline | 50 |
| Anthracycline + Taxane | 50 |
| Chemotherapy schedule | |
| Sandwich | 60 |
| Sequential | 40 |
| Response to chemotherapy | |
| Complete response | 25 |
| Partial response | 75 |
| Post NACT T and N status | |
| pT0:T1:T2:T3p | 24:15:44:17 |
| pN0:N1:N2:N3 | 54:27:16:3 |

**Table 2**
Shape, character and location of POC.

| Shape of POC | Percentage |
|---|---|
| Irregular | 50 |
| Oval | 40 |
| Irregular ellipsoid | 10 |
| Character of POC | |
| Homogenous | 28 |
| Heterogenous | 72 |
| Location of POC | |
| Medial | 2 |
| Mediocentral | 28 |
| Central | 30 |
| Mediolateral | 35 |
| Lateral | 5 |
| Volume of postoperative complex | |
| < 25 cc | 42.6 |
| >25-50 cc | 31.5 |
| >50–75 cc | 18.5 |
| >75–100cc | 1.9 |
| >100 cc | 5.5 |
| Median (range) | 30 (2.3–286) |
| Involvement of chestwall, skin | |
| Chestwall | 93 |
| Skin | 75 |

**Table 3**
Cavity visualization score.

| CVS score | Description of cavity/cavity walls | Percentage |
|---|---|---|
| CVS score 5 | All margins clearly seen | 3.6 |
| CVS score 4 | Cavity with the majority of margins distinct | 32.1 |
| CVS score 3 | Cavity visualized with some distinct margins | 28.6 |
| CVS score 2 | Cavity visualized but margins indistinct | 32.1 |
| CVS score 1 | Cavity not visualized | 3.6 |

The median POC volume was 30cc, mean 39 cc (range 2.3cc to 286 cc) (Table 2). The POC was unidentifiable in two patients. The median POC volume of sandwich NACT was 25cc and that of sequential NACT was 30cc and this difference was not statistically significant. Clips were identifiable in 41.6% (n = 25) patients. The median clip volume was 40 cc (range 17cc to 120 cc). The concordance of POC volume with clip volume was seen in 80% (n = 20) of patients. The reason for discordance in POC and clip volume in 20% of patients was clip migration (n = 5). POC was situated in the medial (28%), central (30%) and lateral (35%) region (Table 2). The POC shape was irregular in 50%, oval in 40% and irregular ellipsoid in 10%. The POC texture was homogenous in only 28% and heterogeneous in 72%. The cavity visualization score was 5 with all margins clearly imaged in only 4% cases, 4 in 33%, 3 in 30%, and 2 in 28% and 1 in 5% cases (Table 3). The POC was in direct contact with the chest wall in 93% of patients and with the skin in 75% of patients. The proportion of patients with chest wall and skin involvement was 67%. Craniocaudally the mean extent and range of chest wall involvement was 2.99 cm (1–6 cm) and of skin involvement was 1.36 cm (0–7 cm) (Table 2, Fig. 1). 61.6% patients (n = 37) received conventional radiotherapy and the rest, hypo-fractionated radiotherapy. At a median follow-up of 65 months (IQ range 32–84 months), and a lost to follow-up rate of 11.6 %, 3.3% (n = 2) patients had local recurrence (LR) (one had multicentric and Her-2 positive disease and the other had triple negative disease). Both patients with LR had synchronous distant metastases. 5 patients (8.3%) had regional recurrence (LRR) in the supraclavicular region (in triple negative, Her-2 type or huge nodal burden). The distant metastases rate (DMR) was 23.3 % (n = 14). No patient with CR had LR, but the LRR was 13.3% (n = 2). The LR rate in PR was 4.4% (n = 2) and LRR rate was 6.6% (n = 3). 80% of recurrences (n = 4) were in women aged 40 or less. The DMR in CR was 6.6% (n = 1) and 28.8% in PR (n = 13). 63% of patients (n = 38) are alive and on follow-up.

## 4. Discussion

Breast conservation after NACT in LABC is possible in 17%–50% patients and it yields local control rates of 90%–96% at a median follow-up of 60 months.[1,2] Excision of post-chemotherapy volume

is now considered a safe practice.[14] Even patients with T4 tumors with favorable response to NACT and BCS are able to achieve 94% local control rates.[15] Our series. although small, shows low LR in a predominantly advanced T and node positive subset (70% being T3 and T4 and 84% node positive) of patients, and is comparable to other series. LR or LRR was seen in patients with adverse prognostic features like biology, high nodal burden, young age and partial responders to NACT. Patients achieving pathological CR had no local recurrence as compared to those with pathological PR. Pathologic CR has been found to be an independent predictor of recurrence in LABC treated with NACT.[16]

RT after NACT and BCS involves addressing few pertinent issues, like the safety of post NACT POC delineation, the need of comprehensive loco-regional RT. The safety of delineation of post-chemotherapy POC in LABC has not been described earlier. In this study, patients underwent excision of post-chemotherapy tumor volume and delineation of post-chemotherapy excision cavity with 1 cm margin as boost CTV. Using this technique, we found 3.3% ipsilateral breast tumor recurrence rate at a median follow-up of 65 months.

We observed that the median volume of POC (30cc) at a median time interval of 3 months between surgery and radiotherapy was large compared to the median of 9.3 cc reported for early breast cancers and results in large irradiated volume.[5] Sandwich chemotherapy was administered in our patients before the release of international consensus guidelines for LABC which recommends administration of the entire course of neoadjuvant chemotherapy prior to local treatment.[17]

Expansion of POC results in cubical expansion of the CTV and any under dosage of a CTV could result in surviving clonogenic cells, repopulating as true recurrences. The definition of CTV in intact breast with early breast cancer (EBC) has been shown to be prone to error, not only because of the difficulties inherent in the POC definition, but because even when boundaries appear relatively distinct, there are differences in perception between observers leading to inter-observer variability and conformity indices of only 50%.[18,19] Although we did not do an inter-observer variability study, our results are based on target delineation by two radiation oncologists with a similar methodology as stated above. This was based on POC visibility, architectural distortion in breast tissue and inclusion of clips. CVS score in EBC has been reported to be 3 in 11% cases as compared to 28.6% in the present study. A CVS score of 2 was seen in 7% EBC patients as compared to 32.1% in the present study. The greater proportion of low CVS score in our study was seen in women who received sandwich chemotherapy and it reflects the time elapsed before radiotherapy. The GEC-ESTRO guidelines published in 2015 suggest asymmetric expansion of POC for CTV delineation, but we used symmetric expansion based on the prevalent practice during that time (year 2007–2014).[20]

The POC texture was heterogeneous in 85% in EBC as compared to 72% in the present study while its shape was irregular in 52% in EBC as compared to 60% in the present study. The POC shape and texture in our study was dependent on time elapsed after surgery. The importance of clips in CTV definition for intact breast has already been established.[11] In our study clips were used in 40% of our patients, and clip volume was smaller than POC volume. It served as a good surrogate for CTV in 80% patients. Where clips appeared to be distant from the POC it was not taken as a surrogate for CTV definition.

Chest wall involvement by the POC has been observed in 53% patients with EBC as compared to 93% patients in the present study. Hence inclusion of the chest wall in the CTV in such patients is inevitable against the guidelines for EBC where the chest wall should be excluded from the CTV. The median contact of CTV with the chest wall is 2.99 cm which implies inclusion of a large ipsilateral lung and heart volume (in left breast patients). The implications of this proximity to the chest wall and heart needs to be systematically addressed. This proximity of CTV to the chest wall is also likely to deprive women with pendulous breast of any advantage of treatment in a prone position.

Proximity of the POC to the skin was observed in 75% of patients in the present study, with a median contact distance of 1.36 cm. This has implications for cosmesis which needs to be evaluated further. This has not been observed in EBC. This has implications for cropping the CTV margin to less than the standard margin of 5 mm for planning purposes. Opposing curvatures make off axis deep geographic misses common, especially at extreme margins and this was observed in 63% of patients in this study.[21]

Based on the data from NSABP-27, patients with clinically involved lymph nodes before neoadjuvant chemotherapy who become pathologically node negative at surgery have low rates of LRR (approximately 10% or below) regardless of surgical approach.[16] Rates of recurrence are even lower when a complete response is concurrently seen in the breast. Highest rates of recurrence are seen in patients who remain node positive after neoadjuvant chemotherapy. Hence, regional RT to supraclavicular and internal mammary RT is advocated with a boost to involved nodal region. In this study all patients received supraclavicular RT and the LRR rate is 8.3%. In our series patients who had LRR had adverse prognostic features (young age and node positive disease after NACT or triple negative subtype).

The drawback of this analysis is the small number of patients, which can be explained by the presentation of predominantly advanced staged patients in our clinic, where chances of downsizing with NACT to enable BCS are low. The dosimetric impact of large POC on heart and lung doses and the late effects of heart and lung irradiation were not evaluated.

## 5. Conclusions

Delineation of post NACT excision cavity as POC for boost radiotherapy seems to be safe. Clips serve as a good surrogate in more than three fourth of patients. Since POC is large in such cases and has proximity to the chest wall and skin in 75% of patients, it is likely to impact heart and lung doses in left sided breast cancer and cosmesis. Recurrences are dependent on adverse biology. These findings need to be validated in a larger database.

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## Conflict of interest

None declared.

## References

1. Wolmark N, Wang J, Mamounas E, et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr*. 2001:96–102.
2. Bear HD, Anderson S, Brown A, et al. The effect on tumour response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol*. 2003;21:4165–4174.
3. Akay CL, Meric-Bernstam F, Hunt KK, et al. Evaluation of the MD Anderson Prognostic Index for local-regional recurrence after breast conserving therapy in patients receiving neoadjuvant chemotherapy. *Ann Surg Oncol*. 2012;19:901–907.
4. Huang EH, Strom EA, Perkins GH, et al. Comparison of risk of local-regional recurrence after mastectomy or breast conservation therapy for patients treated with neoadjuvant chemotherapy and radiation stratified according to a prognostic index score. *Int J Radiat Oncol Biol Phys*. 2006;66:352–357.

5. Whipp EC, Halliwell M. Magnetic Resonance Imaging appearances in the post-operative breast: the clinical target volume–Tumor and its relationship to the chest wall. *Int J Radiat Oncol Biol Phys*. 2008;72(1):49–57.
6. International Commission on Radiation Units and Measurements. Prescribing, recording, and reporting electron beam therapy. Part 2. *J ICRU*. 2004;4:95–100.
7. Jacobson G, Betts V, Smith B. Change in volume of lumpectomy cavity during external-beam irradiation of the intact breast. *Int J Radiat Oncol Biol Phys*. 2006;65:1161–1164.
8. Coles CE, Cash CJ, Treece GM, Miller FN, Hoole AC, Gee AH. High definition three dimensional ultrasound to localise the tumour bed: a breast radiotherapy planning study. *Radiother Oncol*. 2007;84:233–241.
9. Regine WF, Ayyangar KM, Komarnicky LT, Bhandare N, Mansfield CM. Computed CT planning of the electron boost in definitive breast irradiation. *Int J Radiat Oncol Biol Phys*. 1991;20:121–125.
10. Bedwinek J. Breast conserving surgery and irradiation: the importance of demarcating the excision cavity with surgical clips. *Int J Radiat Oncol Biol Phys*. 1993;26:675–679.
11. Alm El-Din Mohamed A, Taghian Alphonse G. Breast conservation therapy for patients with locally advanced breast Cancer. *Semin Radiat Oncol*. 2009;19(Oct(4)):229–235.
12. Agarwal G, Ramakant P. Breast cancer care in India: Current situation and challenges for the future. *Breast Care (Basel)*. 2008;3:21–27.
13. Smitt MC, Birdwell RL, Goffinet DR. Breast electron boost planning: comparison of CT and US. *Radiology*. 2001;219:203–206.
14. Nakamura R, Nagashima T, Sakakibara M, et al. Breast-conserving surgery using supine magnetic resonance imaging in breast cancer patients receiving neoadjuvant chemotherapy. *Breast*. 2008;17(Jun (3)):245–251.
15. Shen J, Valero V, Buchholz TA, et al. Effective local control and long-term survival in patients with T4 locally advanced breast cancer treated with breast conservation therapy. *Ann Surg Oncol*. 2004;11(9):854–860.
16. Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol*. 2012;30:3960–3966.
17. Kaufmann M, Minckwitz VG, Mamounas EP, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. *Ann Surg Oncol*. 2012;19:1508–1516.
18. Landis DM, Luo W, Song J, et al. Variability among breast radiation oncologists in delineation of the postsurgical lumpectomy cavity. *Int J Radiat Oncol Biol Phys*. 2007;67:1299–1308.
19. Pena PC, Kirova YM, Campana F, et al. Anatomical, clinical and radiological delineation of target volumes in breast cancer radiotherapy planning: individual variability, questions and answers. *Brit J Radiol*. 2009;82:595–599.
20. Major T, Gutiérrez C, Guix B, et al. Recommendations from GEC ESTRO Breast Cancer Working Group (II): target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery. *Radiother Oncol*. 2016;118(Jan (1)):199–204.
21. Krawczyck J, Engel B. The importance of surgical clips for adequate tangential beam planning in breast conserving surgery and irradiation. *Int J Radiat Oncol Biol Phys*. 1999;43(2):347–350.