

A clip-based protocol for breast boost radiotherapy provides clear target visualisation and demonstrates significant volume reduction over time

Lorraine Lewis, MAppSci, BAppSci (MRS),¹ Jennifer Cox, PhD, BA (Hons), ARMIT (Med Radther),^{1,2} Marita Morgia, MBBS FRANZCR,¹ John Atyeo, PhD, MHIthScEd, BSc (Psych), BA, Assoc Dip Rad Tech,² & Gillian Lamoury, BMed, FRANZCR¹

¹Department of Radiation Oncology, Northern Sydney Cancer Centre, Royal North Shore Hospital, Sydney, New South Wales, Australia

²Faculty of Health Sciences, University of Sydney, Sydney, New South Wales, Australia

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Correspondence

Lorraine Lewis, Department of Radiation Oncology, Northern Sydney Cancer Centre, Royal North Shore Hospital, Pacific Highway, St Leonards, 2065 NSW, Australia.
Tel: +61 2 9463 1326; Fax: +61 2 9463 1087;
E-mail: lorraine.lewis@health.nsw.gov.au

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Abstract

Introduction: The clinical target volume (CTV) for early stage breast cancer is difficult to clearly identify on planning computed tomography (CT) scans. Surgical clips inserted around the tumour bed should help to identify the CTV, particularly if the seroma has been reabsorbed, and enable tracking of CTV changes over time. **Methods:** A surgical clip-based CTV delineation protocol was introduced. CTV visibility and its post-operative shrinkage pattern were assessed. The subjects were 27 early stage breast cancer patients receiving post-operative radiotherapy alone and 15 receiving post-operative chemotherapy followed by radiotherapy. The radiotherapy alone (RT/alone) group received a CT scan at median 25 days post-operatively (CT1rt) and another at 40 Gy, median 68 days (CT2rt). The chemotherapy/RT group (chemo/RT) received a CT scan at median 18 days post-operatively (CT1ch), a planning CT scan at median 126 days (CT2ch), and another at 40 Gy (CT3ch). **Results:** There was no significant difference ($P = 0.08$) between the initial mean CTV for each cohort. The RT/alone cohort showed significant CTV volume reduction of 38.4% ($P = 0.01$) at 40 Gy. The Chemo/RT cohort had significantly reduced volumes between CT1ch: median 54 cm³ (4–118) and CT2ch: median 16 cm³, (2–99), ($P = 0.01$), but no significant volume reduction thereafter. **Conclusion:** Surgical clips enable localisation of the post-surgical seroma for radiotherapy targeting. Most seroma shrinkage occurs early, enabling CT treatment planning to take place at 7 weeks, which is within the 9 weeks recommended to limit disease recurrence.

Introduction

Breast conservation surgery followed by whole breast radiotherapy is considered the standard of care for early stage breast cancer.^{1–3} For those patients undergoing breast-conserving surgery and receiving 50 Gy of radiation to the whole breast, an additional boost dose of 16 Gy to the tumour bed reduces the risk of local recurrence.⁴ Accurate tumour bed localisation for radiotherapy ensures adequate tumour doses by defining tissue at risk of recurrence.⁵

Historically, tumour bed localisation was imprecise.⁶ A seroma forms after breast conservative surgery and

computed tomography (CT)-based radiotherapy tumour bed localisation relies on this post-operative seroma formation plus the location of the scar to define the clinical target volume (CTV).^{7–10} Accurately localising the tumour bed on CT can be challenging. With full-thickness closure of the excision cavity, it is difficult to locate the tumour bed due to minimal seroma volume formation. Additionally, dense breast parenchyma can be difficult to interpret and researchers have documented inter-observer variability when contouring the post-operative seroma on CT scans.⁷

The skin incision and surgical induration are unreliable for boost field localisation,¹¹ so the surgical cavity should

be demarcated with surgical clips. Hunter *et al.*¹² reported that without clips, the boost would not have been dosed adequately 46% of the time. The surgical scar is now often placed some distance from the tumour site for better cosmesis, and it is recommended^{13,14} that clips be placed at the excision margins prior to tissue relocation, to be representative of the original tumour site. Thus, there is now a body of evidence that has demonstrated that clips are a good surrogate for the lumpectomy tumour bed^{15–19} and their use is recommended in the United Kingdom 2009 surgical guidelines.²⁰ Such clips would be useful for tracking changes in the boost volume over the course of treatment.

Shrinkage of the boost CTV has been investigated by other researchers.^{7,9,17,21–26} Over time, the interface between seroma and breast tissue becomes difficult to visualise as the seroma is reabsorbed. This occurs particularly when patients undergo chemotherapy prior to irradiation, due to the longer time frame to radiotherapy. Since the aim of radiotherapy is to treat as little healthy tissue as possible, the treatment planning images should be taken when the CTV is at its smallest and most stable to avoid both over-dosage and potential future replanning.

In 2010, a radiation therapist-led project introducing a surgical clip-based CTV delineation protocol for patients undergoing radiation therapy for breast cancer commenced at the Northern Sydney Cancer Care Centre Department of Radiation Oncology. The aim of this investigation was to determine the optimal time pattern for radiotherapy simulation by relating it to seroma shrinkage over time. It was hypothesised that, as with the general wound healing process, the majority of CTV reduction would occur shortly after surgery, and would slow with time.

Materials and Methods

Ethics approval was gained in June 2010 from the Northern Sydney Health Network HREC protocol no. 1003-78M. All subjects gave informed consent to participate.

Subject group

Forty-two sequential patients with histologically defined T1–T2 breast cancer who were about to have surgery participated, including one T3 patient classified by the Radiation oncologist as warranting radical RT. Fifteen of these patients were scheduled to have chemotherapy prior to radiotherapy and 27 to have radiotherapy alone post-surgery (see Table 1). A sequential retrospective control

Table 1. Subject characteristics.

Subjects	Radiotherapy alone	Chemotherapy and radiotherapy
Numbers	27	15
Age at surgery (years)		
Mean	59	56
Range	41–79	42–72
Tumour stage		
T-1	24	5
T-2	3	9
T-3	0	1
N stage		
0	24	6
1	3	5
2	0	0
3	0	4
Pathology type		
Infiltrating ductal	20	15
Infiltrating lobular	2	0
Ductal carcinoma in situ	5	0
Side		
Left	12	9
Right	15	6
Days from surgery to CT1		
Median	25	18
Range	10–37	10–28

CT1, initial study CT scan.

group of 25 patients who had received chemotherapy prior to radiotherapy was also selected for validity assessment of seroma visualisation.

Implant equipment and procedure

Thomas *et al.*²⁷ and Buehler *et al.*²⁸ identified appropriate clips to be placed at the time of breast surgery that could be used both for tumor localisation and treatment verification. Medium titanium clips in a ligiclip multi-applicator system (EthiconEndo-surgery, LLC, Cincinnati, OH) with a clip height after closure of 6 mm were chosen.

The clip protocol, adapted from that developed by Coles and Yarnold²⁹ was developed in consultation with the surgeons and the radiation oncologists. For each subject, a minimum combination of four medium titanium clips was placed at the medial, lateral, inferior, and superior extent of the tumour bed, and at the deep posterior base of the cavity, usually fixed to the pectoralis fascia.

The 15 subjects undergoing chemotherapy prior to radiotherapy were scanned at median 18 days post-surgery in treatment position on a radiotherapy breast board, using a GE Lightspeed CT with 3 mm slice thickness (CT1ch). Scans encompassed the whole breast. The visible seroma, surgical information, and surgical

clips were used to identify the CTV. All clips were to be encompassed in the CTV. A second scan, (CT2ch), which is normally the one used for radiotherapy planning, was taken at the completion of chemotherapy, at median 126 days post surgery. This Chemo/RT cohort had a third scan during radiotherapy at 40 Gy, (CT3ch), at median 161 days. The RT/alone cohort received two similar CT scans, the first (CT1rt) at median 25 days post-surgery and the second (CT2rt) taken during radiotherapy at 40 Gy, at median 68 days post-surgery, according to normal protocol. All boost CTVs were contoured for treatment by the radiation oncologists (GL or MM).

The British Columbia Cancer Agency Seroma Clarity Scale (see Table 2), a numeric scale ranging from 0, no visible seroma, to 5, seroma easily visible, homogenous with sharp boundaries, was used to evaluate the ease of delineating the seroma on the first CT for each group, as if no clips were present.⁷ When seroma visibility was scored as ≤ 3 (seroma identifiable with minor uncertainties), the clips were considered necessary to ensure consistent accurate CTV delineation.

Figure 1A and B shows two subjects' seroma clarity scores. Figure 1A shows an example where the clips were not needed to facilitate accurate, consistent CTV delineation. In contrast, Figure 1B represents a patient who had an excessive delay before the start of radiotherapy, with a seroma score of 1. In this case, there is complete seroma absorption and without clips inserted during surgery, the CTV would have been very difficult to identify. One observer (LPL) scored the seromas reaching consensus with a second observer when uncertainties arose, noting when the seroma was clearly visible without the clips matching these borders, which could have been caused by possible clip migration. There were no discrepancies between the volumes bounded by the clips and the corresponding seroma boundaries. No instances of migration were observed, as has previously been reported by Coles et al.¹³

Table 2. Seroma scores using The British Columbia Cancer Agency Seroma Clarity Scale.⁸

Seroma score	RT/alone number (%)	Chemo/RT number (%)	No clips control number (%)
0–1	3 (11.1)	4 (26.7)	13 (52)
2–3	18 ¹ (66.7)	11 ¹ (73.4)	12 (42)
4–5	6 (22.7)	0 (0)	0 (0)
Total	27 (100)	15 (100)	25 (100)

RT/Alone, cohort with radiotherapy treatment only; Chemo/RT, cohort treated with chemotherapy followed by radiotherapy.

¹One patient in each of these groups had no clips placed.

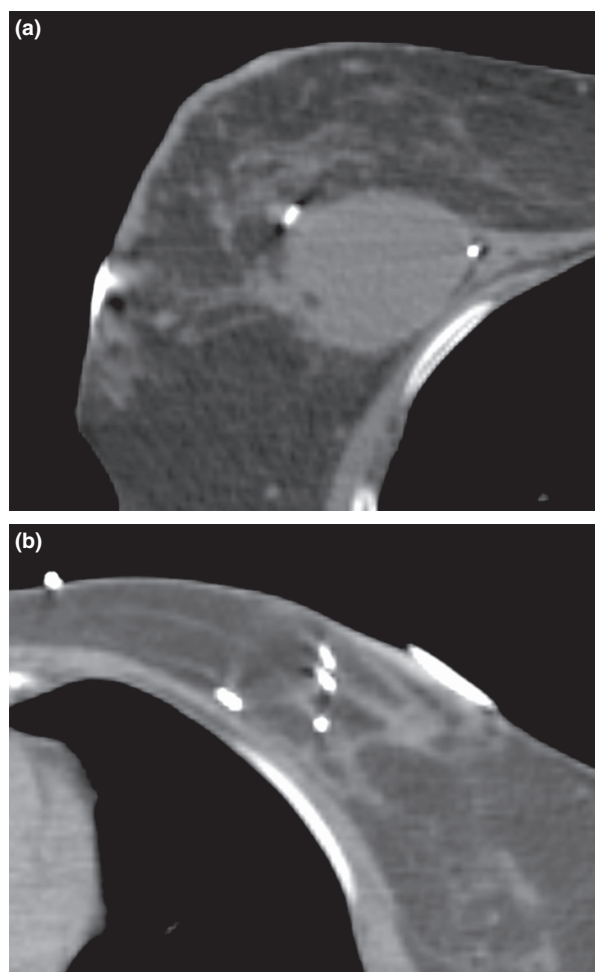


Figure 1. Examples of seroma and clip visualisation. (A) Seroma score = 5 easily identifiable, homogenous with sharp boundaries, clips not necessary. (B) Seroma score = 1 scar/shadow, clips necessary.

As a validation process, to determine the effect of clips on seroma visualisation, a controlled retrospective study was performed. Reviewers could not be blinded to the clips by removing them from the CTs, so CT scans from a randomly selected control group of 25 previously treated patients who had received three to four cycles of chemotherapy prior to radiotherapy and had no clips placed during surgery was used. The seroma scores for the control group were compared with those of the clipped chemotherapy patients. If a significant difference was detected between the seroma scores of the two groups, the clips would be considered to have influenced the reviewers' seroma scoring.

Data analysis

The data were analysed using the statistical package STATA Version 11 (StataCorp LP, College Station, TX).

CTV sizes were compared between each CT time point within each cohort and between cohorts using the Wilcoxon rank sum test ($P < 0.05$). It was hypothesised that there would be a significant rate of CTV change between CT1 and CT2 for both the Chemo/RT and the RT/alone groups, but no significant rate of change between CT2ch and CT3ch for the Chemo/RT group. The Spearman Rho Coefficient was used to test the rates of CTV change ($P < 0.05$).

Results

See subject demographics in Table 1. One subject in each cohort who had consented to clip placement had no clips identified on CT, but their seromas were clearly visible. The clips aided CTV delineation in 14/15 Chemo/RT subjects (93%) and in 21/27 (78%) RT/alone patients (see Table 2). No statistical test of seroma scoring could be performed due to the small sample size, but comparison of the data from the Chemo/RT group with the non-clipped control group, which had also been delayed due to chemotherapy, indicates that the presence of clips had no influence on the visibility scores allocated to the seroma in the study group, with all patients in these groups having seroma scores of 0–3.

The tumour bed could only be successfully localised without the aid of clips for patients with a seroma score of 4 or 5 ($n = 6$). For the remaining 34 cases, with scores ≤ 3 , clip position was required to localise the tumour bed. In the absence of seromas (one patient with a previous breast implant and another with a previous breast reduction), surgical clips assisted with tumour localisation. For one subject, the clips were visible, but were not all encompassed by the delineated volume.

CTV change

The pattern of CTV change is illustrated in Figure 2. The first CT for each cohort (CT1rt and CT1ch) was completed at similar median time points post-surgery (25 median days RT/alone and 18 median days Chemo/RT), with all subjects scanned at less than 5.3 weeks. There was no significant difference ($P = 0.08$) between the initial mean CTVs for each cohort. The second CT scans (CT2rt and CT2ch) were completed at considerably different time points: median of 68 days for the RT/alone cohort and median of 126 days for the Chemo/RT cohort.

There was no significant difference ($P = 0.89$) between the CTVs for the two cohorts at 40 Gy. The RT/alone cohort experienced a significant volumetric reduction of 38.4% in CTV ($P = 0.01$) from CT1rt: median 25 cm³ (range: 6–186 cm³); to CT2rt at 40 Gy: median 15 cm³ (range: 2–121 cm³).

In the Chemo/RT cohort, with an increased time delay of 4–6 months for chemotherapy, there was also a significant reduction in volumes between CT1ch: median 54 cm³ (range: 4–118 cm³) and CT2ch: median 16 cm³, (range: 2–99 cm³), ($P = 0.01$), but no significant reduction between CT2ch and CT3ch at 40 Gy: median 14 cm³ (range 7–110 cm³ 25), ($P = 0.89$). This indicates a significantly reduced rate of volume change from 18 weeks onwards (CT1ch to CT2ch [43.6%] and CT2ch to CT3ch [15.7%] [$P = 0.019$]).

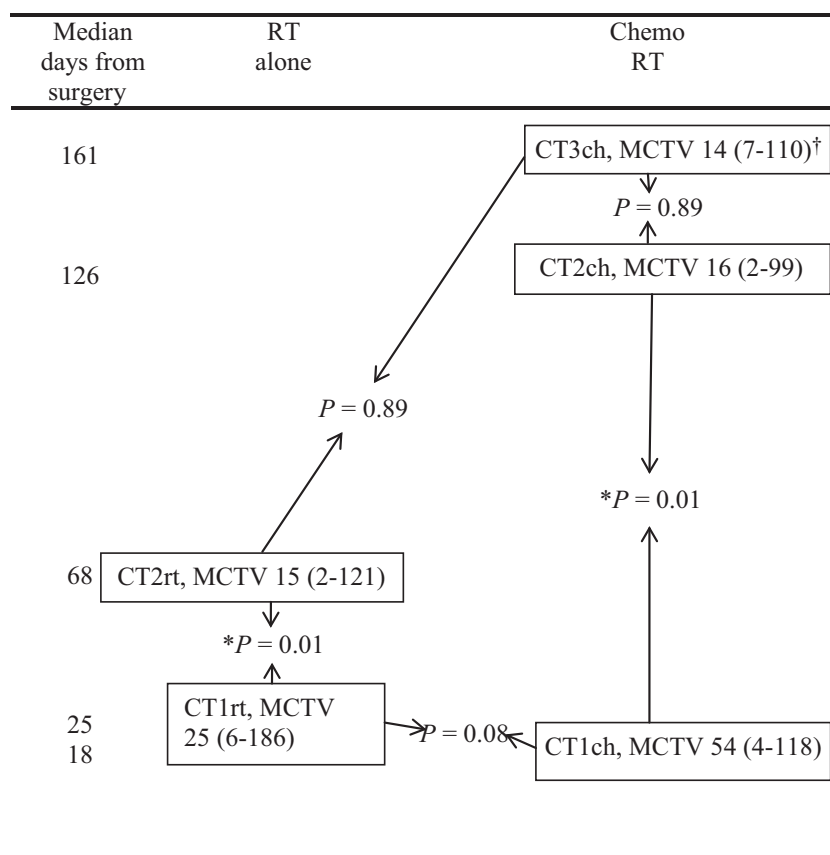
For the combined data of both groups (42 subjects), there was no significant correlation between initial volume and change of volume at CT2 (Spearman Rho coefficient 0.09, $P > 0.05$). Of the 15 subjects with an initial CTV >50 cm³ at the first CT, approximately 3 weeks after surgery, 11 (73%) had a greater than 50% volume reduction at the 40 Gy imaging point.

Discussion

In radiotherapy, the volume of normal tissue irradiated must be minimised to limit normal tissue toxicity. It is therefore optimal to identify the PTV when it is at its smallest. Surgical clips applied to the breast tumour bed have been shown, both here and in the work of others,^{13–15} to assist accurate CTV delineation. This is particularly important for patients who have undergone chemotherapy before irradiation where, due to the longer time delay, the seroma might be undetectable on CT.

The research reported here took place concurrently with the development of a standardised breast tumour bed surgical clipping protocol to enable accurate localisation of the CTV for radiotherapy boost planning. This was achieved, with placement of surgical clips now common practice at NSCC, and acceptable visualisation of the clips assisting accurate target delineation.

The application of the second CT scan for the Chemo/RT group of patients at median 126 days allowed investigation of the rate of CTV reduction over time. The significant ($P = 0.02$) volume reduction between scan 1 at 3.5 weeks and scan 2 at 10 weeks for the RT/alone group was mirrored by a similar and only slightly larger reduction between scan 1 at 2.5 weeks and scan 2 at 18 weeks for the Chemo/RT group, illustrating that the most rapid volume reduction occurred by at least 10 weeks post-surgery. Hurkmans *et al.*⁹ carried out an initial planning CT on 10 subjects with surgical clips to the tumour bed, then repeated the scan at 3, 5, and 7 weeks thereafter. Their results are similar to those with our larger cohort, with volume reduction ‘most pronounced between CT1 (approximately 7 weeks) and CT2 (approximately 9 weeks) post-surgery’. Alderliesten *et al.*²¹ similarly found significant volume reduction



CT = computed tomography imaging
 CT1rt = first CT scan for RT/Alone group
 CT2rt = second CT scan for RT/Alone group
 CT1ch = first CT scan for Chemo/RT group
 CT2ch = second CT scan for Chemo/RT group
 CT3ch = third CT scan for Chemo/RT group
 MCTV = median (range) clinical target volume (cm³)
 * = statistically significant difference
[†] 1 subject had an increase in volume between CT2ch and CT3ch

Figure 2. Schematic illustration of the imaging process and seroma volume changes over time.

between 4 weeks and approximately 7 weeks post-surgery ($P < 0.001$). Thus, the shrinkage rate of the CTV is initially rapid and reduces with time, stabilising at 7–10 weeks.

It has been generally suggested that time delay from surgery to radiotherapy should be as short as reasonably possible.^{30,31} Stefoski et al.³² reported that in a group of 7800 patients receiving breast-conserving surgery, surgery to radiotherapy intervals of greater than 9 weeks had a trend towards an increased relative risk of death, which was not statistically significant until the interval was 20 weeks post-surgery. In contrast, a meta-analysis of 22 studies found a continuous relationship between waiting

time to radiotherapy and local control of breast cancer, with a relative risk of recurrence per month of 1.10 (CI 1.04–1.15).³⁰ Patients understandably wish to complete treatment and return to a normal life as soon as possible, but a fourfold increase in risk of fibrosis for each increase in irradiated volume of 100 cm³ has been observed,³³ so treatment with a large CTV is inadvisable.

We found a 9-week wait from surgery to radiotherapy was feasible for patients who do not receive chemotherapy, by carrying out the planning CT 6–7 weeks post-surgery. This allows the CTV to be stable for radiotherapy, but also provides adequate time for the pre-treatment planning. In contrast, radiotherapy after

chemotherapy for node negative patients can be delayed by up to 7 months,³⁴ when CTVs will be smaller and stable.

Clinically relevant volume changes might be expected for patients with an initial volume >50 cm³. Although we found no statistically significant relationship between initial volume and rate of volume reduction, similar to Hurkmans et al.³⁵ Tersteeg et al., with a cohort of 77 subjects, reported a strong positive correlation.²⁶ Further research with a larger cohort is required to test this hypothesis.

Conclusion

Four surgical clips placed at the boundaries of the tumour bed enable localisation of the post-surgical seroma for radiotherapy targeting. Most seroma shrinkage occurs early, enabling CT planning and treatment to occur within the 9 weeks recommended to limit disease recurrence. Further imaging during radiotherapy might be necessary for patients whose initial seromas are greater than 50 cm³, due to an unpredictable shrinkage pattern with these larger tumours.

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Conflict of Interest

The authors declare no conflict of interest.

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