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, MHlthScEd, BSc (Psych), BA, Assoc Dip Rad Tech, 2 & Gillian Lamoury, BMed, FRANZCR 1

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

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.\textsuperscript{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\textsuperscript{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\textsuperscript{15–19} and their use is recommended in the United Kingdom 2009 surgical guidelines.\textsuperscript{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.\textsuperscript{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 group of 25 patients who had received chemotherapy prior to radiotherapy was also selected for validity assessment of seroma visualisation.

**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.

**Implant equipment and procedure**

Thomas et al.\textsuperscript{27} and Buehler et al.\textsuperscript{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, Cincinatti, OH) with a clip height after closure of 6 mm were chosen.

The clip protocol, adapted from that developed by Coles and Yarnold\textsuperscript{29} 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. When seroma visibility was scored as $\leq 3$ (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.\(^\text{13}\)

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.

| 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)                    |

\(\text{RT/Alone, cohort with radiotherapy treatment only; Chemo/RT, cohort treated with chemotherapy followed by radiotherapy.}

\(^\text{1One patient in each of these groups had no clips placed.}\)

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.

Table 2. Seroma scores using The British Columbia Cancer Agency Seroma Clarity Scale.\(^8\)

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 cm$^3$ (range: 6–186 cm$^3$); to CT2rt at 40 Gy: median 15 cm$^3$ (range: 2–121 cm$^3$).

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 cm$^3$ (range: 4–118 cm$^3$) and CT2ch: median 16 cm$^3$ (range: 2–99 cm$^3$), ($P = 0.01$), but no significant reduction between CT2ch and CT3ch at 40 Gy: median 14 cm$^3$ (range 7–110 cm$^3$ 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 cm$^3$ 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, 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.$^{11}$ similarly found significant volume reduction.
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.\textsuperscript{30,31} Stefoski et al.\textsuperscript{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).\textsuperscript{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 cm\textsuperscript{3} has been observed,\textsuperscript{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

### Table

| Median days from surgery | RT alone | Chemo RT |
|-------------------------|---------|----------|
| 161                     | CT3ch, MCTV 14 (7-110)$^{\dagger}$ |
| 126 |
| 68 | CT2ch, MCTV 16 (2-99) |
| 25 | CT1rt, MCTV 25 (6-186) |
| 18 | CT1ch, MCTV 54 (4-118) $^{\dagger}$ |

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 (cm\textsuperscript{3})  
* = statistically significant difference  
$^{\dagger}$ 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.
chemotherapy for node negative patients can be delayed by up to 7 months,\textsuperscript{34} when CTVs will be smaller and stable.

Clinically relevant volume changes might be expected for patients with an initial volume $>50$ cm$^3$. Although we found no statistically significant relationship between initial volume and rate of volume reduction, similar to Hurkmans et al.\textsuperscript{35} Tersteeg et al., with a cohort of 77 subjects, reported a strong positive correlation.\textsuperscript{36} 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 cm$^3$, due to an unpredictable shrinkage pattern with these larger tumours.

**Acknowledgement**

The authors gratefully acknowledge the assistance of breast surgeons Katrina Moore and Mark Sywak.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**

1. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; 347: 1227–32.
2. Fisher B, Anderson S, Bryant J, 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: 1233–41.
3. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: Long-term results of a randomized trial. *Ann Oncol* 2001; 12: 997–1003.
4. Bartelink H, Horiot JC, Poortmans PM, 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: 3259–65.
5. International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy (report 62). 1999.
6. Denham JW, Sillar RW, Clarke D. Boost dosage to the excision site following conservative surgery for breast cancer: It’s easy to miss! *Clin Oncol* 1991; 3: 257–61.
7. Petersen RP, Truong PT, Kader HA, et al. Target volume delineation for partial breast radiotherapy planning: Clinical characteristics associated with low interobserver concordance. *Int J Radiat Oncol Biol Phys* 2007; 69: 41–8.
8. 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: 1299–308.
9. Hurkmans C, Admiraal M, van der Sangen M, Dijkmans I. Significance of breast boost volume changes during radiotherapy in relation to current clinical interobserver variations. *Radiother Oncol* 2009; 90: 60–5.
10. Hansen CJ, De Winton E, Gugliani S, et al. Target localisation for tumour bed radiotherapy in early breast cancer. *J Med Imag Radiat Oncol* 2012; 56: 452–7.
11. 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: 675–9.
12. Hunter MA, McFall TA, Hehr KA. Breast-conserving surgery for primary breast cancer: Necessity for surgical clips to define the tumor bed for radiation planning. *Radiology* 1996; 200: 281–2.
13. Coles CE, Wilson CB, Cumming J, et al. Titanium clip placement to allow accurate tumour bed localisation following breast conserving surgery – audit on behalf of the IMPORT trial management group. *Eur J Surg Oncol* 2009; 35: 578–82.
14. Kirby AM, Evans PM, Evans PM, Nerurkar AY. How does knowledge of three-dimensional excision margins following breast conservation surgery impact upon clinical target volume definition for partial-breast radiotherapy? *Radiother Oncol* 2010; 94: 292–9.
15. 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: 484–92.
16. Hepel JT, Evans SB, Hiatt JR, 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.
17. Oh KS, Kong FM, Griffith KA, Yanke B, Pierce IJ. 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.
18. Goldberg H, Prosnitz RG, Olson JA, Marks LB. Definition of postlumpectomy tumor bed for radiotherapy boost field.
planning: CT versus surgical clips. *Int J Radiat Oncol* 2005; 63: 209–13.
19. Harrington KJ, Harrison M, Bayle P, et al. Surgical clips in planning the electron boost in breast cancer: A qualitative and quantitative evaluation. *Int J Radiat Oncol* 1996; 34: 579–84.
20. AoB Surgery. Surgical guidelines for the management of breast cancer. *Eur J Surg Oncol* 2009; 35(Suppl. 1): 1–22.
21. Alderliesten T, den Hollander S, Yang TJ, et al. Dosimetric impact of post-operative seroma reduction during radiotherapy after breast-conserving surgery. *Radiother Oncol* 2011; 2011: 265–70.
22. Kim LH, De Cesare S, Vicini F, Yan D. Effect of lumpectomy cavity volume change on the clinical target volume for accelerated partial breast irradiation: A deformable registration study. *Int J Radiat Oncol* 2010; 78: 1121–6.
23. Prosnitz RG, Haffty BG. Re: What do recent studies on lumpectomy cavity volume change imply for breast clinical target volumes? *Int J Radiat Oncol* 2009; 73: 1603.
24. Prendergast B, Indelicato DJ, Grobmeyer RR, et al. The dynamic tumor bed: Volumetric changes in the lumpectomy cavity during breast conserving therapy. *Int J Radiat Oncol* 2009; 74: 695–701.
25. Sharma BJ, Meyer OWM, Njo KH, Karim ABMF. Importance of timing of radiotherapy in breast conserving treatment for early stage breast cancer. *Radiother Oncol* 2009; 30: 206–12.
26. Tersteg RJHA, Roosink JM, Albrechts M, Wârlam-Rodenhuis CC, van Asselen B. Changes in excision cavity volume: Prediction of the reduction in absolute volume during breast irradiation. *Int J Radiat Oncol* 2009; 74: 1181–5.
27. Thomas CW, Nichol AM, Park JE, et al. An anthropomorphic phantom study of visualisation of surgical clips for partial breast irradiation (PBI) setup verification. *Radiother Oncol* 2009; 90: 56–9.
28. Buehler A, Ng SK, Lyatskaya Y, Stsepankou D, Hesser J, Zygmanski P. Evaluation of clip localization for different kilovoltage imaging modalities as applied to partial breast irradiation setup. *Med Phys* 2009; 36: 821–34.
29. Coles C, Yarnold J. Localising the tumour bed in breast radiotherapy. *Clin Oncol* 2010; 22: 36–8.
30. Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: A systematic review of the literature. *Radiother Oncol* 2008; 87: 3–16.
31. Hebert-Croteau N, Freeman CR, Latreille J, Rivard M, Brisson J. A population-based study of the impact of delaying radiotherapy after conservative surgery for breast cancer. *Breast Cancer Res Treat* 2004; 88: 187–96.
32. Stefoski MJ, Haward R, Johnston C, et al. Trends in postoperative radiotherapy delay and the effect on survival in breast cancer patients treated with conservation surgery. *Br J Cancer* 2004; 90: 1343–8.
33. Borger JH, Kemperman H, Smitt HS. Dose and volume effects on fibrosis after breast conservation therapy. *Int J Radiat Oncol* 1994; 30: 1073–81.
34. Arcangeli G, Pinnarò P, Rambone R, Giannarelli D, Benassi M. A phase III randomized study on the sequencing of radiotherapy and chemotherapy in the conservative management of early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2006; 64: 161–7.
35. Hurkmans C, Dijkstra, Reijnen M, van der Leer J, van Vliet-Vroegindeweij C, van der Sangen M. Adaptive radiation therapy for breast IMRT-simultaneously integrated boost: Three year clinical experience. *Radiother Oncol* 2012; 103: 183–7.