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Improving Radiotherapy for Breast Cancer:

Identification of the tumour bed and characterisation of target volume changes

Lorraine Lewis, BAppSc (MRT)

A Thesis submitted in the fulfilment of the requirements for the degree of

Masters of Applied Science,

The University of Sydney

2013
Declaration

I hereby declare that this thesis is my original work, to the best of my knowledge; it contains no previously published material unless otherwise acknowledged and has not been accepted for an award at any other institute of higher learning. Ethical approval was granted by the Northern Sydney Human Ethics Committee (HREC) for the two studies presented in this thesis. Participants were required to read a participant information document and informed consent was gained prior to data collection.

SIGNED:.......................... DATE…02/09/2013

NAME: Lorraine Lewis SIB: 199091835
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I would also like to thank my friends for listening to my never ending gripes of not having enough time. Finally, I would like to thank my family. To my children Greta and Hamish who always took it in their stride when “Mummy was always studying”. To my “rock solid” parents who have always been there for me. Thank you to my husband David for your love and encouragement over the last four years. I could not have done this without you.
Summary

Radiotherapy (RT) of the breast for early stage breast cancer traditionally requires whole breast irradiation followed by a small boost area of treatment to the original tumour bed. Accurate localisation of the tumour bed is essential. With the advent of new complex treatment strategies and computer tomography (CT) simulated radiotherapy planning there is a need to develop an expert localisation procedure that represents best practice. The use of a defined surgical clipping program and suitable on-treatment imaging should assist with accurate delineation of tumour volumes for radiotherapy to the breast.

Patients who require chemotherapy prior to radiotherapy pose significant delineation issues when using CT without clips. This group experiences a considerable time period between surgery and their radiotherapy planning CT and often has complete resolution of the seroma by the commencement of treatment, so would most benefit from breast lumpectomy clipping at the time of surgery. The clips would allow for localisation and verification of the tumour bed in breast lumpectomy patients, regardless of visible seroma.

At different time points post-surgery the lumpectomy cavity can vary greatly in size and shape, so the best time following surgery to delineate the cavity should be established. This cavity is delineated by the Radiation Oncologist (RO) at the time of the initial planning CT within our institution. If the cavity is clinically deemed too large a second scan may be requested and replanning requested.

This project was designed (1) to examine the feasibility issues of a new procedure for breast radiotherapy to improve tumour bed localisation with surgically inserted clips for clinical target volume (CTV) delineation, (2) to determine whether the optimal time for the CT planning scan can be predicted, and (3) to evaluate the best method for breast imaging on the treatment machine.
Forty-two (42) individuals with pathologically diagnosed early stage breast cancer who were either post-menopausal or over the age of forty years were recruited for this study. These patients were split into two study cohorts: those who commenced conservative breast therapy with a breast lumpectomy followed by radiotherapy, and those who had breast lumpectomy surgery, then chemotherapy (Chemo), followed by radiotherapy. This ethics approved study consisted of radio opaque surgical clips being placed around the surgical bed at the time of surgery. These clips were then used by the radiation oncologist to ensure consistent CTV delineation of the tumour bed. The CTV volume was measured on serial CT data sets taken at differing time points post-surgery and during radiotherapy.

Characterisation of the CTV changes post-surgery and during radiotherapy with or without chemotherapy delay demonstrated that the breast boost CTV changed significantly and that the initial defined CTV is not a predictor of relative CTV reduction. Regardless of the addition of chemotherapy, significant volume reductions were demonstrated in both groups of patients, with a 38.4% reduction at median 9 weeks for the RT group and 43.6% reduction at median 19 weeks for the Chemo/RT group (see Table 3.2 page 49). Commencement of treatment by no later than 9 weeks post-surgery is recommended based on both reported primary literature and from our observations of slowing seroma reduction over time. Thus due to planning time frame constraints, planning CT scans should be completed between 6-7 weeks after surgery, which would allow treatment to commence within the next several weeks. After 19 weeks, very little extra volume reduction was seen in the Chemo/RT cohort, with a mean CTV of 3.6 cc at 40 Gy (Table 3.2 page 49). There is therefore no need for an additional CT for either cohort to be completed at 40 Gy except for those patients who have an initial CTV greater than 50 cm³ (Figure 3.5 page 50). CTV reduction correlates to time post-surgery and appears to have no relationship to either radiotherapy or chemotherapy.

In study three a thorough literature review was carried out into on board kV imaging (OBI) for breast radiotherapy. Recommendations about routine on treatment verification imaging are based on the following factors: the purpose for kilovoltage (kV) imaging, collision risks,
image quality/contrast, radiation dose, accurate registration methods, and marker based matching and CTV monitoring. For robust radiotherapy techniques such as the traditional two field tangential technique, megavoltage (MV) imaging with current CTV-PTV margins of 10mm is adequate. When implementing complex radiotherapy breast treatment techniques such as Intensity Modulated Radiotherapy (IMRT), Accelerated Partial Breast Irradiation (APBI), Sequential Integrated Boost (SIB) and sequential photon beam boosts, to accommodate changing target volumes, volumetric kV CBCT becomes more important.

The work carried out for this thesis has informed practice in the following areas: routine insertion of surgical clips at the time of lumpectomy, characterisation of change of CTV over time leading to recommendations regarding the optimum time to carry out pre-treatment CT, and recommendations regarding routine on-treatment verification imaging.
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## Abbreviations

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<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>APBI</td>
<td>Accelerated Partial Breast Irradiation</td>
</tr>
<tr>
<td>ART</td>
<td>Adaptive Radiotherapy</td>
</tr>
<tr>
<td>BCT</td>
<td>Breast Conserving Therapy</td>
</tr>
<tr>
<td>CBCT</td>
<td>Cone beam Computer Tomography</td>
</tr>
<tr>
<td>Chemo</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Chemo/RT</td>
<td>study cohort 2, chemotherapy followed by radiotherapy</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
<tr>
<td>cm³</td>
<td>centimetre cube</td>
</tr>
<tr>
<td>CT</td>
<td>computer tomography</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
</tr>
<tr>
<td>DCIS</td>
<td>Ductal Carcinoma in situ</td>
</tr>
<tr>
<td>EBRT</td>
<td>External Beam Radiotherapy</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EPI</td>
<td>Electronic Portal Imaging</td>
</tr>
<tr>
<td>GTV</td>
<td>Gross Tumour Volume</td>
</tr>
<tr>
<td>Gy</td>
<td>gray</td>
</tr>
<tr>
<td>ICRU</td>
<td>International Commission on Radiation Units and measurement</td>
</tr>
<tr>
<td>IGRT</td>
<td>image guided radiotherapy</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiotherapy</td>
</tr>
<tr>
<td>kV</td>
<td>kilovoltage</td>
</tr>
<tr>
<td>LINAC</td>
<td>linear accelerator</td>
</tr>
<tr>
<td>LCIS</td>
<td>Lobular Carcinoma in situ</td>
</tr>
<tr>
<td>mm</td>
<td>millimetres</td>
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<tr>
<td>MV</td>
<td>Mega voltage</td>
</tr>
<tr>
<td>OBI</td>
<td>On board Imaging</td>
</tr>
<tr>
<td>RO</td>
<td>Radiation Oncologist</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
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<tr>
<td>RT</td>
<td>Radiotherapy/ Radiation therapy</td>
</tr>
<tr>
<td>RT alone</td>
<td>study cohort surgery followed by radiotherapy</td>
</tr>
<tr>
<td>RTOG</td>
<td>radiation therapy oncology group</td>
</tr>
<tr>
<td>RNSH</td>
<td>Royal North Shore Hospital</td>
</tr>
<tr>
<td>SIB</td>
<td>Sequential Integrated Boost</td>
</tr>
<tr>
<td>Vol</td>
<td>volume</td>
</tr>
<tr>
<td>WBI</td>
<td>whole breast irradiation</td>
</tr>
<tr>
<td>Wk</td>
<td>week</td>
</tr>
<tr>
<td>2D</td>
<td>two-dimensional</td>
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<tr>
<td>3D</td>
<td>three dimensional</td>
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Presentations

Conference Presentations – Oral

- Breast Boost Localisation using clips after breast conserving surgery: A study to investigate the changes in breast boosts volumes from breast surgery to the completion of radiotherapy: Study Design. Faculty of Health Sciences Post Graduate Research Symposium November 2009.
- Breast Boost Localisation using clips after breast conserving surgery: A study to investigate the changes in breast boost volumes from breast surgery to the completion of radiotherapy. Royal North Shore Hospital Breast Cancer Care Conference Terrigal NSW 25th June 2010.
- kV Imaging and Cone beam CT guided radiation Therapy of the Breast: A systematic review. Department of Radiation Oncology RNSH Multidisciplinary Meeting March 2011
- Breast Boost Localisation using clips after breast conserving surgery: A study to investigate the changes in breast boost volumes from breast surgery to the completion of radiotherapy. NSW Radiation Therapy Research Symposium, RPAH, November 2011.
- You’re only a radiation therapist: what do you know about research? The 10th Annual Scientific meeting of Radiation Therapy. ASMIRT 2013, Hobart.
Conference Presentations – Poster


Scholarships and Research Related Activities

- Brenda Grosz Research Grant: This grant enabled three months patient recruitment and data collection within the clinical setting at the Northern Sydney Cancer Centre. Department of Radiation Oncology, RNSH.
- Joint Funded (USYD and RNSH) site visit to Royal Marsden Hospital UK and attendance at ESTRO London 2011. This allowed opportunities to network with colleagues internationally on my research topic.
Introduction

Significance

The advent of computer tomography (CT) simulated radiotherapy planning for breast cancer has allowed the development of an expert clinical target volume (CTV) localisation procedure that represents best practice (Hansen et al., 2012; Wang, French, & Boyages, 2012). A defined surgical bed clipping program will assist with the accurate delineation of tumour volumes for radiotherapy to the breast (Weed et al., 2004), but to date there has been no published Australian institutional study describing such a protocol.

The identification of breast boost volume changes over time using a standardised clip CTV delineation protocol has also not been investigated in an Australian patient population. Moreover, there is limited published data available on the relationship between time from surgery and the size of the CTV. Thus, before embarking on new radiotherapy treatment techniques such as SIB, APBI, IMRT or ART, the issues of CTV delineation and how these volumes change from surgery to the completion of radiotherapy should be explored.

The use of image guided radiotherapy (IGRT) enables real time treatment verification, which is the final step in ensuring consistent accurate treatment delivery for radiotherapy patients. A growing number of recent studies have shown that it is possible to use IGRT to improve treatment delivery for complex radiotherapy treatment (Coles et al., 2007; Topolnjak et al., 2010a; White et al., 2007). This thesis explores this issue in the context of utilising commercially available kV On Board Imaging (OBI) systems both in the 2D and 3D setting. A particular focus will be the use of imaging to match to surgically placed radio opaque clips in preparation to initiate a kV OBI verification protocol for photon boost treatments.
Structure

The thesis is arranged into five chapters. Chapter One is an overview of the thesis and provides the background literature relevant to the context of breast radiotherapy.

This thesis covers three research projects, described in Chapters Two, Three and Four, that can each be read independently. Each project has an introduction, method, results and conclusion, and the intention is to submit them all for publication after submission of the thesis.

Chapter Two describes the design and implementation of a radiation-therapist led trial to develop a protocol for insertion of surgical clips into the breast surgical bed.

Chapter Three presents a prospective research study analysing CTV changes over time. It is an investigation into the relationship between time after surgery and seroma size, using a comparison between radiotherapy alone patients and patients having radiotherapy delayed due to post-surgical chemotherapy.

Chapter Four is an analysis of the on-treatment imaging options for localisation of the breast CTV, using a systematic review of the published literature.

Chapter Five is an overall discussion of the project as a whole.

The appendix at the end of the thesis provides supplementary material related to study design, including relevant institutional ethical approval statements and protocol development documents.

Aims

1) To develop expert standards of practice in breast tumour localisation utilising surgical clips.

2) To inform clinicians of the best time to CT plan patients in terms of stable breast boost clinical target volumes (CTVs), by evaluating the rate and extent of CTV shrinkage for those
undergoing radiotherapy alone as well as those having radiotherapy delayed due to chemotherapy.

3) To analyse on board treatment kilovoltage (kV) imaging to verify complex breast radiotherapy treatments.
CHAPTER 1

Background and Literature Review

1.1 Incidence and treatment of breast cancer

Breast cancer is the most common cancer among Australian women, accounting for 27% of all cancer diagnoses in 2007. Eighty eight per cent of women in Australia who are diagnosed with breast cancer live beyond 5 years (AIHW, 2010). In NSW, breast cancer accounts for 28% of new cancers and 16% of female cancers (Tracey, Kerr, Dobrovic, & Currow, 2010). On average, one in eight Australian females will develop breast cancer and one in 37 females will die from it before the age of 85 years. More than 69% of breast cancers were diagnosed in those aged 40–69 years in 2011. The management of breast cancer is therefore an important topic for the Australian health system (AIHW, 2012).

Breasts consist mainly of fat and glandular tissue arranged in lobules which in women of child bearing age can produce milk. Their weight and dimensions differ at different periods of life, and in different individuals. The deep surface of each is nearly circular, flattened, or slightly concave, and has its long diameter directed upward and lateral toward the axilla. It is separated from the fascia covering the pectoralis major, serratus anterior, and obliquus externus abdominis muscles by loose connective tissue. The breast has 15 to 20 sections that are called lobes which have smaller sections called lobules where milk is produced. The lobes and lobules are all linked by small tubes called ducts. The nipple and areola are situated on the surface of the breast at the end of these ducts (Standrig, 2005). Figure 1.1 depicts the anatomy of the breast.
Breast lumps can be either benign in nature or have the potential to invade surrounding tissues. In the majority of invasive breast cancers, the abnormal cell growth begins in the ducts; this type of breast cancer is referred to as infiltrating (or invasive) ductal carcinoma. Invasive lobular carcinoma is another type of invasive breast cancer which begins in the lobules. Other, less common types of breast cancers include inflammatory breast cancer, medullary carcinoma and Paget’s disease. In Australia in 2008, more than three-quarters of breast cancer in females were classified as invasive ductal carcinoma (AIHW, 2012). There are two non-invasive forms of breast cancer that, if they remain untreated, have a high chance of subsequently becoming invasive breast cancer. These are ductal carcinoma in situ (DCIS), a non-invasive carcinoma which is contained in the milk ducts at diagnosis, and lobular carcinoma in situ (LCIS) in the lobules. Women diagnosed with DCIS have about a 10 per cent chance of being diagnosed with a subsequent invasive breast cancer within 10 years. Breast cancer is categorized as Stage I, II (A or B), III (A, B, or C), or IV. The stage is
based on the size of the tumour and whether the cancer has spread. Stages I, IIA, IIB, and IIIA are considered "early-stage" breast cancer and refer to cancers that may have spread to nearby lymph nodes but not too distant parts of the body (U.S. Department of Health, 2012).

Therapeutic options for breast cancer depend on several factors including the size of the tumour, its location, the tumour type, the risk of spread and the overall health status of the patient. The treatment of early stage breast cancer can consist of surgery, chemotherapy, radiotherapy, hormonal therapy and specific target drugs. Some of these will be used in isolation but most in combination, depending on the disease type and stage. The removal of the cancer by surgery is the primary means of treatment for early stage breast cancer, either as total mastectomy or wide local excision, which is usually followed by radiotherapy. For those patients with slightly more aggressive features where the risk of regional or systemic spread are high, the sequence of treatment will be surgery, followed by chemotherapy, and then radiotherapy (Edward, C. Perez, C & Brady, L. 2008).

1.2 Radiotherapy of the breast

The main aim of external beam radiotherapy (EBRT) for early stage breast cancer is to destroy any cancer cells that may remain in the breast and surrounding area after surgery, while chemotherapy is used to prevent spread to other anatomical sites outside the breast. Historically, a total mastectomy was carried out for patients who had small breast tumours. However, breast conserving therapy (BCT), which consists of a lumpectomy followed by breast irradiation, produces survival results similar to mastectomy. A meta-analysis by the Early Breast Cancer Trialist Group confirmed that both mastectomy and radiotherapy following lumpectomy reduce the 5-year local recurrence rate from 26 to 7% (Clarke et al., 2005). Poortmans et al. (2008), using 10 year randomized data from over 5000 patients, demonstrated the effects of the addition of a 16 Gy boost dose to the primary tumour site following BCT, and reported improved local control. Whole breast irradiation (WBI) generally consists of a simple two field tangential field arrangement followed by a direct electron field called the boost that is delivered to the primary tumour site.
In a meta-analysis of 17 randomised trials, radiation delivered after breast conservation surgery was shown to reduce mortality by 3.3% in node negative patients and 8.5% in patients with node positive disease (Buchholz, 2011). Veronesi et al. (2002) published 20 year follow results of a randomised study comparing the efficacy of radical mastectomy (n=349) with breast conserving surgery followed by radiotherapy (n=352). For those patients with relatively small breast cancers there was the same long term results of those who undergo radical mastectomy,

The area of highest risk of recurrence is the region closest to the primary tumour site (Clark et al., 1996; Fisher et al., 2002; Veronesi et al., 2001). Romestaing et al. (1997) reported reduced recurrence rates with no decrease in cosmetic outcome after 50 Gy was delivered to the whole breast followed by a 10 Gy boost to the primary tumour site, compared to earlier dosing regimens with no boost. Bartelink et al. (2007), moreover, in a 10-year study of 5,318 patients, the randomised boost versus no boost EORTC 22881-10882 trial, 50 Gy was delivered to the whole breast with stratification to either no boost or a 16 Gy boost delivered to the primary site. After a median follow up of 10.8 yrs the 16 Gy boost improved overall regional control for all age groups, however demonstrated no overall survival difference. Therefore, good quality irradiation and particularly tumour bed boost irradiation prevent local tumour recurrence. EviQ Online version 1.4.0. (Cancer Institute NSW, 2013) has collated this information into an online evidence based resource for radiation oncology providers to ensure that they are using up to date evidence based treatments and practices for all cancer sites

Technical excellence is an important factor in the delivery of all forms of radiotherapy. The importance of expert technical delivery of RT for cancer was demonstrated in a large international phase III trial (n=589) the TROG 02.02 head and neck study by Peters et al. (2010). In this landmark Australian driven study inferior radiotherapy resulted in a 24% reduction in loco regional control and a 20% reduction in overall survival at 2 years. Abe et al. (2005), in a meta-analysis of randomized trials that began in 1995 assessing local
regional control and mortality of breast cancer patients, showed that the technical quality of radiotherapy delivered is also important for breast cancer patients.

1.3 Current advancements in breast radiotherapy

The simple whole breast tangential beam technique has the potential to induce contralateral breast tumours and cardiac and lung toxicity (Borger et al., 2007; Harris et al., 2006). New technologies and techniques for the improved delivery of early stage breast radiotherapy aiming to reduce these toxicities have appeared in the last few years: currently there are a number of these under investigation in phase III trials throughout the world (Danish Breast Cancer Cooperative Group, 2009; Wolmark & Curran 2007; Yarnold & Coles, 2009).

Intensity Modulated Radiotherapy (IMRT) and on-treatment imaging have provided opportunities to deliver EBRT to both the whole breast and tumour bed using techniques that reduce treatment fractionation and irradiated volume (Hurkmans et al., 2012; Offersen, Overgaard, Kroman, & Overgaard, 2009).

IMRT has been shown to improve dose homogeneity and volume conformity for breast radiotherapy (Harsolia et al., 2007; Johansen, Cozzi, & Olsen, 2009; Mell, Mehrotra, & Mundt, 2005). Conventionally, the boost irradiation was planned and delivered after completion of whole breast irradiation. However, it is now possible to treat the whole breast volume and boost volume simultaneously. The simultaneous integrated boost (SIB), which incorporates simultaneous delivery of the boost, is in some departments throughout the world replacing the older sequential electron boost technique. IMRT SIB not only improves dose homogeneity, but also decreases the number of treatment fractions. (Hurkmans, Meijer, van Vliet-Vroegindeweij, van der Sangen, & Cassee, 2006; Mayo, Lo, Fitzgerald, & Urie, 2004; McDonald, Godette, Whitaker, Davis, & Johnstone, 2010). IMRT SIB has provided more conformal plans than conventional sequential boost planning (Hurkmans et al., 2006).
This conformity, however, can be lost over the course of treatment if there are changes in the boost clinical target volume (CTV). This issue will be discussed in chapter 3.

If recurrence most commonly occurs close to the tumour bed, a long course of radiotherapy to the whole breast does not seem necessary (Boyages et al., 1990; Swanson & Vicini, 2008). There have been moves to decrease the amount of breast tissue irradiated, by only irradiating the post-surgical cavity with a margin of adjacent breast tissue. This partial breast irradiation (PBI) technique is administered either as EBRT or delivered as interstitial brachytherapy. In accelerated partial breast irradiation (APBI) the dose is delivered in a hypo-fractionated treatment scheme to small tumour bed volumes plus a margin of healthy tissue. There has been growing interest in APBI and various approaches to this which have been developed and are undergoing phase I-III clinical studies (Mannino & Yarnold, 2009). Polgár et al., (2004) reported after 7 years on a prospective study of accelerated partial breast irradiation (APBI) using interstitial high-dose-rate brachytherapy. The results were compared with those achieved by standard, whole breast radiotherapy (WBRT), with or without a tumour bed boost and recurrence rates equivalent to those of whole breast irradiation followed by boost were reported. Since its introduction, APBI has been under continuous debate regarding its efficacy, and results are pending for many of the clinical trials. Regardless of the lack of results, many institutions have implemented this technique. The American Society of Radiation Oncology (ASTRO) has published consensus guidelines to help with its implementation (Smith et al., 2009). Some issues relating to the implementation of this technique are patient selection in terms of histopathology, tumour margins and risk of recurrence. An important aspect of APBI is ensuring accurate CTV delineation. Kirby et al. (2010) in a review of published literature on CTV delineation for complex treatment techniques such as APBI stressed the importance of accurate definition of the CTV. APBI involves irradiating a small, potentially mobile breast CTV, so if a small
CTV changes across the radiotherapy treatment course, relatively major target localisation errors could occur.

Another new technological advancement to improve breast radiotherapy and to reduce heart and lung toxicity is deep inspiration breath hold (Korreman, Pedersen, Nøttrup, Specht, & Nyström, 2005; Remouchamps et al., 2003; Stranzl & Zurl, 2008; Wang, Purdie, et al., 2012). Treatment is delivered in a breath hold position where the heart becomes displaced posteriorly by the inflation of the lungs and thus the amount of irradiated heart and lung is reduced. This is not the topic of this thesis, so will not be discussed further.

1.4 Contouring CTVs for breast radiotherapy

Whole breast irradiation (WBI) plus a boost, PBI, and SIB all require CTV delineation. The boost CTV for breast cancer is located at the site from which the tumour has been removed (tumour bed) and this volume of tissue requires a tumouricidal dose. Historically, the tumour bed and thus the breast boost CTV of breast radiotherapy patients has been defined by a variety of methods that have included clinical palpation, visualisation of the surgical scar, pre surgical imaging such as mammography, ultrasound, or MRI and even patient recollections of the tumour site. Even with surgical notes clinical palpation by the Radiation Oncologist is a very subjective technique that also requires the patient to remember where the tumour was located. The surgical scar has also been used as an indicator of the tumour bed, but with modern cosmetic surgeries the scar often bears no relation to the actual tumour site (Denham, Sillar, & Clarke, 1991); with Machtay et al. (1994) reporting that boost coverage using the scar based approach was inaccurate 20%-88% of the time. Ultrasound has also been used to localise the breast boost field and improved on clinical mark up by 20-50% (Ringash et al., 2004). Poor accuracy in CTV delineation has resulted in under dosing of the tumour bed and has increased the dose to normal tissues (Coles & Yarnold, 2010).

With the introduction of Computer Tomography (CT) there has been an 80% improvement in CTV delineation compared to clinically defined boost CTVs (Messer, Kirikuta, Bratengeier, & Flentje., 1997). However, there have been many studies indicating that there
is inter-observer variability in defining the tumour bed on CT (Landis et al., 2007; Lee et al., 2012; Li et al., 2009; Petersen et al., 2007; Struikmans et al., 2005).

Following most wide local excisions, when breast surgical cavity fluid is under pressure the interface between fluid and breast tissue defines the tumour bed and is known as a seroma, which can be observed on CT. There are a number of problems when using the seroma alone to define the boost CTV, which include seroma definition, clinical factors such as infections, post-operative complications and changes in surgical techniques. Clearly defined seromas are unusual, which leads to inter-observer variability (Landis et al., 2007). Clinical factors associated with reduced concordance between CTV delineation were found to include the following: tissue stranding from the surgical cavity, proximity to muscle, dense breast parenchyma, and benign calcifications that could be mistaken for surgical clips. The largest variation in boost CTV delineation occurs in the medio-lateral and cranio-caudal directions (Li et al., 2009; Petersen et al., 2007).

Post-operative complications such as haematomas (Paterson, Nathanson, & Havstad, 1994) and infection (Indelicato et al., 2007) add to the difficulties of accurate CTV delineation. The open closure surgical technique is a method where a large incision is made, diseased tissue is removed, and the wound is closed, resulting in a fluid-filled cavity, and has been routinely used for breast conserving surgery. Even with drains inserted to remove excess surgical fluid, a large seroma can result, which can lead to post-operative complications. A newer technique, full thickness closure, involves close apposition and suturing of the walls of the cavity. This reduces post-operative infection and results in better cosmesis (Mukesh et al., 2012). Full thickness closure does not result in large seromas. More patients are now undergoing oncoplastic surgery and/or breast reductions at the time of removal of the primary tumour. These surgical procedures often result in distortions of the seroma shape and thus are not necessarily a true representation of the location from which the tumour was removed. These distortions create difficulties for the Radiation Oncologist (RO) in defining the CTV (Kader et al., 2008). Studies of inter-observer variation of the boost volume
highlight the need to implement definition guidelines to improve consistency in CTV delineation (Landis et al., 2007; Lee et al., 2012; Li et al., 2009; Petersen et al., 2007; Struikmans et al., 2005)

New tools to aid in defining the breast CTV include pre-operative CTs and Magnetic Resonance Imaging (MRI). Boersma et al. (2012), in a study of 30 patients, investigated whether using a pre-operative CT scan decreases inter observer variation of boost-CTV delineation in breast conserving therapy (BCT), and whether the pre-operative CT influences the size of the CTV. However, pre-operative CTs are not commonly used and have only had modest success in limiting inter observer variability. MRI, with its high resolution sensitivity in breast tissue, offers superior soft tissue definition for CTV delineation, but it is difficult to image breast patients’ supine on the MRI couch to simulate the treatment position. MRI is also an expensive option for CTV delineation (Whipp, Beresford, Sawyer, & Halliwell, 2010; Whipp & Halliwell, 2008).

The Radiation Therapy Oncology Group (RTOG) Breast Cancer Atlas (White et al., 2013) defines a ‘lumpectomy GTV’ which includes the seroma (because gross tumour has been removed surgically) and surgical clips when present. A one centimetre margin is then added to create the CTV (ICRU, 1999). If local relapse occurs at the foci of the residual disease or in the vicinity of the tumour bed after complete microscopic resection, the CTV margin logically takes into account the primary tumour position (Vicini, Kestin, & Goldstein. 2004). There were no consensus guidelines for CTV definition within the Australian setting when this research was instigated in 2010. Wang et al. (2012) in the article entitled, “Put the felt pen away: Time to move on from a clinical mark-up for a breast boost”, emphasised the need to move towards CTV delineation within Australia using more complex methods such as seroma definition and the use of surgical clips. This move towards CTV delineation using more complex techniques such as identification of the seroma with clips was the drive behind this research in 2010.
The term CTV is used in this thesis (based on the departmental breast voluming protocol, 2010), and is defined as the surgical cavity, seroma and surgical clips as seen on a diagnostic quality planning CT. The CTV is then expanded by a fixed margin to create the planning target volume (PTV). The term tumour bed plus a small margin can also be used to describe a breast CTV and is often used when describing CTVs where no seromas are present. Authors often use the terms surgical cavity, excision cavity, seroma and tumour bed interchangeably in literature, but all describe the primary site from which the tumour has been removed during surgery. The following figures depict the boost CTV delineation using surgical radio opaque clips at the Northern Sydney Cancer Centre (see Figures 1.2 and 1.3).
Figure 1.2 Transverse view of Right Breast with Boost CTV in Green, PTV in Orange and Breast PTVeval in Red

Figure 1.3 Sagittal view of Right Breast with Boost CTV in Green, PTV in Orange and Breast PTVeval in Red
1.5 Surgical clips to aid CTV delineation

Surgical clips have been used as radio opaque markers to define the depth of the surgical bed for some time (Bedwinek, 1993; Harrington et al., 1996). These clips can be seen on CT and can therefore be used to delineate the boost CTV. Clips have also been used to define tangential beam placement (Krawczyk & Engel, 1999). The value of surgical clips was established by Denham et al. (1991) and Harrington et al. (1996), who found that the electron boost fields of the early 90s would have inadequately irradiated the CTV up to 68% of the time, as the clip placed at depth during surgery showed significant under dosing.

Surgical clips not only define the depth of the tumour bed, but have the potential to be attached to the excision cavity walls. These clips, used in conjunction with CT, help the delineation of the CTV. Weed et al. (2004) demonstrated on 28 patients that clips are a strong radiographic surrogate for the excision cavity and that, due to this improved accuracy of definition, the planning target volume (PTV) margin could potentially be reduced safely from 1 cm to 5mm. Larger randomised studies would be required before margin reduction would be recommended for this population of patients. Based on an analysis of seven peer reviewed articles utilising clips Kirby et al. (2010) when describing the current approaches of CTV delineation for PBI, recommended tumour bed delineation using CT and implanted excision cavity wall markers for the purpose of external beam radiotherapy and or partial breast irradiation. These clips are inexpensive to use and are recommended in UK surgical guidelines to ensure consistent CTV delineation (BASO 2009) and for specific clinical trials (Coles et al., 2009).

The optimal number of clips to be used has been under investigation for a number of years. Goldberg et al. (2005) used a single chest wall clip as visualised on CT as the surrogate for the tumour bed, while Kirova et al. (2010) suggested at least 3 or more clips to improve tumour bed delineation. However more recent researchers (Coles et al., 2009; Coles et al., 2007) have suggested that 6 clips should be placed radially around the tumour, which would enable more accurate CTV delineation. Kokubo et al. (2001) looked at the impact on local
control of boost irradiation 42 months post treatment with 4 surgically placed clips. They found a significant advantage for local recurrence free survival of 97% for those with clip localisation compared to 88% with no clip boost localisation. The possibility of clip migration has been suggested as the reason for the slow uptake of this method of CTV delineation but Coles and others (2009) successfully implemented a localisation clipping program for 30 patients as part of the UK IMPORT (Intensity Modulated Partial Organ Radiotherapy) trial and demonstrated no clip migration.

1.6 The timing of radiotherapy post-surgery

Radiotherapy is usually given following surgery but if chemotherapy is recommended, radiotherapy will commence soon after chemotherapy has been delivered. Researchers suggest that there should be limited time delay from surgery to treatment, either radiotherapy or chemotherapy, to inhibit progression of the disease and enhance cure rates (Chen, King, Pearcey, Kerba, & Mackillop, 2008; Hébert-Croteau, Freeman, Latreille, Rivard, & Brisson, 2004; Huang, Barbera, Brouwers, Browman, & Mackillop, 2003; Slotman, Meyer, Njo, & Karim, 1994). Stefoski et al. (2004) reported that surgery to radiotherapy intervals of greater than 9 weeks had a trend towards an increased relative risk of death.

Patients who require chemotherapy prior to radiotherapy experience considerable delays from surgery to their pre-radiotherapy planning CT and often have complete resolution of the seroma by the commencement of treatment (Kader et al., 2008). This issue will be discussed in chapters 2 and 3. Radio opaque surgical clips would allow for localisation and verification of the CTV of the breast lumpectomy patients regardless of seroma visualisation (Coles et al., 2009; Smith et al., 2009).

1.7 Dynamic CTVs

Radiotherapy depends upon accurate delineation of the CTV. Systematic errors can be introduced at the preparation stage of treatment or at any time throughout the treatment
course (Van Herk, 2004). Organ delineation uncertainty is one example of a systematic error that is initiated at the beginning of a course of radiotherapy.

The contour of the breast CTV at the time of planning is usually considered to be representative of the CTV during the full course of radiotherapy. Generally, once surgery has been completed, a planning CT is taken with or without surgical clips as guidance. These scans may be taken as little as three weeks post-surgery, when the healing process is far from complete and the tissue remodelling may still be occurring as part of this process. As the planning CT is a “snap shot in time” of the size and shape of the breast tissue, any changes in the CTV from surgery to the completion of radiotherapy have the potential to lead to over or under dosing of healthy tissue. In clinical practice, the time interval between surgery and treatment planning and even the experience of the radiation oncologists (ROs) may hinder accurate CTV delineation (Kader et al., 2008; Weed et al., 2004; Wong et al., 2006). These inconsistencies in CTV delineation have the potential to create large systematic errors.

Many authors have demonstrated that the lumpectomy cavity, and thus ultimately the CTV, change significantly over a course of treatment (Jacobson, Betts, & Smith, 2006; Kader et al., 2008; Kim, DeCesare, Vicini, & Yan; Oh, Kong, Griffith, Yanke, & Pierce, 2006; Tersteeg, Roesink, Albrégts, Wárlám-Rodenhuis, & van Asselen, 2009; Weed et al., 2004). Kim et al. (2008), in a meta-analysis of the work of four groups, plotted mean cavity volume versus mean days from surgery and demonstrated that there was an initial increase in cavity volume at approximately two weeks followed by considerable shrinkage. Most cavity reduction was found to occur when the initial CT scan had been acquired at 2-4 weeks post-surgery. Since the aim is to treat as little healthy tissue as possible, radiotherapy planning images should be taken when the CTV is at its smallest to avoid over-dosage and potential future re-planning. Planning should therefore be completed when the CTV is at its most stable.
No Australian consensus guidelines exist describing when the best time to CT plan for the breast boost. In the department where this research was carried out in 2010, the planning CT, on which the boost CTV is delineated, was acquired approximately 2-3 weeks after surgery. This worked well when the boost CTV did not greatly change size and shape over time. Part of the department’s radiotherapy protocol in 2010 was to rescan for the boost if the CTV was considered too large (> 30 cm$^3$ volume, based on local clinical experience), or to have changed dramatically during treatment. A second scan was then acquired during radiotherapy for the purpose of breast boost planning. This second scan would then be used to re-plan the patient’s remaining course of treatment, in a simple form of adaptive radiation therapy (ART). ART is a closed-loop radiation treatment process where the treatment plan can be modified using systematic feedback of measurements. Adaptive radiation therapy improves radiation treatment by systematically monitoring treatment variations and incorporating them to re-optimize the treatment plan early on during the course of treatment. In this process, field margins and treatment doses can be routinely customized to each individual patient to achieve more precise targeting. This, in turn, can lead to dose escalation, as irradiation of healthy tissue is kept to a minimum (Yan, Vicini, Wong, & Martinez, 1997). Alderstien et al. (2011) analysed three different boost radiotherapy planning techniques by scanning patients at one week before RT and in the third and fifth weeks of RT. For each patient, three plans were generated: (1) sequential whole breast irradiation planned on the initial CT, followed by sequential boost planned on the week 5 CT; (2) SIB: planned on the initial CT; (3) SIB adaptive radiation therapy (SIB-ART): planned on the initial CT and re-planned on the week 3 CT. They demonstrated a dosimetric advantage for patients with changing seroma sizes when SIB-ART was used with re-planning halfway through treatment. Hurkmans et al. (2012) also reported on an ART protocol where the initial planning CT and lumpectomy were carried out less than 30 days post-surgery and patients who had an initial seroma volume > 30 cm$^3$ were rescanned at day 10 of treatment. This protocol for IMRT SIB led to a clinically significant reduction of the high dose volumes within the treatment plans.
Breast CTV delineation using a conventional CT data set requires the patient to return to the CT scanner for tumour volume monitoring or for re-planning purposes. This means that for most busy clinical practices an additional planning CT scan can only be performed once during a course of treatment. However, Yang et al. (2010) have demonstrated that kilovoltage (kV) cone beam CT (CBCT) could be used daily to monitor seroma volume changes. This concept is discussed as part of a systematic review in chapter 4.

1.8 Treatment verification studies: kV imaging and surgical clips

Accurate treatment delivery is important to achieve the prescribed dose in radiotherapy, and improved treatment targeting might facilitate dose escalation. Dose escalation and fractionation regimes have increased the probability of tumour control for many tumour sites such as prostate and breast. For prostate cancer, Zelefsky et al. (1998), as part of a phase I study, safely increased the tumour target dose from 64.8 to 81 Gy in increments of 5.4 Gy. Pollack et al. (2000) between 1993 and 1998 investigated the effect on disease free survival on 305 stage T1 through T3 patients who were randomized to receive 70 Gy or 78 Gy of external-beam radiotherapy and indicated that 70 Gy or more should be given to the prostate to ensure disease free survival. For early stage breast cancer patients as previously discussed, increasing the boost from 10 Gy to 16 Gy is required to minimise recurrence (Bartelink et al., 2007). Liao et al. (2000) also demonstrated, when increasing dose from 60 Gy to 66 Gy and comparing different fractionation schedules, that twice-daily post mastectomy radiation to a total of 66 Gy for patients with inflammatory breast cancer resulted in improved loco regional control, disease free survival, and overall survival. However, dose escalation does carry a risk of greater adverse side effects unless the irradiated volume is kept to a minimum and targeting of this volume is accurate.

There are three types of correction protocols generally used for radiotherapy to ensure accurate treatment delivery: offline corrections, online corrections and intra-fraction corrections (van Herk, 2007). All these corrections require verification imaging on the treatment machine. For traditional external beam breast radiotherapy using two tangential
beams, online electronic Mega voltage (MV) portal images (EPIs) that are compared to
digitally reconstructed radiographs (DRRs) were sufficient (van der Laan, Hurkmans, Kuten,
Westenberg, & Breast, 2010). However for complex treatments such as IMRT and those
requiring 3 dimensional (3D) internal anatomy visualisation and monitoring, such as APBI
and SIB, online kilovoltage (kV) imaging is replacing EPIs as the imager of choice for
Image Guided Radiotherapy (IGRT) (Topolnjak et al., 2010).

The implementation of new techniques such as APBI and SIB has been slow, partly due to
the mobile structure of the breast and the need for accurate treatment localisation. Factors
implicated in CTV mobility in the breast, as in any other region of the body, include patient
stability, positioning, breathing motion, and contour changes. Immobilisation of the patient
is an important factor in ensuring accurate treatment and has been investigated by several
authors (Mitine, Dutreix, & Van der Schueren, 1991; Thilmann et al., 1998). The method of
breast patient immobilisation used for the patients in this study is discussed in chapter 2.

There is a range of image guidance methods available, as is discussed in Chapter 4,
consisting of orthogonal planar imaging, both MV and kV, and volumetric imaging via kV
cone beam CT (CBCT) and MV systems. MV CBCT is used on helical tomotherapy
treatment systems. The helical tomotherapy unit itself is essentially a hybrid between a
linear accelerator and a helical CT scanner for the purpose of delivering IMRT (Welsh et al.,
2002). Tomotherapy has not been considered in this thesis as it is an expensive treatment
option and is not readily available in Australia. IGRT allows online matching and treatment
adjustments to be made and anatomy changes to be monitored on a daily basis. Jain et al.
(2009) used CBCT to measure patient movements during treatment and reported similar
results to those of EPIs. A comparative study comparing EPIs to CBCT found that EPIs
underestimate CBCT set up error using bony landmarks for breast cancer patients 20-50% of
the time.
The quality of the 2D or 3D kV images has a major impact on the ability to visualise either soft tissues such as the breast seroma, bony anatomy or radio opaque materials such as surgical clips. Orthogonal 2D kV images allow isocentre verification. 3D images such as those produced by kV CBCT enable internal structures and external patient contours to be visualised. The ability to identify internal structures while the patient is in the treatment position enables tumour bed tracking, with or without the presence of surgical clips (Weed et al., 2004; Z. Yang et al., 2010). Kim et al. (2007) demonstrated the ability to automatically track clips in the CBCT image using in house software, making possible the reduction of CTV-PTV treatment margins. Also Penninkhof et al. (2009) for a cohort of 30 patients showed that surgical clips were relatively stable during radiotherapy treatment and can be used as a radiotherapy surrogate for the tumour bed in set up and verification protocols. The use of kV imaging for breast radiotherapy is discussed in depth as part of a systematic review in chapter 5. This systematic review will facilitate evidence based practice decisions to be made on the use of kV imaging for breast radiotherapy within Australia.

The three studies that follow describe investigations into localisation of the surgical tumour bed using surgical clips to aid in pre-radiotherapy visualisation, the relationship between time post-surgery and CTV shrinkage before and during radiotherapy, and an analysis of the imaging options for on-treatment verification of the location of the CTV. The results of these studies should support improved breast cancer radiotherapy protocols.
CHAPTER 2.

The Successful Implementation of a Multidisciplinary Clip-Based Protocol for Boost Radiotherapy in Breast Cancer

2.1 Introduction

Radiotherapy after breast conserving surgery (BCS) of patients with breast cancer is effective in reducing the risk of local recurrence. In a meta-analysis by the Early Breast Cancer Trialist Collaborative Group (EBCTCG) it was confirmed that both mastectomy and radiotherapy following lumpectomy reduce the 5-year local recurrence rate from 26 to 7% (Clarke et al., 2005). Over the last 20 years, breast conservation surgery followed by whole breast radiation has been considered standard of care for early stage breast cancer and is used in Australia as part of evidence based practice (Veronesi et al., 2002; Cancer Institute NSW., 2013). The area of highest risk of recurrence is the region closest to the primary tumour site (Clark et al., 1996; Fisher et al., 2002; Veronesi et al., 2001). For patients with early breast cancer who undergo breast-conserving surgery and receive 50 Gy of radiation to the whole breast, an additional dose of 10-16 Gy to the tumour bed reduces the risk of local recurrence, especially in those younger than 50 years of age (Bartelink et al., 2007).

Accurate tumour bed localisation for radiotherapy facilitates optimum CTV by defining tissue at risk of recurrence, ensuring adequate tumour dose (ICRU, 1999).

Historically, a combination of pre-operative imaging (mammograms), histopathology review, surgical scar location and palpation have aided identification of the tumour bed to create the clinical target volume (CTV), but there are limitations with all these techniques (Denham et al., 1991). The advent of CT simulated radiotherapy planning enabled internal structures and the boost CTVs to be delineated. Authors described the use of CT to improve the delineation of the breast boost CTV over clinically based techniques (Bedwinek, 1993; Benda et al., 2003). Radiotherapy planning localisation has relied on this post-operative seroma formation as seen on CT to define the breast CTV. Hansen et al. (2012) compared clinical mark up to that defined by the seroma on CT (with or without surgical clips).
Similarly, Benda et al. (2003) compared clinical mark up with a combination of CT seroma and or surgical clip delineation. Both authors concluded that there was improved boost dose coverage using a CT based delineation of the boost CTV. However, accurately localising the tumour bed to create the CTV on CT can be challenging. If full-thickness closure of the excision cavity is performed during surgery a minimal seroma forms making it difficult to locate the tumour bed. Dense breast parenchyma can be difficult to interpret on CT and researchers have documented inter-observer variability when contouring the postoperative seroma (Petersen et al., 2007). Breast surgical techniques have changed so the scar is now often placed some distance from the tumour site for better cosmesis, and a UK protocol (Coles et al., 2009) recommends that clips be placed at the excision margins prior to tissue relocation in order for them to be representative of the original tumour site.

Kirby et al. (2010) suggested for the purpose of both external beam radiotherapy and partial breast irradiation (PBI) that the optimal method of tumour bed delineation requires CT imaging with implanted excision cavity wall markers. The practice of accelerated partial breast irradiation (APBI) is being investigated in clinical trials in many countries around the world; the hypo fractionated dose is delivered to a target volume that is closely related to the size and shape of the surgical cavity (Baglan et al., 2003; Smith et al., 2009). Although irradiating a reduced volume, recurrence rates for APBI are equivalent to those of whole breast irradiation followed by a boost (Polgár et al., 2004). Due to the smaller CTVs, accurate tumour bed delineation is critical when embarking on an APBI protocol, so a standardised clipping protocol needs to be used in this circumstance. The placement of radio opaque tumour markers (surgical clips) during surgery is now recommended in the UK 2009 surgical guidelines (Association of Breast Surgery, 2009), however, this procedure has yet to be standardised as routine practice within Australia.

As early as 1993, Bedwinek et al. (1993) demonstrated that the skin incision and surgical induration are not reliable landmarks for boost field localization and recommended that the surgical cavity should be demarcated with surgical clips. Hunter, McFall, & Hehr. (1996) in
assessing the radiation field dose coverage using radiographic film of the boost, reported that without clips, the boost cavity would not have been dosed adequately 46% of the time.

Goldberg, Prosnitz, Olson & Marks. (2005), compared CT CTV boost delineation to surgical clip delineation and determined that a single clip used as a surrogate for the tumour bed underestimates the extent of the tumour. The authors suggested that a combination of both CT and surgical clips should be used to improve CTV boost delineation. Coles et al. (2009), as part of the UK IMPORT (Intensity Modulated Partial Organ Radiotherapy) trial, audited the value of titanium clips for tumour bed localisation following BCS for the purpose of breast RT planning, and presented a clip based delineation protocol that used 6 titanium clips placed around the tumour bed at the time of BCS.

The addition of radiopaque surgical clips enables the CTV to be delineated on CT data sets even in the absence of a seroma. This is particularly important for a subset of patients who have increased time delays post-surgery such as those having adjuvant chemotherapy that can take four to six months to complete. The accepted sequencing of treatment for these patients is surgery, chemotherapy, then radiotherapy to commence 3-4 weeks after the completion of chemotherapy. (Jobsen, van der Palen, Brinkhuis, Ong, & Struikmans, 2012) Kader et al. (2008) reported that after after 9-14 weeks’ post-surgery there is often complete resolution of the seroma by the time of treatment CT planning, and that the seroma should not be the sole tool used for CTV delineation.

Although clips aid in the localisation of the tumour bed for CTV delineation they also play an important role in radiotherapy treatment and verification, two of the fundamental elements for accurate radiotherapy delivery. Kim et al. (2007) compared manually matching treatment verification images to chest-wall and skin with matching to surgical clips, and concluded that using current CTV-PTV margins a clip-based online setup protocol should be used.
Serial CT imaging has demonstrated clips to be a stable surrogate for a changing tumour bed volume (Weed et al., 2004). There is now a large body of evidence that has demonstrated that clips are a good surrogate for the surgical tumour bed. (Goldberg et al., 2005; Harrington et al., 1996; Hepel et al., 2009; Oh et al., 2006; Weed et al., 2004).

In 2010 a multidisciplinary surgical clip based marker localisation protocol was introduced and evaluated for patients undergoing radiation therapy for breast cancer at the Northern Sydney Cancer Care Centre (NSCC) Department of Radiation Oncology at Royal North Shore Hospital (RNSH). The primary aim of this study was to improve tumour bed localisation and introduce a standard surgical clip based CTV delineation protocol for breast radiotherapy patients. The secondary aim was to assess the acceptability of the protocol by members of the multidisciplinary team (MDT).

2.2 Materials and methods

The issues that were considered and resolved for the introduction of an implanted surgical clip program included: selection of the patient group, the implant equipment, procedure, and quality assurance process.

2.2.1 Patient group

Ethics approval was gained in June 2010 from the Northern Sydney Health Network HREC protocol No: 1003-78M and data was collected between September 2010 and December 2011. As ligature clips are routinely used as a localisation tool to indicate nodal involvement, the consent process for surgical clip placement and its complications was considered by the surgeons to be part of the normal consent process for surgery.

Patients were eligible for this study if they had histologically defined early stage breast cancer with T1-T2 staging. Due to recruitment issues, recruitment was ceased after 14 months, with a final cohort of forty two subjects. Of these patients, 15 were required to have chemotherapy prior to radiotherapy (Chemo/RT) and 27 were having radiotherapy alone (RT/alone) post-surgery. Patients who have more aggressive disease markers often undergo
up to 6 months of chemotherapy. Within our referred population many of these women were often excluded on the basis of age or menopausal status. More chemo radiotherapy patients were excluded due to aggressive disease markers which required up to six months of chemotherapy. The combinations of study exclusion criteria and candidature time limits limited the Chemo/RT cohort to 15 study patients. As with any statistical test, even with small sample sizes, significance can be reached, suggesting that the effect is large enough to be clinically relevant.

A sequential retrospective control group of 25 patients who had chemotherapy prior to radiotherapy was also selected.

2.2.2 Implant equipment and procedure
An extensive literature review was undertaken to investigate the types of materials that could be used as a tumour surrogate. Thomas et al. (2009) and Buehler et al. (2009) identified appropriate clips to be placed at the time of surgery that could be used both for tumour localisation and treatment verification. Availability, ease of use, visibility on kilovoltage (kV) On Board Imaging (OBI) for treatment verification and cost were all important factors that were considered when deciding which clips to use (see chapter 5). These clips needed to be available to all surgeons across a range of public and private sector hospitals. Medium titanium clips in a ligiclip multi-applicator system (EthiconEndo-surgery, LLC) with a clip height after closure of 6mm were chosen.

The clip protocol was developed in consultation with the surgeons performing the procedure and the radiation oncologists who would use the clips for localisation. The protocol as described by Coles et al (2009) for the UK IMPORT (Intensity Modulated Radiotherapy Partial Organ Radiotherapy) trial used 6 paired clips to determine the incidence of clip migration and reported clip migration to be less than 10%, so paired clips were not thought necessary for this study.
Initially, the principal researcher delivered an education package to the two surgeons and four radiation oncologists involved in this study. This included several PowerPoint presentations describing the literature and importance of utilising clips for breast RT, protocol design meetings, surgical localisation documentation procedures and surgical visits. The development and practice of delineating the CTV using clips on planning CTs by the radiation oncologists (RO’s) was also included. At surgery on the first subject, clips were placed with a radiation oncologist and radiation therapist present to ensure protocol compliance. For all subjects the plan was to place a minimum of 5 medium titanium clips at locations around the tumour bed that included the anterior, 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.

2.2.3 Volume delineation and quality assurance
Subjects had a planning CT taken in the treatment position on a radiotherapy breast board using a GE Lightspeed CT with 3 mm slice thickness. Scans were taken to encompass the whole breast, extending superiorly to include the supra-clavicular margin and inferiorly the entire breast tissue plus 2 cm. The CTV was created using the visible seroma, surgical information and surgical clips, with all clips to be encompassed in the CTV. The British Columbia Cancer Agency Seroma Clarity Scale (Petersen et al., 2007) was used to evaluate the ease of delineating the seroma on the planning CT as if no clips were present. This is a numeric scale ranging from 0, no visible seroma, to 5, seroma easily visible, homogenous with sharp boundaries. For subjects whose seroma visibility score ranged from 0 - 3 (3=seroma identifiable with minor uncertainties) the clips were considered necessary to ensure consistent accurate CTV delineation. Seroma scores of ≥4 were easily identifiable without the need for clips; thus the clips were considered to have provided no extra information and therefore did not improve delineation of CTV by the radiation oncologist.

To determine the effect of clips on seroma visualisation, a controlled retrospective study was performed. It was not possible to blind reviewers to the clips by removing them from the...
planning CTs, so a control group of 25 randomly selected patients from the 2009 patient database was selected. These patients had received 3-4 cycles of chemotherapy prior to radiotherapy and had no clips placed during surgery. Therefore, when evaluating the benefits of the clips, the seroma scores for the retrospective control groups were compared with the seroma scores for the clipped chemotherapy patients. If a significant difference was detected between the seroma scores of the control group and those of the pre chemo study group, the clips would be considered to have influenced the reviewers’ seroma scoring.

Figures 2a, and 2b are examples of study subjects’ seroma clarity scores. Figure 2a shows a very clearly defined seroma with sharp identifiable boundaries. This would have been given a seroma score of 5 and the clips would have not been required to produce accurate, consistent CTV delineation. In contrast, Figure 2b is representative of a patient who had an excessive time delay post-surgery 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 accurately delineate. One observer scored the seromas and a second observer was consulted when uncertainties arose. It was noted when the seroma was clearly visible but the clips did not match these borders.
Figure 2a Seroma score = 5 easily identifiable, homogenous with sharp boundaries. Clips not necessary

Figure 2b Seroma score = 1 scar/shadow. Clips are necessary.
2.2.4 Satisfaction survey

To gauge compliance and acceptability of this new surgical clipping protocol a small open ended satisfaction survey was completed at the end of subject recruitment (see Appendix E and F). The survey was completed by the surgeons placing the clips at the time of surgery and the radiation oncologists utilising the clips to aid in accurate CTV delineation.
2.3 Results

The table below depicts the subject characteristics of the two cohorts of study patients.

Table 2.1 Subject characteristics

<table>
<thead>
<tr>
<th>Subjects</th>
<th>RT/Alone N=27</th>
<th>Chemo/RT N=15</th>
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<tr>
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<td>Range</td>
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<tr>
<td>4-5</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

*British Columbia Cancer Agency Seroma Clarity Scale.
# One patient in each of these groups had no clips placed.
2.3.1 Tumour bed localisation

The clips aided CTV delineation in 14/15 chemotherapy subjects (93%) and in 20/27 (74%) radiotherapy alone patients (see Table 2.2). No statistical comparison of CTV delineation between groups could be performed due to the small sample sizes. The seroma scores for the chemotherapy study group and the control group, who also had been delayed due to chemotherapy, were similar, with no seromas receiving a 4-5 score on the seroma visualisation scale. This indicates that the scorer’s seroma rating was unlikely to have been influenced by the presence of the clips.

Table 2.2 Seroma Visualisation Score

<table>
<thead>
<tr>
<th>Seroma Score*</th>
<th>RT/alone (%)</th>
<th>Chemo/RT (%)</th>
<th>No clips control Chemo/RT (%)</th>
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<td>0-1</td>
<td>3 (11.1)</td>
<td>4 (26.7)</td>
<td>13 (52)</td>
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<td>2-3</td>
<td>18# (66.7)</td>
<td>11# (73.4)</td>
<td>12 (42)</td>
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<tr>
<td>4-5</td>
<td>6 (22.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>27 (100)</td>
<td>15 (100)</td>
<td>25 (100)</td>
</tr>
</tbody>
</table>

*British Columbia Cancer Agency Seroma Clarity Scale *

One patient in each of these groups had no clips placed #

Two patients (one from each cohort) who were consented for clip placement had no clips identified on CT. Both these patients were consented at the beginning of the study and were therefore entered for completeness of data analysis. Of the 42 study subjects, the tumour bed could be successfully localised when using the visible seroma (score 4-5) for only 6 subjects. These subjects were in the radiotherapy alone cohort. The clips gave additional delineation information for the remaining 33 cases (those patients with a score ≤3), including 14/15 of the chemotherapy subjects (see Table 2.2). In the absence of seromas (i.e. score 0-1) tumour localisation relied totally on the surgical clips. For one subject the clips were visible, but one clip was not encompassed by the delineated volume. In this case and with those where the
clips were not placed, visible seroma and surgical reports became the predominant guide for CTV delineation.

2.3.2 Satisfaction survey of surgeons and radiation oncologists

Both surgeons said the procedure was easy to carry out and that they would continue this procedure post study. They reported difficulty placing the anterior clip close to the superficial skin surface due to concerns of cosmesis and marker palpability, so this clip for some patients was not inserted. In all subjects surgeons placed at least 4 clips around the tumour bed with the deep clip fixed to the pectoralis fascia. They agreed that the implementation process gave them a sound knowledge of the problems experienced by the radiation oncologist associated with CTV delineation. Four radiation oncologists completed the satisfaction survey. All agreed that prior to the introduction of this protocol there were difficulties with breast boost CTV delineation. When asked whether it was easier to delineate the volumes in patients who had volume resolution after chemotherapy, three agreed and one strongly agreed. All agreed that this protocol was beneficial for CTV delineation.

2.4 Discussion

In radiotherapy normal tissue toxicity must be kept to a minimum, which for patients with breast cancer is particularly important for the heart and lung (Cuzick et al., 1994). As recurrences are often close to the tumour bed, accurate localisation of the CTV to ensure adequate dose coverage is important. With modern surgical procedures it is no longer necessary to rely on the surgical scar as the basis for delineating the CTV for breast radiotherapy patients (Bedwinek, 1993; Denham et al., 1991; Kovner et al., 1999; Machtay et al., 1994).

When relying on the seroma alone to define the boost CTV there is uncertainty for the radiation oncologist because with time, the seroma becomes re absorbed, and the interface between the seroma and breast tissue is difficult to visualise. Due to the long time delays
experienced by those patients undergoing chemotherapy prior to irradiation, the seroma is often undetectable on CT. Clips therefore aid accurate CTV delineation.

This study describes the successful implementation of a protocol led breast boost localisation procedure utilising surgical clips within the Australian context. In order to complete this project in a timely manner data collection was limited to a 14 month period, thus small subject numbers were recruited for the Chemo/RT cohort. However, since the implementation of this clipping protocol the MDT surgeons now routinely place four to five surgical clips during surgery and the radiation oncologist uses these to aid in accurate CTV delineation for all early stage breast cancer patients. As well as improving breast boost CTV delineation the surgical clips can also be visualised during daily treatment to improve accurate treatment delivery, as other authors have demonstrated (Buehler et al., 2009; Kim et al., 2007; Thomas et al., 2009). The surgeons clipping these patients and the radiation oncologists using clips to delineate the CTV all agreed that the procedure was easy to implement. The clips used were relatively inexpensive and are often already used as part of the operating procedure for homeostasis or specimen localisation. During the implementation phase, even with an extensive education program to the entire MDT team before the commencement of this procedure, two patients at the beginning of recruitment failed to be clipped due to operating theatre constraints. However, once all stakeholders became familiar with the procedure, the process was adhered to. The deletion of the anterior clip from the protocol, due to difficulties in its placement, has not limited accurate CTV delineation, as the remaining clips and CT density data provide adequate information.

This study supports the findings of others (Coles et al., 2009; Weed et al., 2004) that surgical clips can be used as a radiotherapy surrogate for breast boost localisation and that a protocol of this nature can be consistently adhered to. In the context of oncoplastic surgery, clips should be placed prior to tissue translocation to ensure they represent the original tumour
site. Moreover, if re excision is required, clips should be repositioned at the borders of the surgical cavity. CTV delineation is very difficult, and in the absence of any distinguishable seroma the clips are an invaluable aid in delineating the CTV. This was particularly evident for the post-chemotherapy patients, whose seromas had often completely disappeared by the time of radiotherapy planning.

During the seroma scoring process it was not possible to blind the scorer to the clips due to limitations of the planning software. To ensure the clips had not confounded the data, the CT images of a retrospective group without clips were tested and the findings indicated that the clips had not influenced the seroma scores. In the absence of seromas tumour location relied totally on the addition of surgical clips. Some authors have reported that electron boost fields would not have been adequately dosed at depth, while others have reported that the boost field parameters were modified when using clips (Benda et al., 2003; Coles et al., 2009). It is recommended that a study be carried out on this cohort of patients where the clips can be blinded, using special software. This could confirm planning target volume coverage to confirm the findings of Coles at al. (2009) and Benda et al. (2003).

The use of On board kV imaging to verify breast treatment is discussed as part of a literature review in chapter 5. The addition of surgically implanted clips has facilitated a new breast photon boost on treatment verification protocol at the NSCC (Department of Radiation Oncology) in March 2013. Non-coplanar kV on treatment verification images are acquired for the first 2 boost fractions and the surgically inserted clips are used as tumour surrogates for OBI matching. The ease of clip visualisation and shifts measured are currently under investigation as a feasibility study for 10 patients.

### 2.5 Conclusion

Medium titanium clips inserted at the time of surgery were accepted by the MDT at RNSH as an effective aid to improve the delineation of the breast boost CTV for breast radiotherapy patients. This clip based protocol which was introduced for all early stage breast
radiotherapy patients ensures not only for accurate CTV delineation but for accurate tumour bed treatment verification a necessity for all boost treatments and partial breast irradiation techniques. This protocol will also enable the NSCC to take part in clinical trials requiring accurate breast CTV delineation and verification.
CHAPTER 3.

The Influence of Time on Clinical Target Volumes for Breast Cancer Radiotherapy

3.1 Introduction

Over the last 20 years breast conservation surgery has largely supplanted whole mastectomy for early stage breast cancer treatment. This has taken the form of a surgical lumpectomy followed by whole breast irradiation and a boost to the tumour bed as reported in two large randomized trials (Fisher et al., 2002, Bartelink et al., 2007). The benefit of improved local control by boosting the tumour bed for early stage breast cancer patients has been well documented (Bartelink et al., 2001; Bartelink et al., 2007; Romestaing et al., 1997). Boost treatment to the breast using external beam radiotherapy can be delivered either sequentially or as a simultaneous integrated boost (SIB) (Hurkmans et al., 2006). In the recently developed practice of accelerated partial breast irradiation (APBI) for early stage breast cancer, the hypo fractionated dose is delivered to a target volume that is closely related to the size and shape of the surgical cavity, producing equivalent recurrence rates to whole breast irradiation followed by boost (Baglan et al., 2003; Polgár et al., 2004; Smith et al., 2009). Tissue at risk of recurrence should be covered by optimum CTVs. In the ICRU 62 report (ICRU, 1999), the boost CTV is defined by the excision cavity, seroma and surgical clips as seen on CT. The CTV is then expanded by a fixed margin to create the planning target volume (PTV). As the planning CT is a “snap shot in time” of the size and shape of the breast tissue, any change in the breast CTV over time from surgery to the completion of radiotherapy has the potential to lead to over or under dosing of healthy tissue.

In the past the boost CTV was defined by clinical landmarks and the surgical scar, which has led to over treatment of uninvolved tissues while at the same time under dosing tissues that are at risk of recurrence (Benda et al., 2003; Denham et al., 1991; Machtay et al., 1994).
Researchers have investigated whether the CTV could be defined consistently, reporting large inter observer variability in the delineation of the tumour bed (Landis et al., 2007; Li et al.; Petersen et al., 2007; Struikmans et al., 2005). However, CT has improved localisation by as much as 80% (Messer et al., 1997) and researchers have demonstrated improved PTV boost coverage using CT-based delineation (Hansen et al., 2012). The use of a CT-scan for delineation and treatment planning has led to an increase of the irradiated boost volume by a factor of 1.5-1.8 compared to conventional simulator-based plans (Al Uwini et al., 2009).

One method of defining the CTV that has improved tumour bed voluming (Hepel et al., 2009; Oh et al., 2006; Weed et al., 2004) is the placement of surgical clips at the edges of the cavity at the time of surgery (Bedwinek, 1993; Deniaud-Alexandre et al., 2001; Kirova et al., 2010; Weed et al., 2004). Kirova et al. (2008) recommended a multidisciplinary approach to tumour bed localisation and Coles et al. (2009) recommend inserting 6 titanium clips at the time of surgery to reduce intra and inter observer variability of tumour bed localisation. Boersma et al. (2012) also found the delineation of smaller and more consistent CTVs by using pre-operative CT’s with clinical guidelines.

Traditionally within our department a planning CT is acquired before the first fraction of radiotherapy, which is used to delineate the boost CTV. This works well when the size and shape of the tumour volume does not greatly change over time. A second scan can be acquired during radiotherapy if the first boost volume is deemed too large. This second scan would then be used to re-plan the patient’s remaining course of treatment, in a simple form of adaptive radiotherapy. The use of adaptive radiotherapy planning protocols (ART) is under investigation (Hurkmans et al., 2012), and Yang et al. (2010) have suggested that cone beam computer tomography (CBCT) might also be useful for monitoring boost volume reduction, but as yet this has not been accepted as routine practice.

Shrinkage of the boost CTV has been investigated by other researchers (Hurkmans, Admiraal, van der Sangen, & Dijkmans, 2009; Kim et al.; Oh et al., 2006; Petersen et al.,
Since the aim of radiotherapy is to treat as little healthy tissue as possible, the images used for treatment planning should be taken when the CTV is at its smallest and most stable to avoid both over-dosage and potential future replanning. When developing ART protocols for SIB techniques, clinicians need to take into account these changing boost CTVs. Alderstein et al. (2011) recommended when using a SIB technique, to replan halfway through a course of treatment as this adaptive technique produced a dosimetric advantage for patients with large seromas.

When relying on the seroma alone to define the boost CTV there is uncertainty on the part of the radiation oncologist. Over time, the interface between seroma and breast tissue is difficult to visualise as the seroma becomes re-absorbed. This is of particular importance when patients are undergoing chemotherapy prior to irradiation, due to the longer time frame to treatment. A clip based CTV delineation program is a necessity for these patients to ensure consistent CTV delineation. Strauss et al. (2010), discovered that those patients who had chemotherapy prior to radiotherapy had smaller boost volumes treated than those having radiotherapy after surgery.

Within our institution, before introducing complex APBI and SIB techniques utilising clip based CTV, we felt it was important to investigate boost CTV changes from surgery to the completion of radiotherapy. The aim of this study was to establish the best time to CT plan patients in terms of stable CTVs for those undergoing radiotherapy alone as well as those having radiotherapy delayed due to chemotherapy.

### 3.2 Methods and materials

#### 3.2.1 Patient group

This ethics board approved study (Northern Sydney Health Network HREC protocol No:1003-78M) recruited 42 women who received treatment between September 2010 and December 2011. Participants were eligible if they had histologically defined early stage
breast cancer with T1-T2 staging and were post-menopausal or over 40 years of age. Due to recruitment issues, recruitment was ceased after 14 months, with a final cohort of forty two subjects. Of these patients, 15 were required to have chemotherapy prior to radiotherapy (Chemo/RT) and 27 were having radiotherapy alone (RT/alone) post-surgery. Patients who have more aggressive disease markers often undergo up to 6 months of chemotherapy. Within our referred population many of these women were often excluded on the basis of age or menopausal status. The combinations of study exclusion criteria and candidature time limits limited the Chemo/RT cohort to 15 study patients. As with any statistical test even with small sample sizes, significance can be reached, suggesting that the effect is large enough to be clinically relevant.

These patients all underwent lumpectomy surgery in the Northern Sydney Central Coast catchment area in both public and private institutions and their radiotherapy was carried out at The Northern Sydney Cancer Centre (Royal North Shore Hospital), Australia. Four surgical clips were placed around the tumour bed as follows: medial, lateral, superior and inferior and one clip was fixed deep to the pectoral fascia. These clips were used to aid in accurate consistent CTV delineation (see Chapter 2). The 15 subjects undergoing chemotherapy (Chemo/RT) were scanned 2-3 weeks post-surgery. A second scan, which is normally the one that is used for radiotherapy planning, was taken at the completion of chemotherapy, approximately two weeks prior to the commencement of radiotherapy. This Chemo/RT cohort had a third scan during radiotherapy at 40 Gy, for a total of 3 CT scans. The radiotherapy alone (RT/alone) cohort had only 2 scans, the first 2-3 weeks post-surgery and the second taken during radiotherapy at 40 Gy, as per normal protocol (see study schema Figure 3.1).
Figure 3.1 Study Schema

#Radiotherapy (RT), Chemo (Chemotherapy)

Wks = weeks
3.2.2 Clinical target volume delineation and analysis

Planning CTs were taken in the treatment position on a CIVCO Medical Solutions Posi board (Civco Medical Solutions, Orange City, Iowa, USA) inclined at a $5^\circ$ angle using a GE Lightspeed RT CT (GE Healthcare USA) with 3mm slice thickness. Scans encompassed the whole breast, extending superiorly to include the supra-clavicle margin. Standardised CTV delineation (see Chapter 2) was performed using 4-5 titanium clips placed at the extent of the tumour cavity and volumes were delineated by three trained (see Chapter 2) breast radiation oncologists (RO) using the Varian Eclipse planning system V10.

The boost CTV was defined using the seroma where it was clearly visible, surgical information, and surgical clips. Seroma visibility was scored using the British Columbia Visualisation Score (Petersen et al., 2007) and where delineation was difficult to interpret, a second observer checked the contouring (see chapter 2).

The RO outlined the boost CTV on each CT data set (see Figure 3.1 for the timing of these scans). An example of the delineated boost CTV for one subject is shown in Figure 3.2 below. These volumes were completed at different time points but superimposed onto the last CT data set. The matching method used for CT fusion were bones, sternum, vertebrae, and ribs as the primary match method with the patient’s breast contour and pectoralis clip as secondary matching tools.
Figure 3.2 Example Overlayed CTV 1, 2, 3 for Chemo/RT cohort

CTV1 Pink, CTV 2 Green planning scan. CTV 3 Blue. at 40 Gy

Each time a CT was acquired and delineated the volumetric size of the CTV in cm$^3$ was measured and volumetric changes were recorded. Statistical analyses were carried out to quantify the CTV changes and to test whether patients undergoing chemotherapy had a different rate of CTV reduction compared to those having only radiotherapy post-surgery. The data was analysed using the statistical package STATA Version 11 (StataCorp LP). CTV size differences were compared between each CT time point within each cohort and between cohorts using the Wilcoxon rank sum test (significance value of p<0.05). It was hypothesised that there would be a significant rate of CTV change between CT1 and CT2 for each cohort but no significant rate of change between CT2 and CT3 for cohort 2. The Spearman Rho Coefficient was used to test the rates of CTV change (p< 0.05).
The correlation between initial CTV volumes for both groups and rate of CTV reduction was plotted against the subjects initial CTV to investigate if there is a relationship between CTV change and initial CTV post-surgery.

3.3 Results

3.3.1 Subject characteristics
The subject characteristics are shown in Table 3.1. A total of 42 early stage breast radiotherapy participants were recruited. Of these, 27 were recruited into RT/alone (cohort 1) and had surgery followed by radiotherapy. The remaining 15 subjects in Chemo/RT (cohort 2), had surgery, chemotherapy and then radiotherapy. The median days elapsed from surgery to the first CT scan for each cohort was 18 and 25 days respectively. The median time that elapsed between surgery to the second scan for the RT/alone cohort was 68 days while for the Chemo/RT cohort it was 126 days. Chemotherapy is delivered over 3-4 months, hence the large time difference to the second scan for the two cohorts. The Chemo/RT cohort also had a third scan completed during radiotherapy, at 40 Gy, at a medium of 161 days post-surgery.
**Table 3.1 Subject characteristics**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>RT/ alone n=27</th>
<th>Chemo/RT n=15</th>
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<tr>
<td><strong>Age at Surgery (years)</strong></td>
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<tr>
<td>Median (SD)</td>
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<td>65 (11)</td>
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<tr>
<td>Range</td>
<td>n/a</td>
<td>137-228</td>
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</tbody>
</table>
A clip-based protocol had been implemented previously (see Chapter 2). This was shown to improve visibility of the CTV even in the absence of a seroma, and for this volume change investigation enabled consistent CTV delineation by the Radiation Oncologists.

3.3.2 Elapsed time, dose and CTV changes

The first CT performed for each cohort (CT1) was completed at similar median time points post-surgery (25 median days RT/alone and 18 days Chemo/RT cohort) with all subjects less than 5.3 weeks. There was no significant difference (p=0.08) between the initial mean CTV for each cohort: RT alone: mean 40 cm$^3$ (SD 39), median 25 cm$^3$ (range 6-186 cm$^3$); and Chemo/RT: at 61 cm$^3$ (SD 37), median 54 cm$^3$ (range 4-118 cm$^3$). The second CT scans (CT2) 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 (See Table 3.1 and Figure 3.1). As indicated in Figure 3.1 both cohorts had a CT scan taken at 40 Gy. For the Chemo/RT cohort this was a third CT scan (CT3).

There was no significant difference (p=0.89) between the CTVs for the two cohorts at 40 Gy: RT/alone: mean 22 cm$^3$ (SD 26), median 15 cm$^3$ (range 2-121 cm$^3$); Chemo/RT: mean 20 cm$^3$ (SD 25), median 14 cm$^3$ (range 7-110 cm$^3$). For the RT/alone cohort, there was a significant reduction in CTV (p=0.01) from CT1: mean 40 cm$^3$ (SD 39); to CT2 at 40 Gy: mean 22 cm$^3$ (SD 26). This represents a mean volumetric change of 38.4% (see Table 3.2 and Figure 3.3).
Figure 3.3 demonstrates that some patients in the RT/alone cohort had large volume reductions although most had relatively small changes.

![Cohort 1- RT Alone](image)

**Figure 3.3 Change in volumes between CT1 and CT2 for the RT alone subjects**

Figure 3.4 demonstrates the volume reductions measured for each patient at each scanned time point for the Chemo/RT cohort. For the majority of patients there are large differences in the volumes measured between the first scan and the remaining two scans, with very little difference in the measured volumes between CT2 and CT3. Three patients at random time points had slightly larger CTV2 volumes measured than CTV1. Of these, patient 5 had a minor increase of 2 cm$^3$ and patients 7 and 14 had post-operative complications resulting in swelling. Four patients had large volume reductions between CTV1 and CTV2. Of these, patients 1, 10 and 17 had large initial seromas (84 cm$^3$, 123 cm$^3$, and 186 cm$^3$). Patient 20 had an early CT at 12 days post-surgery so less wound healing was likely to have occurred.
Figure 3.4 Changes in volumes between CT1-CT2 and CT3 for the Chemo/RT subjects.

In the Chemo/RT cohort, with an increased time delay of 4-6 months for chemotherapy, there was a significant reduction in volumes between CT1: mean 61 cm$^3$ (SD 37) and CT2: mean 24 cm$^3$, (SD 22), (p=0.01). There was no significant reduction in volume between CT2: mean 24 cm$^3$ (SD 22) and CT3 at 40 Gy: mean 20 cm$^3$ (SD 25), (p=0.89). Hence, with the chemotherapy related delay there is a significantly lower rate of change of CTV for the second phase of treatment with CT1-CT2 (43.6%) and CT2-CT3 (15.7%) (p=0.019) (see Table 3.2).
<table>
<thead>
<tr>
<th>Time elapsed from surgery to scan (days)</th>
<th>Volumetric change cc (% change)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>Chemo/RT#, CT1 to CT2</td>
<td>15</td>
<td>132</td>
</tr>
<tr>
<td>Chemo/RT#*, CT2 to CT3 (at 40 Gy)</td>
<td>15</td>
<td>174</td>
</tr>
<tr>
<td>Chemo/RT#, CT1 to CT3 (at 40 Gy)</td>
<td>15</td>
<td>174</td>
</tr>
<tr>
<td>RT alone*, CT1 to CT2 (at 40 Gy)</td>
<td>27</td>
<td>66</td>
</tr>
<tr>
<td>All subjects CT1 to CT2</td>
<td>42</td>
<td>89</td>
</tr>
</tbody>
</table>

* = Patients receiving RT alone

#= Patients receiving chemotherapy followed by RT

†= significant at the p<0.05 level
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, \( p > 0.05 \)). Most subjects in each group had an initial CTV \( \leq 50 \text{ cm}^3 \) and Figure 3.5 clearly shows the unpredictability of volume change for these patients. Of the 15 subjects with a CTV >50cm\(^3\), eleven (73%) had a volume reduction >50%. The pattern shown in Figure 3.5 demonstrates that large volume changes would be expected for patients with an initial volume >50 cm\(^3\), but greater numbers of subjects would be required to verify the significance of this finding.

![Figure 3.5 Relationship between initial volume and volumetric reduction (combined groups)](image)

**3.4 Discussion**

In radical radiotherapy for breast cancer, the presence of a changing CTV will have an impact on the accurate delivery of breast boost radiotherapy. Variability of the CTV is of even greater importance when using treatment techniques such as those that irradiate smaller
partial breast volumes or when using a simultaneous integrated boost (SIB) technique. As far as we are aware this is the first prospective volume change study which delineated the CTV using both seroma and surgical clips as standard practice for study patients. Two patients at the beginning of the study failed to have clips placed during surgery (chapter 2 pages 32). Their seroma scores at the time of the first scan and the ability of the RO to consistently delineate the CTV on successive CT scans were considered justification for inclusion in the volume data analysis. Some researchers have suggested that clips aid the RO in CTV delineation on CT. This is of particular importance for those patients who have undergone chemotherapy prior to irradiation where, due to the longer time delay to radiotherapy, the seroma becomes undetectable on CT. Patients undergoing chemotherapy have less favorable disease markers and often require more extensive surgery. This could explain why the subjects in Chemo/RT cohort had consistently larger CTVs recorded after just 2-3 weeks post-surgery compared to those only requiring radiotherapy, although these CTV values were not significantly different (p=0.08).

Our newly implemented clip based tumour bed localisation procedure (see Chapter 2) has enabled the characterisation of volumetric changes of the post lumpectomy CTV. Similarly to other investigators, we found that breast CTVs can change dramatically with time from initial surgery (Hurkmans et al., 2009; Jacobson et al., 2006; Kader et al., 2008; Oh et al., 2006; Prendergast et al., 2009; Tersteeg et al., 2009; T. I. J. Yang et al., 2010). However, we have also found that most CTV shrinkage (38.4%) occurs by a median of 68 days, as demonstrated by the RT/alone cohort. The Chemo/RT cohort with the large time period to CT (overall median 126 days), showed a decrease in the CTV volume of 43.6% (see Table 3.2). There is a significantly smaller reduction in volume (p=0.018) from CT2 to CT3 for the Chemo/RT group compared with CT1 to CT2 for this group, showing slower volume reduction with time from surgery.

The significant reduction in volume for the Chemo/RT group at 40 Gy compared with the RT/alone group at 40 Gy (see Table 3.2) must relate either to the extra time delay
experienced or to the chemotherapy, or to a combination of the two. As both groups received the same radiation dose, no relationship can be deduced between radiation dose and CTV shrinkage.

Strauss et al. (2010), for 29 patients who received chemotherapy before radiotherapy in spite of reporting larger lumpectomy specimens for chemotherapy patients, found consistently small (<10 cm$^3$) volumes irradiated when radiotherapy was delayed for chemotherapy. He also suggested this was due to the increased time delay or perhaps the chemotherapy itself. Our findings with small numbers of 15 patients supports the time delay theory, suggesting that after 9 weeks post-surgery, with or without the addition of chemotherapy, small CTVs are more likely. Regardless of the size of the initial CTV, the rate of volume shrinkage was similar.

Kim et al. (2008) demonstrated large outlined volumes initially as the seroma fills with fluid less than 2-4 weeks post-surgery, then dramatic shrinkage. Similarly, Yang (2010) and Kader (2008) discovered a significant linear regression between seroma volume and time interval after surgery up to and including 8 weeks, with no significant relationship after this time. We also found, for the RT/alone cohort, that when the CT is taken in the first 9 weeks after surgery large volume reductions are seen. It appears that as long as there is sufficient post-surgical wound healing, the addition of chemotherapy does not produce significantly greater volume reductions. Assuming that stable small volumes are preferable for enabling consistent dose coverage, our research suggests that if volumes do not change significantly after 9 weeks post-surgery then there is little value in rescanning at 40 Gy for this group.

Researchers suggest that time delay from surgery to radiotherapy should be as short as reasonably possible (Chen et al., 2008; Hébert-Croteau et al., 2004; Huang et al., 2003), with Stefoski et al (2004) reporting that surgery to radiotherapy intervals of greater than 9 weeks had a trend towards an increased relative risk of death. On the other hand, Borger et al. (1994) reported that for each increase in irradiated volume of 100 cm$^3$ a fourfold increase in
risk of fibrosis was observed. Thus, in order to reduce the irradiated volume and keep it relatively stable for those patients having radiotherapy immediately after surgery, while allowing for planning time frames, the planning CT should be performed as late as possible post-surgery (approx. 6-7 weeks) and the patient should commence radiotherapy no later than 9 weeks post-surgery. This allows the CTV to be at its most stable for radiotherapy, but also provides adequate time to carry out the pre-treatment planning CT. In contrast, Arcangeli et al. (2006) reported that radiotherapy after chemotherapy for node negative patients could be delayed by up to 7 months. As our data indicates, planning CT scans performed after chemotherapy is in most cases sufficient to produce small stable CTVs.

The introduction of a simultaneous integrated boost technique can be hampered by substantial reductions in CTVs. Alderstein et al. (2011) suggested rescanning during radiation treatment to adapt the treatment plan to these changing volumes. They concluded that patients with initial seromas ≥40 cm\(^3\) should be monitored and those patients who have a ≥20 cm\(^3\) reduction in the first four weeks should be rescanned. In our study, 11 subjects who had initial volumes ≥50 cm\(^3\) at CT1 had large volume reductions recorded at their subsequent CT2 scan. The pattern shown in Figure 3.5 demonstrates that for those with initial volume ≥50 cm\(^3\) rescanning is recommended as large volume changes for these would be expected. However, increased numbers of subjects would be required to verify this significance.

All our subjects who were scanned between 7-9 weeks (CT2) post-surgery had volumes ≤30 cm\(^3\). Hurkmans et al. (2012) designed and tested an adaptive radiotherapy technique requiring only those patients to be rescanned for planning who had volumes ≥30 cm\(^3\) and /or those whose initial scan was performed ≤30 days post-surgery. Based on their criteria, with a large sample size of 1274 patients, only 9% of patients needed a second CT scan. Using Hurkmans’ criteria very few of our patients would have required replanning.
We therefore recommend that patients having radiotherapy post-surgery receive their planning CT as late as possible while still ensuring they commence treatment by 9 weeks following surgery.

3.5 Conclusion

This research has demonstrated that following surgery, patients receiving chemotherapy and/or radiotherapy experience significant breast boost CTV reductions post-surgery and during radiotherapy. It appears that volume reduction has little relationship to either radiotherapy or chemotherapy, and is more a result of time given for post-surgical healing. CTVs for both groups become relatively stable after 9 weeks post-surgery. Due to planning time frame constraints, planning CT scans should therefore be performed between 6-7 weeks after surgery, allowing treatment to commence within the next several weeks. When introducing treatment techniques that particularly require stable CTVs (SIB, APBI) a second CT should be performed for patients whose initial CTV is ≥50 cm³, as large volume reductions for this group could be expected.
CHAPTER 4.

The Role of On Board KV Imaging and kV Cone-beam CT for Treatment Verification and Guided Radiation Therapy of the Breast: A Systematic Review

4.1 Introduction

Breast cancer is the second most common form of cancer affecting women internationally, accounting for 15.3% of cancer related deaths in 2006 (Yarnold, 2009). As radiotherapy is an important treatment option, accurate treatment delivery is essential to deliver the required dose and improving treatment targeting and delivery may facilitate dose escalation. Many factors need to be considered to ensure accurate localisation of the treatment area. These factors include: patient stability, positioning, breathing motion, and contour changes of the breast. Factors that influence the ability to visualise clinical target volumes (CTVs) are image quality and/or whether three dimensional (3D) or two dimensional (2D) images are required. Orthogonal 2D kilovoltage (kV) images allow isocentre verification, but 3D images such as those produced by Cone Beam Computer Tomography (CBCT) enable internal structures and external patient contours to be visualised.

Image guided radiotherapy (IGRT) can be used daily to improve localisation, patient positioning and external beam alignment in radiotherapy, allowing online matching and adjustments to a tolerance of 0 mm. IGRT can use several different imaging modalities including optical tracking methods (Bert et al., 2006; Chang et al., 2012), ultrasound (Chadha, Young, Geraghty, Masino, & Harrison, 2011; Smitt, Birdwell, & Goffinet, 2001), kV CBCT or megavoltage (MV) CBCT (Pouliot et al., 2005). kV CBCT has been successfully implemented for clinical use, for tumour sites such as prostate and lung (Jaffray, Siewerdsen, Wong, & Martinez, 2002; Purdie et al., 2007; Smitsmans et al., 2005), but has been slow in being implemented widely for breast radiotherapy treatment verification.
IGRT has the potential to facilitate planning target margin reductions. Target volumes for treatment are produced by definition of the CTV by the radiation oncologist at the time of planning CT, where treatment margins are added around the CTV to produce a planning target volume (PTV). This margin accounts for set up uncertainty and can be potentially reduced by using on treatment IGRT correction protocols.

For many years whole breast irradiation (WBI) following breast conserving surgery has been delivered to reduce the risk of recurrence in the affected breast (Clark et al., 1996; Fisher et al., 2002). An additional boost to the tumour bed achieves a further decrease in local recurrence (Bartelink et al., 2001; Romestaing et al., 1997). Over the last decade there have been a number of advances in treatment delivery using techniques such as intensity modulated radiotherapy (IMRT), partial breast irradiation (PBI), and accelerated partial breast irradiation (APBI). IMRT has demonstrated reductions in radiotherapy side effects and improvements in dose uniformity for breast cancer patients (Harsolia et al., 2007; Vicini et al., 2002). PBI is a radiotherapy technique that localises treatment to the tumour bed and treats only a small volume. APBI is also being investigated (Smith et al., 2009), and is a technique that has the advantage of not only reducing dose to the entire breast but also decreasing fractionated delivery regimes for patients.

For many years setup verification for breast cancer treatment has involved tangential electronic portal images (EPIs) that are routinely compared to digitally reconstructed radiographs (DRRs) (van der Laan et al., 2010). Relying on bony anatomy as a surrogate for breast location, setup errors using a 5 mm tolerance protocol have been measured with this MV verification method (Michalski, Atyeo, Cox, & Rinks, 2012). Michalski et al., (2012) suggested that due to large maximum systematic inter- and intra-fraction variations observed in individual patients, there is a need for daily imaging before introducing modulated techniques and partial breast irradiation. kV imaging is now being used to minimize the effect of inter-fraction motion through daily analysis of images and immediate online correction protocols to correct set-up error. The major advantages of kV based imaging
protocols over EPIDs are improvements in image quality and contrast, along with reduced radiation dose (Lawson et al., 2008). This technology has been widely accepted as a tool to reduce setup errors and improve tumour site localisation for many tumours (Jaffray, 2007). The kV imaging technology consists of an X-ray tube mounted orthogonally to the treatment beam with a detector mounted on the other side. This On Board Imaging (OBI) device has the advantage of being able to rotate around the patient to produce a 3D CBCT rather than a 2D representation of a patient’s anatomy. kV CBCT has become the imaging device of choice for many tumour sites (Lawson et al., 2008), but literature is scarce on using kV orthogonal or kV CBCT imaging for early stage breast cancer radiotherapy.

There are many methods of measuring the accuracy of breast cancer radiotherapy treatment. On treatment imaging methods include: utilising skin marks, bone, soft tissue matching and radiographic markers such as surgical clips. Skin marks are variable daily and therefore not very accurate. Image matching using bones has greater stability than skin and has good contrast on kV imaging modalities, but assumes a constant relationship between the breast PTV and the underlying bones. However, perhaps for the most reliable verification method of the tumour bed for breast RT would be to use a combination of tumour surrogates: the surgical lumpectomy cavity (a fluid filled post-surgical cavity known as the seroma) and surgical clips (placed around this cavity). Recently Yang T.I. et al. (2010) verified that the seroma could be visualised on kV CBCT and thus has the potential to be used for IGRT.

There are several challenges for users of kV imaging and particularly kV CBCT for breast radiotherapy. The breast is a mobile structure and the arm position of patients can be difficult to reproduce, so different immobilisation devices have been used to increase patient comfort and stability (Mitine et al., 1991; Nalder, Bidmead, Mubata, Tait, & Beardmore, 2001; Thilmann et al., 1998). Extension of the patient’s arms, laterality of the breast treatment region and stabilisation devices all pose a collision risk between the gantry and the patient. Small fields of view are often produced when using kV CBCT which can decrease image quality. Radiation dose must also be kept to a minimum during kV CBCT because of the
secondary risk of cancers induced at low levels of radiation dose (Preston et al., 2002). This is particularly important for breast cancer patients, as the previously used tangential EPI’s did not irradiate the contralateral breast.

Both 2D and 3D images are produced for EBRT on a linear accelerator using an OBI. The OBI extends from either side of the linear accelerator treatment head (at an angle of 90°) and consists of a kV X ray tube and detector. The linear accelerator can rotate from -180° to +180° to produce both planar kV images and kV CBCT. The OBI produces the X-rays to enable on treatment breast position verification and image guidance for the treatment of early stage breast cancer. See Figure 4.1 below.

![Varian Linear Accelerator with On Board Imaging (OBI) arms parallel extending from the gantry of the machine.](image)

In this review, kV imaging of the breast is discussed in terms of its ability to produce good quality 2D and 3D CBCT images. The acquisition of the images also relies upon the equipment being free of collision risk and the registration of these images needs to be quick
and accurate. This review will evaluate research using both kV orthogonal and kV CBCT images to verify treatment setup errors. As discussed in chapter 2, surgical clips and gold seed fiducials are frequently present in the tumour bed to ensure accurate CTV visualisation, so it is important to discuss the use of kV imaging to visualise these tumour surrogates. This information will inform radiotherapy departments’ decisions to implement new complex treatment verification techniques for breast cancer patients. This systematic review aims to collate literature available on the use of 2D and 3D kV imaging using an OBI and to define how different kV imaging can be used to verify breast radiotherapy.

4.2 Methodology

The methodology for this review was based on the Cochrane Handbook of Systematic Reviews of Interventions (Higgins, 2009). A systematic search of the literature was conducted using Medline, Cinhal, Embase, Scopus and Web of Science. Studies had to be published after 1990 and prior to December 2012 and were limited to women having radical radiation therapy to the breast in the supine or prone position using tangential or intensity modulated radiotherapy techniques. Studies needed to have described the effectiveness of the use of kV imaging and/or kV CBCT, in terms of measuring reproducibility (the ability to accurately treat the patient over successive fractions) and treatment verification (ensuring that daily treatment is delivered to the prescribed location). In this review articles on kV imaging of the breast are grouped into tables in terms of image quality, setup error and kV imaging using tumour surrogates.

Inclusion criteria are listed in table 4.1. Studies needed to describe (in addition to inclusion categories found in Table 4.1) the method of on treatment field verification using Image Guided Radiotherapy techniques for breast cancer treatment using kV Imaging devices with or without the use of commercially available fiducial markers.

Studies were excluded if they used optical guidance systems, kV cone-beam tomosynthesis, kV imagers on rails and the helical tomotherapy solution MVCT. This systematic review
only reviews kV imaging using commercially available kV OBI integrated systems which are readily available to most radiotherapy departments within Australia. Studies using MV imaging devices such as electronic portal imaging devices (EPID) were also excluded as they do not allow the same image quality as that of kV imaging and the production of good quality 3D CBCT images. Phantom studies investigating the use and visualisation of clips using kV imaging are described, these are articles discussing image quality and dose.

**Table 4.1 Criteria for selecting studies in this review**

<table>
<thead>
<tr>
<th>Types of Studies</th>
<th>English Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human and phantom studies</td>
<td></td>
</tr>
<tr>
<td>Tangential, IMRT and/or APBI techniques</td>
<td></td>
</tr>
<tr>
<td>Published articles in peer reviewed journals</td>
<td></td>
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<td>Departmental QA</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Types of Participants</th>
<th>Females undergoing treatment for breast cancer with radical intent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast or chest wall irradiation</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Method of treatment verification</th>
<th>kV imaging devices with or without fiducial markers.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Types of outcomes</th>
<th>Evidence available to inform the implementation of an expert IGRT protocol for breast radiotherapy.</th>
</tr>
</thead>
</table>

### 4.2.1 Search strategy

A literature search was conducted from November 2010 to December 2012 using Medline, Cinhal, Embase, Scopus and Web of Science databases using the keywords listed in table 4.2. A total of 120 articles were identified and exported into Endnote™, a bibliographical software package used to manage the search results.
After duplicates were removed, articles were excluded based on their title and abstract review (using exclusion criteria as previously described). The full text of the remaining articles was reviewed and reference lists were hand searched for any other relevant articles. Replication of the search criteria was carried out by a second researcher (JC) to ensure inclusion of all relevant articles.

**Table 4.2 Keyword search**

<table>
<thead>
<tr>
<th>Terms related to on-treatment localisation or verification of radiotherapy in breast cancer using on-board kV imaging.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Radiation Therapy.</td>
</tr>
<tr>
<td>3. Radiotherapy.</td>
</tr>
<tr>
<td>4. 1 and 2 or 1 and 3.</td>
</tr>
<tr>
<td>5. image-guided radiotherapy.</td>
</tr>
<tr>
<td>6. kV imaging.</td>
</tr>
<tr>
<td>7. cone-beam CT.</td>
</tr>
</tbody>
</table>

**4.2.2 Analysis**

Articles that were included were placed into tabular form and analysed. This analysis was descriptive and where possible outcome measures were presented. Some articles had fewer than 10 subject data sets and were included in the study for completeness of the systematic review; however they are unlikely to be statistically valid. No two articles that were included measured the same parameters, so a meta-analysis could not be performed.

**4.2.3 Definition of Terms**

The term set up error in this document refers to the discrepancy between what is intended to be treated and the actual treatment position. Radiotherapy treatment set up errors can be random and systematic. Systematic error is an error that occurs with similar magnitude and direction on a regular basis. Systematic error may be due to such factors as the patient
relaxing as treatment progresses, incorrect set-up instructions and equipment inaccuracies, while random error is less predictable. The individual systematic error for an individual patient is the mean error over a course of treatment. Population systematic errors are reported as an indication of a spread of individual means with an average standard deviation. Random errors can occur anytime throughout the course of treatment and can vary each day in direction and magnitude (Van Herk, 2004). Random errors can be introduced by such factors as the introduction of a new patient stabilisation device and variable patient compliance. Setup error measured by a single image will have both a random and systematic component.

Inter fractional errors assess the correct patient setup with respect to the desired reference image from one fraction to the next and have both systematic and random components. Intra fraction movement is measured within one fraction of treatment. This movement may occur throughout the delivery of a single exposure or at any time during the delivery of a single treatment and is measured using displacements of the landmarks on the images recorded at certain intervals during the treatment fraction compared with the original CT image. This is often known as “real time imaging”. Only one article within this review reports intra fraction motion by comparing one matching method (bones) to another using gold seeds at a single time point during the treatment fraction (see table 4.3).

Systematic inter fraction error is the average variation in treatment position for a particular patient, calculated from all treatment verification images compared to their reference image, which is the planning CT (Hurkmans, Remeijer, Lebesque, & Mijnheer, 2001). The mean systematic error refers to the average error of all patients in a given study. Some authors define residual error as the error that remains once all corrections have been applied. Michalski et al. (2012) discussed the variety of ways of reporting errors and decided to use the term ‘average movement’ to describe error across a course of treatment.

Due to the great variability of reporting with small sample sizes and few similar studies to enable data pooling, this review has reported the studies in a tabulated descriptive manner.
4.3 Results

Of 120 articles that were originally identified (see Figure 4.2), 13 proceeded to full review. These articles are discussed in terms of themes related to kV imaging for breast cancer patients. Table 4.3 presents a summary of studies that have used kV imaging for determining setup accuracy and Table 4.4 summarises studies that used surrogates for on-treatment tumour bed localisation. Four studies that relate to image quality/phantom studies or the use of clips for treatment verification are discussed in the text. Table 4.5 presents studies that relate to possible implementation issues for kV imaging or kV CBCT.
Most breast studies using kV imaging had small sample sizes of fewer than 25 subjects, making their data difficult to interpret. Table 4.3 shows six studies where random and systematic errors of inter fraction motion have been reported, in three descriptive and three comparative studies.

Jain et al. (2009), White et al. (2007) and Lawson et al. (2008) described the role of kV imaging in the measurement of inter fraction motion during breast radiotherapy. All studies except Lawson et al. (2008) used kV CBCT imaging as an assessment tool. Lawson et al. (2008) used automatic co registration methods with kV orthogonal imaging and performed daily setup corrections using bony anatomy matched back to digitally reconstructed
radiographs (DRRs). White et al. (2007) followed up with a second kV CBCT after correction of patient localisation, to calculate ‘residual error’. All authors concluded that kV CBCT was no less accurate than EPIs or kV planar imaging, and that these were acceptable for routine use. White et al. (2007) assessed the role of kV CBCT for conventional skin mark setup error (Table 4.3) and determined there was good visibility of post-lumpectomy seromas. It must be noted that kV CBCT shifts were only actioned when a >3 mm shift was detected (White et al., 2007).

All authors reported errors for individual points, such as bony landmarks or fiducial markers, while kV CBCT offers the ability to visualise the structure as a 3D soft-tissue structure. This was recognised by White et al., (2007), Yue et al., (2011), Fatanuse et al., (2008) and Topolnjak et al., (2010), who found substantial differences between matching points and localisation with CBCT. Yue et al. (2011) reported intra fraction motion by comparing gold seed matching to that of bony anatomy. Although variations were noted in the magnitude of set up error kV CBCT appears useful for clinical subsets of patients, for those with large breasts or anatomical variations during treatment. Both White et al. (2007) and Fatanuse et al. (2008) reported doses of approximately 3c Gy per kV CBCT.
### Table 4.3 kV imaging errors in breast cancer patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample size</th>
<th>Purpose</th>
<th>Results (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jain et al.</td>
<td>10</td>
<td>Assess CBCT for inter fraction motion and dose homogeneity Match method skin and bones - descriptive</td>
<td>5.9(SD 3.9) Lat 2.3(SD 3.2 LG 2.8(SD 3.5) Vert</td>
</tr>
<tr>
<td>White et al.</td>
<td>20</td>
<td>CBCT for setup error and soft tissue matching Assessed the setup error based on conventional skin marks. - descriptive</td>
<td>Systematic errors detected using CBCT 2.7 Lat, 2.4 LG 1.7 Vert Random Errors 1.5 Lat, 1.5 LG, 1.6 Vert</td>
</tr>
<tr>
<td>Lawson et al.</td>
<td>25</td>
<td>Clinical experience with kV imaging for inter fraction motion - descriptive</td>
<td>Range of Shifts -2.0 to +2.2 Lat -1.9 to +4.3 LG -1.8 to +2.0 Vert</td>
</tr>
<tr>
<td>Yue et al.</td>
<td>21</td>
<td>CBCT comparison of matches using bony landmarks versus gold fiducials</td>
<td>Intra fraction motion detection 4.2 (SD2.3) fiducials 2.5 (SD2.6) bony matching</td>
</tr>
<tr>
<td>Fatunase et al.</td>
<td>10</td>
<td>Comparing 2-D kV/Mv registration to CBCT - comparison</td>
<td>Residual error: +3.0 Lat +4.0 Long +4.0 Vert</td>
</tr>
<tr>
<td>Topolnjak et al.</td>
<td>20</td>
<td>Quantify setup errors CBCT Vs EPID (bones matching)- comparison</td>
<td>EPID underestimates setup error 20-50% of the time.</td>
</tr>
</tbody>
</table>

*Standard Deviation (SD)
@ Lat (lateral), LG (longitudinal) and Vertical (Vert)
# Magnitude of Average movement
+ residual error (translational shifts after aligning the CBCT with the planning CT in the three major axis)
An Australian group which has published in this field, Willis et al. (2011) designed a kV non-orthogonal imaging system to verify APBI by matching surgical clips back to the original DRRs. If fewer than 4 clips were available, ribs were also used to aid in matching. After assessing their protocol, 17 patients were imaged using this system. The system was considered optimal in terms of image quality, clearance and dose. Surgical clips could be visualised and the images were performed at isocentre with minimal collision risk. Quick online automatic matching was reported, but additional training on the part of the treating Radiation therapist would be required to interpret these matched non orthogonal kV images.

Penninkhof et al. (2012) described the practical use of the the ‘No action level’ (eNAL) setup correction protocol for 80 patients with surgical placed clips. An eNAL correction protocol requires the patient to be imaged for the first three fractions with an average correction measurement applied on the fourth fraction. This is then repeated weekly. As with Willis et al. (2011), two non-coplanar kV images were acquired and matched to the planning DRRs. The researchers reported that the application of an eNAL on clip matching resulted in improved setup accuracies for both tumour bed and whole breast treatments.

Several authors discuss the use of CBCT in conjunction with soft tissue or clip based ‘on-treatment’ verification. Kim et al. (2007) presented an on-line verification procedure based on CBCT imaging of surgical clips for 10 patients in target based matching for APBI. Initially the patients were setup to lasers and skin marks, and then the first CBCT was taken and matched to clips on the planning CT. The second CBCT was completed and small residual errors were reported; thus CBCT matching using clips was feasible in reference to equipment, time and process. Table 4.4 reports the average magnitude of corrections and the residual errors detected using CBCT clip based matching. Donovan et al. (2012) assessed a CBCT treatment verification protocol on 38 surgically clipped breast boost patients. Yang et al., in 2010, investigated the use of CBCT for the monitoring of seroma reduction, the importance of which has been discussed as part of Chapter 4 of this thesis.
Table 4.4 The use of CBCT with or without Tumour surrogates

<table>
<thead>
<tr>
<th>Author</th>
<th>Purpose</th>
<th>Results (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (2007)</td>
<td>Using clips located on CBCT with the potential to decrease margins. The treatment couch is translated according to the shift in the clips’ centre of mass between the planning CT and CBCT</td>
<td>Average magnitude of clip based translocations was 7mm (SD2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Residual error magnitude 1.6mm (SD1.3)</td>
</tr>
<tr>
<td>Yang et al. (2010)</td>
<td>Comparing the use of CBCT to planning CT in reference to voluming.</td>
<td>Voluming agreement between CBCT and Planning CTs.</td>
</tr>
<tr>
<td>Donovan. (2012)</td>
<td>Assessed the implementation of CBCT for treatment verification breast boosts.</td>
<td>Systematic error was reduced from 3mm to 1.5 mm using a eNAL correction protocol.</td>
</tr>
</tbody>
</table>

The image quality of kV CBCT and kV orthogonal OBI was addressed by two groups. McBain et al., (2006) investigated the image quality of kV CBCT for 10 different sites and reported on the images taken for three breast cancer patients, stating that these produced clear resolution images approaching that of planning CTs. A phantom study by Ueltzhoffer et al. (2010) was used to analyse the image quality produced by the Varian OBI V1.4. They reported that acceptable image quality was produced by decreasing the mAs, with doses measured as low as 0.02 -1.6 cGy (full fan mode) and 0.6 -3.2 cGy (half-fan mode).

The remaining two studies by Thomas et al. (2009) and Buehler et al. (2009), identify the types of surgical clips that can be used for clip based online treatment verification using kV imaging. These authors found that medium titanium clips were affordable but can only be clearly visualised 55% of the time, while small tantalum clips are clearly visible 90% of the time but are three times the price. Buehler et al. (2009) reported difficulties visualising clips on orthogonal radiographs and recommended the use of CBCT to decrease artefacts.

In spite of the advantages of the improved image quality of orthogonal kV imaging and the 3D visualisation of soft tissue using kV CBCT, there have been challenges in the implementation of kV imaging for the breast. Some issues that require consideration when
implementing a kV based imaging protocol for the breast include: the dose delivered to the patient, the risk of equipment collision and the ease of accurate image co registration. A section of Table 4.5 reports whether authors have discussed any of these implementation issues. As discussed in Chapter 3, the size and shape of CTVs change over a course of treatment and these changes can be monitored using kV CBCT. Hence routine CBCTs performed as part of the treatment imaging protocol reduce the need to rescan the patient using a diagnostic quality planning CT.
Table 4.5 Articles that discuss doses, anatomy matching methods and seroma visualisation

<table>
<thead>
<tr>
<th>KV imaging Method</th>
<th>Author</th>
<th>Matched Method</th>
<th>Sample Size&gt;20</th>
<th>Seroma Visible</th>
<th>Surgical clips</th>
<th>Auto co-registration</th>
<th>Reported imaging dose to patient.</th>
<th>Safe to acquire at iso centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBCT</td>
<td>Jain et al. (2009)</td>
<td>Bones</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>White et al. (2007)</td>
<td>Lung/external contour</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Potential</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Kim et al. (2007)</td>
<td>Clips</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Topolnjak et al. (2010)</td>
<td>Sternum/ribs</td>
<td>Yes</td>
<td>Unknown</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Yang et al. (2010)</td>
<td>Unknown</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Donovan et al. (2012)</td>
<td>Clips</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>kV*</td>
<td>Yue et al. (2011)</td>
<td>Bony to gold fiducials</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Lawson et al. (2008)</td>
<td>Bony</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>kV* vs. CBCT</td>
<td>Fatunase et al. (2008)</td>
<td>Bones, then soft tissue</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No for both.</td>
</tr>
</tbody>
</table>

*orthogonal kV imaging
4.4 Discussion

This review describes how in room kV imaging systems have been introduced to improve treatment verification and treatment guidance for breast radiotherapy. Orthogonal EPIs (MV imaging) have been used for many years to verify a patient’s daily course of treatment, with setup errors measured consistently to a value of 5 mm (Michalski et al., 2012). However, with the introduction of treatment techniques such as SIB, IMRT and APBI, as well as changing CTVs, volumetric daily kV imaging becomes more important. kV imaging with its increased contrast and 3D capabilities is the preferred imaging method when implementing IGRT of the breast.

4.4.1 Selection of kV imaging method

When using on board kV imaging, a decision must be made to determine the purpose of this type of imager. An EPID enables field boundaries and the amount of lung to be detected within the field while the patient is being treated and is suitable for tangential beam field arrangements. However, in the case of the beamlet delivery technique that is used for IMRT, verification of the treatment field boundaries is no longer possible. kV imaging and kV CBCT allow verification of the isocentre and in the case of kV CBCT, internal soft tissue anatomy visualisation. kV CBCT is also useful for PTV localisation for APBI, as the target will not necessarily be close to the bony anatomy in the chest wall, making localisation with EPI difficult. Surgical tumour bed clips are difficult to visualise on EPI imaging. However, both Peninkhof et al. (2012) using kV non-orthogonal verification images and Donovan et al. (2012) using CBCT reported that kV visualisation of surgical clips could be routinely used to verify the whole breast and tumour bed for treatment. As discussed in Chapter 3, CTV can vary in size and shape from the beginning of radiotherapy to the end. Monitoring changing CTVs, as described by Yang et al. (2010), can be achieved with kV CBCT instead of requiring a patient reaching mid treatment to have a new planning CT.
4.4.2 Collision risks

The addition of the source detector arms (OBI arms) for kV CBCT poses collision risks with the patient who is lying supine on a slightly inclined board. The non-central location of the isocentre makes clearance with the linear accelerator even more problematic (Fatunase et al., 2008). The potential collision risk when imaging the breast might be one reason for the slow rate of uptake of this imaging modality by the general radiotherapy community. One way of overcoming this collision risk was explored by Willis et al. (2011) who used non-coplanar kV images, but this technique does not provide 3D soft tissue visualisation of internal structures. One clinical issue that is under investigation is adapting the CTV margins in response to shrinking or growing tumours using kV CBCT imaging protocols, enabling soft tissue monitoring (Hurkmans et al., 2012). Such ART procedures would not be able to be initiated using the non-coplanar kV imaging as discussed by Willis et al. (2011). In contrast, Donovan et al. (2012) overcame collision risks by pre defining simple constraints, by obtaining a single image and a treatment isocentre that was <8 cm from midline and a isocentre-couch distance <30cm.

The need to visualise internal structures for the use of APBI/ SIB or the need to monitor seroma changes might far outweigh the collision risks with OBI kV imagers. When the possibility of a geographic miss of the target is high as might be in the case for APBI, or in the case of changing CTVs (Chapter 3), the issues of the risk of collision with equipment must be overcome. To prevent the possibility of machine and patient collisions, breast kV CBCTs will usually not be acquired at the treatment isocentre but off-centre. Once the image has been acquired the patient is moved either manually or automatically back to the treatment isocentre before the correction shift is applied (Fatunase et al., 2008; Jain et al., 2009b; Kim et al., 2007). This process, whether manual or automatic, adds time and potential errors to the treatment verification process. The kV OBI detector field of view (FOV) for kV CBCT is limited in both the longitudinal and lateral directions. One way of overcoming a limited FOV when using kV orthogonal images is by displacing the detector.
to visualise specific anatomical structures. In the case of kV CBCT by placing a half bow-tie filter into the OBI detector mount an increased FOV is achieved in the longitudinal direction (Lai et al., 2009).

4.4.3 Image quality and contrast
Image quality and contrast are better with kV orthogonal image detectors than with MV EPI devices (Lawson et al., 2008). For kV CBCT, the images are reconstructed in a 3D volume, and the image quality could be variable depending on different reconstruction algorithms and the geometric setup and choices of beam parameters. Ueltzhoffer et al. (2010) and McBain (2006) describe clear image resolution when using kV imaging modalities, but they both suggest the need for organ specific sparing.

4.4.4 Imaging and dose
There is a wide variety of other imaging systems that can be used for IGRT of the breast. These include 3D ultrasound image guidance (Leonard et al., 1993) and optical tracking systems (Baroni et al., 2003; Bert et al., 2006; Chang et al., 2012; Miller, 2008). However, kV imaging is often the imaging modality of choice as the OBI kV imager is widely accessible and considered accurate as an imaging modality. There is a secondary risk of cancer at low dose radiation levels and care must be taken when introducing imaging dose (Preston et al., 2002). There is limited literature related to radiation exposure to breast cancer patients (Kan, Leung, Wong, & Lam, 2008), however, in the case of kV CBCT, the contralateral breast now receives increased doses and in the case of IGRT this could potentially occur daily. White et al. (2007) and Fatunase et al. (2008) reported imaging doses of approximately 3cGy per image.

Most recently Donovan et al., (2012) reported on the clinical implementation of CBCT for the verification of an SIB technique for breast patients. This patient cohort was treated on a Elekta linear accelerator and used kV CBCT IGRT to assess treatment verification The authors reported contralateral breast doses of approximately 2 mGy per scan (right breast)
and 12m Gy (left breast). The differences in contralateral breast dose is due to gantry rotation restrictions where the left limits the contralateral breast dose. Donovan and colleagues report that the right breast protocol used in this study exposes both breasts. Similarly Ueltzhoffer et al. (2010) using the reduced-arc offset imaging protocol on a Varian linear accelerator reported doses of 7.2m Gy to the ipsilateral breast and 0.2m Gy to the contralateral breast. Ueltzhoffer et al. (2010) and McBain et al. (2006) suggest that a reduction of dose to the contralateral breast can be achieved by decreasing the mAs administered when taking a kV image. This has the potential to decrease image quality, but by selecting appropriate start and stop angles and adjusting the mAs accordingly, good image quality can still be achieved using kV CBCT. More work is required in the accurate reporting of imaging doses for breast radiotherapy using commercially available kV CBCT devices.

### 4.4.5 Image registration

Once good image quality is achieved, the method of image registration needs to be decided. Should bones, soft tissue or tumour bed surrogates be used? The method used will partly depend on the main reason for the imaging. As discussed previously, EPIDs are sufficient for whole breast radiotherapy verification, but the use of kV CBCT provides full volumetric information including path length, contour variation, internal anatomy and internal tumour location utilising clips.

Lawson et al. (2008) demonstrated the use of daily kV imaging, matching bony anatomy back to planning digitally reconstructed radiographs (DRR’s). However Topalnjak et al. (2010) reported that EPIDs underestimate bony setup error and that CBCT has the added advantage of 3D soft tissue visualisation, and thus better co-registration. White et al. (2007) suggested that soft tissue CBCT co-registration was useful for large random errors for APBI.

The CBCT protocol implemented by Donovan et al. (2012) specifies limits on the plan isocentre distance from midline that enabled the same isocentre to be used for planning and
imaging. They commented that it was unlikely all pairs of six clips would be matched at each session due to possible deformations in the excision cavity. The 95% isodose line in addition to the tumour bed PTV as structures on the reference images were also used as matching structures.

4.4.6 Marker based matching and CTV monitoring
The PTV for partial breast irradiation consists of the surgical cavity plus a margin, resulting in small field sizes for treatment. Due to the tight margins used, small changes in the tumour cavity size or inter or intra-fraction motion could potentially produce over or under dosing of breast tissue. Yue et al. (2011) postulated that the seroma / marker based treatment verification approach would improve treatment accuracy and enable IGRT. As markers are easily visualised using kV imaging and can be a surrogate for the tumour position, this technique would be a better verification tool than matching to skin or bones. By visualising breast soft tissue markers rather than matching to skin or bones, and matching daily to these, there should be fewer inter fraction variations across a course of treatment. Donovan et al.(2012) suggested when using a marker based CBCT verification protocol that boost treatment margins potentially could be reduced to a 5 mm setup error margin.

Thomas et al. (2009) and Buehler et al. (2009)., identified appropriate tumour surrogate clips to be placed at the time of surgery. The location of these clips was not the focus of these papers, but it is clear that at least one clip was fixed to the underlying pectoralis muscle to ensure consistency among patients. The authors reported that surgical clips cannot be visualised using EPIDs and are also difficult at times to visualise on orthogonal kV images. This in part is due to imaging artefacts that can be produced due to bony structures such as the ribs lying close to the clips. In contrast, Willis et al. (2011) reported using non co planer kV imaging to visualise surgical clips and Penninkof et al.(2012) developed a treatment verification protocol utilising these clips that resulted in better setup accuracies for both the tumour bed and whole breast .Artefacts are also sometimes visualised from clips on kV CBCT; one solution to reduce these artefacts is to use incremental arc angles to produce the
kV CBCTs. Instead of matching directly to clips isodose lines can be transferred from the planning system to ensure clips are encompassed in the PTV. Donovan et al. (2012) imported the 95% isodose line from the planning system and ensured that this isodose line encompassed the clips.

Kim et al. (2007) and Yang et al. (2010) discuss the use of kV imaging protocols to accurately deliver APBI which requires accurate tumour localisation as well as on-treatment seroma monitoring. These report that kV imaging that allows internal anatomy visualisation, with its increased image contrast enhancing abilities and CBCT capability, is an attractive option to visualise seroma changes over time. The ability to monitor seroma changes during treatment has the potential to allow consistent on-treatment tumour dose coverage through adaptive radiotherapy (ART) planning techniques. The potential to adapt the plan to these changing planning volumes suggests that treatment margins could be reduced during a course of treatment. Kim et al. (2007) utilised kV CBCT to visualise tumour markers (clips). This online imaging protocol combined with corrections for breathing (intra fraction motion), changes in tumour cavity and other sources of error, has the potential to reduce the CTV to PTV margin from 1 cm to potentially 6mm.

The protocolled introduction of surgical clip insertion around the breast tumour bed cavity, described in Chapter 2, has led to the desire to use these clips for daily treatment verification. Hence this systematic review was used to assist development of a non-coplanar kV imaging protocol utilising surgical clips at the Northern Sydney Cancer Centre Department of Radiation Oncology. The implementation process of matching to surgical clips for boost irradiation utilising the new kV imaging method was under investigation in April 2013. Ultimately it is intended to move towards CBCT verification for IMRT-SIB.

4.5 Conclusion

For robust radiotherapy techniques such as the traditional two field tangential technique, MV imaging with current CTV-PTV margins of 10mm is adequate. kV imaging has an
advantage over MV imaging of lowering radiation doses and thus should be the preferred method for IGRT. To ensure accurate treatment delivery, kV imaging of the breast is necessary because of its increased image contrast, better image quality, tumour surrogate visualisation (clips). For new complex treatment techniques such as IMRT, SIB and APBI, where volumetric information is required, kV CBCT should be used. Although there has been some research conducted using kV OBI devices for treatment verification and IGRT for breast radiotherapy, further research is required to investigate their uses for adaptive radiotherapy and margin reduction.
CHAPTER 5

Discussion and Conclusion

Patients who undergo breast conserving therapy (BCT) require multimodality treatment involving surgery followed by radiotherapy (RT), or a combination of surgery, chemotherapy and radiotherapy. After the completion of surgery there is an initial healing period that takes place prior to the commencement of radiotherapy planning. Accurate definition of the CTV is crucial so it can be treated when it is at its smallest and at its most stable post-surgery. The issues of CTV stability and changing size are of particular relevance for newer techniques involving small volumes, such as APBI or SIB. Older techniques also are risky when the tumour bed is boosted with inadequate knowledge of its size and location.

There has been considerable material published since the commencement of this research that has investigated the size and shape changes of the breast boost CTV form surgery to the completion of radiotherapy. Much of this research relates to small changing CTVs and how these affect APBI or SIB treatment techniques. (Kim et al, 2010, Hurkmans et al, 2012).

The CTV for breast RT has historically been delineated in many ways including: scar based, surgical reporting, ultrasound and with CT / seroma (see Chapter 1 page 9). Researchers, however, have reported the inaccuracies of using clinical delineation methods such as pre-operative imaging, clinical palpation and the location of the surgical scar (Bedwinek, 1993; Denham et al., 1991; Harrington et al., 1996; Krawczyk & Engel, 1999; Machtay et al., 1994). Many of these have also demonstrated considerable inter observer variability (Landis et al., 2007; Li et al., 2009).

With the increased use of oncoplastic surgery, and when no seroma is present, surgical clips provide increased radiographic information that can be used by the RO for CTV delineation purposes. Surgical clip CTV delineation is recommended by surgeons in the UK protocol for
the IMPORT trial (Coles et al., 2009). The issues related to the use of surgical clip CTV localisation are discussed in chapter 2, page 33.

The primary purpose of this research was to investigate the value of surgical clips in the breast cancer surgical tumour bed. This was done by (1) the introduction of an evidence-based protocol for the insertion of clips and an evaluation of their effect on CTV delineation (Chapter 2 pp. 22 to 35), (2) the investigation of the characterisation of changing CTVs post-surgery and during radiotherapy within two distinct cohorts was made possible by visualising the surgical clips (Chapter 3 pp. 37 to 54), and (3) evaluating the application of on-treatment kV imaging using surgical clips to delineate the CTV (Chapter 4 55 to 76).

5.1 Introduction of surgical clip CTV delineation

In 2010 the decision was made to improve breast boost localisation for radiotherapy in preparation to take part in international clinical trials at the Northern Sydney Cancer Centre Department of Radiation Oncology Royal North Shore Hospital (RNSH). This procedure utilised radiopaque surgical clips placed around the tumour cavity using a standard surgical placement protocol. This tumour bed clipping protocol to be used for breast boost CTV delineation is the first developed and evaluated within the Australian context. The experience of the first 42 patients at RNSH from June 2010 to December 2011 inclusive was reported.

The historical development of clip based CT/seroma localisation of the CTV is presented in Chapter 2 page 22. Weed (2004) and Coles (2009) had previously reported, when using serial CT, that clips were a stable representation of the post-surgical cavity.

In order to improve CTV delineation of the surgical bed a small multidisciplinary team (MDT) investigated and assisted in the implementation of a surgical clip protocol for surgical bed delineation. A planning and implementation phase preceded placement of surgical clips around the tumour cavity. This was a prospective cohort study with patients stratified into one of two arms: those who went directly from surgery to radiotherapy and
those who had surgery, chemotherapy and then radiotherapy. At surgery, clips were placed around the tumour bed as follows: medial, lateral, superior and inferior. One clip each was also placed at the pectoral fascia and anteriorly, close to the suture line. The British Seroma Visualisation Scale (Petersen et al., 2007) was used to test the ease of delineating the CTV after clips had been inserted into the tumour cavity. For patients whose seroma score visualised on CT was was graded as ≤3 the clips were considered necessary to ensure consistent accurate CTV delineation. Seroma scores of ≥4 were easily identified on CT without the need for clips and thus the clips were considered to have provided no extra information, and did not improve delineation of the CTV. A satisfaction survey was used to gauge the acceptance of this new practice for both the surgeons and radiation oncologists.

Coles et al. (2009) evaluated the use of medium titanium clips for tumour bed radiotherapy following BCS for 30 subjects. In contrast this study reported on the implications of introducing a clips based CTV protocol for 42 subjects (see page 31) and deliberately separated them into two cohorts: chemotherapy delayed radiotherapy (15 subjects) and those having radiotherapy soon after surgery (27) .The two cohorts were chosen as it was observed by the ROs that there were major difficulties in visualising the seroma on CT some 3-4 months post-surgery. The fifteen patients whose radiotherapy was delayed due to chemotherapy had seroma scores ≤3 and it was difficult to see the seroma at all for many of these patients. Overall, the clips improved CTV delineation in 14 /15 Chemo/RT subjects (one patient was failed to be clipped) and in 20 /27 RT/ alone patients with one patient failed to be clipped (see page 32). As Coles et al. (2009) reported clip migration to be less than 10% of cases (using a paired clip protocol) paired clips were not used in our study, which simplified the process. When surveyed, the surgeons found the procedure was simple to administer, and all radiation oncologists indicated that the clips aided in accurate CTV delineation for treatment planning purposes. Now the surgeons are accustomed to the procedure, compliance is expected to continue.
This research has successfully implemented a protocol based breast boost localisation procedure utilising titanium surgical clips which has improved boost CTV delineation for breast radiotherapy patients. RNSH patients will also be able to take part in breast radiotherapy clinical trials that require more complex localisation and treatment protocols. The ability to delineate the CTV even in the absence of seroma was crucial for the second study; enabling the consistent measurement of the CTV changes for patients over long periods of time (see Chapter 3).

The ability to visualise these radiographic clips using the kV OBI capabilities is discussed in Chapter 4. The use of kV OBI allows 3D CBCT on board matching of surgical clips and a new treatment verification protocol will be developed to ensure consistent accurate treatment delivery.

### 5.2 Dynamic CTVs and the timing of radiotherapy post-surgery

The investigation of dynamic CTVs and the timing of radiotherapy planning post-surgery is the first of its kind within an Australian radiotherapy setting. The objective was to establish the best time to carry out CT planning for patients undergoing radiotherapy alone as well as those having radiotherapy delayed due to chemotherapy, in terms of stable CTV delineation for breast boost radiotherapy.

Excision cavity volumes and tumour bed volumes were investigated by Oh et al (2006), Tersteeg et al. (2008) and Prendergast et al., (2009), Hurkmans et al. (2009) compared visible boost volume changes as delineated by the RO, while Jacobson et al. (2006) in their study contoured what they called ‘lumpectomy cavities’. Strauss et al. (2010) recognized the shrinkage of volumes related to chemotherapy delayed radiotherapy patients. Terminology in the literature has been variable so in this work the important volume to be studied was the CTV, which is defined as the visible seroma plus clips as visualised on a radiotherapy planning CT.
A local standardised clip CTV delineation protocol was needed to ensure consistent CTV delineation and was implemented as part of this research (see Chapter 2). This process enable examination of the change in CTV over time, which was carried out on the same subject cohort as described in section 1.5 (15 Chemo/RT and 27 RT/ alone subjects).

We found, similarly to many other researchers, (Oh et al., 2006, Strauss et al., 2010, Prendergast. 2009, Tersteeg et al., 2009, Jacobson et al., 2006 and Yang et al., 2010) that the breast boost CTV changed significantly post-surgery and during radiotherapy and the initial defined CTV size is not a predictor of relative CTV reduction. Regardless of the addition of chemotherapy, significant volume reductions in both groups of patients occurred. There was a 38.4% reduction at mean 9 weeks for the RT group and 43.6% reduction to a mean CTV of 2.6cc at 40 Gy at 19 weeks for the Chemo/RT group (see Table 3.2 page 49).

Due to planning time frame constraints, to allow treatment to commence within the next several weeks, planning CT scans should be completed between 6-7 weeks after surgery. The slower rate of volume reduction after 9 weeks post-surgery indicates that there is no need for an additional CT to be completed at 40 Gy except for those patients who have an initial CTV ≥50 cm³ (Figure 3.5 page 50).

The knowledge of CTV changes over time should inform the implementation of ART; APBI and SIB techniques for early stage radiotherapy (see Chapter 3 pp. 37 to 54).

5.3 The use of kV on board Imaging for radiotherapy breast patients

A thorough literature review was carried out into on board kV imaging for breast radiotherapy (Chapter 4). Recommendations about routine on treatment verification imaging can be made, based on the following factors: the purpose for kV imaging, collision risks, image quality/contrast, radiation dose, accurate registration methods, and marker based matching and CTV monitoring. As discussed in chapter 4 (pp. 63-76) for robust radiotherapy techniques such as the traditional two field tangential technique, MV imaging with current CTV-PTV margins of 10mm is adequate. When implementing complex treatment techniques
such as IMRT, APBI, photon beam boosts as well as changing clinical target volumes, volumetric daily kV imaging becomes more important.

kV CBCT with the ability to visualise internal structures shows promise for routine use in the future. However, more research is still required investigating issues related to accurate soft tissue visualisation, organ motion, patient positioning and automatic co registration of images with or without radiographic tumour surrogates.

5.4 Limitations

Patients under 40 yrs. of age were not recruited for this research because of ethical requirements that all patients had to be over 40 yrs old or post-menopausal to receive one extra CT beyond clinical purposes. This limited the number of subjects that could be recruited over a reasonable period of time in a moderate sized department. Other authors have used similar or smaller numbers (Hurkmans et al., 2009; Jacobson et al., 2006; Oh et al., 2006; Prendergast et al., 2009; Tersteeg et al., 2009), while Kader et al. (2008) reported seroma reduction on larger numbers (77 participants).

As far as the author is aware this is the first study to deliberately separate out those patients who underwent chemotherapy prior to radiotherapy. The study protocol was designed to have matched numbers of 30 patients. However, in order to complete this project in a timely manner as part of candidature data collection was limited to a 14 month period. As chemotherapy alone has protracted time periods of up to 6 months post-surgery and the ethical eligibility restrictions of over 40 yrs / post-menopausal small subject numbers were thus recruited particularly for the chemotherapy cohort (15). As with any statistical test even with small sample sizes significance can be reached suggesting that the effect is large enough to be clinically relevant. The restricted range of scanning time-points was due to a deliberate decision to keep the number of CT scans per subject to a minimum, in order to satisfy ethical requirements. The study protocol required patients to attend for planning CT’s
on multiple occasions. Patient appointment compliance and the use of specialist equipment such as the CT scanner contributed to the broader range of CT time points.

Weed et al (2004) and Coles et al (2009) reported that clips were a good radiographic surrogate for the changing seroma with minimal clip migration. This was not verified in this study, as it was assumed that the clips placed would behave similarly to those observed by Weed and Coles.

5.5 Recommendations

1. A standardised medium titanium clip based CTV delineation protocol should be implemented as standard practice for all early stage breast cancer patients within the Australian setting. This should include a minimum of 4 clips placed around the tumour bed plus one fixed to the pectoralis muscle.

2. Early stage breast cancer patients who require RT should have their planning CT scans performed at least 6 weeks post-surgery to minimise the need to rescan patients.

3. When introducing treatment techniques that require stable CTVs (eg. SIB, APBI) a second CT is currently recommended for patients whose initial CTV is ≥50 cm³, as large volume reductions for this group are likely. The use of routine kV CBCT would remove the need for a second CT as volume changes would be continuously monitored.

4. kV imaging protocols for breast radiotherapy should be implemented when using photon beam planning. This is particularly important for new complex treatment techniques such as IMRT, SIB and APBI.

5.6 Future Research

This research concentrated on the primary tumour bed volume with whole breast volumes not being investigated. Total breast volume changes during a course of radiotherapy as
compared to the breast boost CTV changes for complex planning techniques such as IMRT SIB warrant further investigation.

The systematic review as presented in chapter 5 has been used to inform the development of a non-coplanar kV imaging protocol utilising surgical clips at the Northern Sydney Cancer Centre Department of Radiation Oncology. Implementation of matching to surgical clips for boost irradiation utilising a kV imaging method is currently under investigation.

Once a kV CBCT treatment verification protocol utilising clips as the matching method is implemented, a more detailed representation of tumour bed shrinkage in the whole period from surgery to the completion of radiotherapy could be investigated. Routine CBCT will make this possible. This has the potential to facilitate the implementation of ART and possible margin reductions.
References


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APPENDIX A

Intra Operative Clip Placement

Intra Operative Clip Placement – Breast boost Localisation using clips after breast conserving surgery: Changes in breast boost volumes from breast surgery to the completion of radiotherapy.

<table>
<thead>
<tr>
<th>Clip Identifier</th>
<th>Anatomical position of clips</th>
<th>O 'clock position</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Medial extent tumour bed</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Lateral extent tumour bed</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Superior extent tumour bed</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Inferior extent Tumour bed</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Anterior extent Tumour bed</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Base of the Cavity and or fixed to the pectoralis fascia</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>Fixed to pectoralis fascia</td>
<td></td>
</tr>
</tbody>
</table>

Front View of Breast

![Diagram of breast and surrounding tissues](image)
APPENDIX B Ethics Approval Documentation

2nd June 2010

Dr G Lamoury
Radiation Oncology Department
RNSH
St Leonards NSW 2065

Dear Dr G Lamoury,

Re: SITE SPECIFIC ASSESSMENT (SSA)
   Protocol 1003-079M(SSA) - G Lamoury, L Lewis, J Cox
   Breast boost localisation using clips after breast conserving surgery:
   Changes in breast boost volumes from breast surgery to the completion of
   radiotherapy. (AU RED Ref. SSA/10/HAWKE/10 and NEAF Ref.
   HREC/10/HAWKE/17)

I am pleased to inform you that on the 2nd June 2010 the delegate of the Chief Executive
authorised the Site Specific Assessment for the above study on behalf of Northern Sydney
Central Coast Health (NSCCH).

It is noted that the approval covers the following NSW Health sites:

- Royal North Shore Hospital

The documentation included in the approval is as follows:

- National Ethics Application Form Version 2.0
- Site Specific Assessment Form Version 2.0
- Research Project Version 4.0 dated 8 May 2010
- Patient Information Sheet Informed Consent Version 3.0 dated 7 May 2010

It is noted that the Ethical & Scientific Approval for this project was reviewed and approved
by Northern Sydney Central Coast Area Health Service Human Research Ethics
Committee who is accredited under the NSW Health model for single ethical review of
multi-centre research.

The HREC recommends that you consult with your Medical Defence Union to ensure that
you are adequately covered for the purpose of conducting this clinical trial.

At this time, we also remind you that in order to comply with the Guidelines for Good
Clinical Research Practice (GCRP) in Australia and in line with NSCCH HREC policy, the
Chief Investigator is responsible to ensure that:

1. The Therapeutic Goods Administration receipt/acknowledgment of the Clinical Trial
   Acknowledgment is provided to the Research Office within 30 days from the date
   which it was issued.

2. The HREC is notified of anything that might warrant review of the ethical approval of
   the project, including unforeseen events that might affect the ethical acceptability of
   the project.

Research Business Unit
Level 2 Building 61, Royal North Shore Hospital
St Leonards NSW 2065 Tel: (02) 9926 8100 Fax: (02) 9926 6179
3. The HREC is notified of all Serious Adverse Events (SAEs) or Serious Unexpected Suspected Adverse Reactions (SUSARs) in accordance with the Serious Adverse Event Reporting Guidelines. Please refer to the Research Office website.

4. Proposed amendments to the research protocol or conduct of the research that may affect the ethical acceptability of the project are submitted to the HREC on an amendment form (including any relevant attachments). For multi-centre studies, the Chief Investigator should submit to the Lead HREC and then send the amendment approval letter to the investigators at each of the sites so that they can notify their Research Governance Officer.

5. The HREC must be provided with a final report upon completion of the study. For multi-centre studies the Chief Investigator should notify the Lead HREC and the investigators at each site should notify the relevant Research Governance Officer.

Please refer to the NSCCAHs Research Office website to access forms such as the amendment form, Annual/Final Report Form, Change in Personnel Form and Serious Adverse Event Guidelines and Forms.

Intranet:

Internet:

Approval lasts for four years, therefore your approval will expire 2nd June 2010. Should you require an extension an amendment form should be submitted.

Yours sincerely,

Leanne Thompson
Ethics Coordinator
Research Office
NORTHERN SYDNEY
CENTRAL COAST HEALTH
APPENDIX C Research Proposal Study 1 and 2

Northern Sydney Cancer Centre
Department of Radiation Oncology
Royal North Shore Hospital

The University of Sydney

Lorraine Lewis – Radiation Therapist (Masters) student
Jennifer Cox – Associate Professor – Medical Radiation Sciences
John Atyeo – Dr Medical Radiation Sciences

Research Project

Breast boost Localisation using clips after breast conserving surgery: Changes in breast boost volumes from breast surgery to the completion of radiotherapy.

Chief Investigator

Lorraine Lewis: Royal North Shore Hospital and Masters Candidate, University of Sydney

Co-Investigators

Assoc. Prof. Jennifer Cox: University of Sydney
Dr John Atyeo – University of Sydney
Dr Gillian Lamoury: Royal North Shore Hospital Radiation Oncology Department

RESEARCH TEAM

Department of Radiation Oncology Royal North Shore Hospital

Radiation Oncologist – Dr Marita Morgia
Physicist Judith Martland and Jeremy Booth
Radiation Therapist- Kylie Grinberg
Clinical Trials Nurse - Bronwyn Raymond
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1.0 FOREWORD

This document is intended to describe a Radiation Oncology Study proposed for the Northern Sydney Radiation Oncology Centre at Royal North Shore Hospital. It will provide information about procedures for entering patients into the study. It is not intended that the protocol be used as a guide for the treatment of other patients. This protocol will be submitted to the local ethics committee and approved prior to entering patients into it.

Amendments to the document may be necessary at times and these will be sent to the local ethics committee for approval as they arise.

2.0 INTRODUCTION

Over the last 20 yrs breast conservative surgery of lumpectomy followed by whole breast radiation and a boost to the tumour bed is considered the gold standard of care for early stage breast cancer (Bartelink et al 2007). In recent years there has been an increasing interest in irradiating the post surgical cavity with a margin of adjacent breast tissue to produce equivalent recurrence rates to that of whole breast irradiation followed by a boost. Trials are underway in most countries including Australia investigating this issue.

Accurate tumour bed localisation is important for all forms of radiotherapy, including breast boost localisation, whether for standard breast conservative treatment or accelerated partial breast irradiation (APBI).

With the advent of computer tomography (CT) simulated radiotherapy planning there is a need to develop an expert localisation procedure that represents best practice. The use of a defined clipping program should assist with accurate delineation of tumour volumes for radiotherapy to the breast. At different time points post surgery the lumpectomy cavity, known as the seroma, can vary greatly in size and shape, so the best time following surgery to delineate the cavity should be established. This cavity is defined currently by what is visualised by the Radiation Oncologist (RO) at the time of the initial planning CT. Peterson et al (2007) among others have demonstrated variability amongst Radiation Oncologists when outlining the seroma using CT data alone, without surgically inserted clips.

This study is designed to examine the feasibility issues of a new procedure for breast radiotherapy to improve tumour bed localisation with surgically inserted clips. It will determine whether one can predict an optimal time for the CT planning scan to be performed.

3.0 BACKGROUND

Whole breast irradiation following breast conserving surgery (BCT) followed by a boost to the tumour bed has been demonstrated to be effective in reducing the risks of tumour recurrence. (Clarke et al 1996; Romestaing et al, 1997; Bartelink et al 2001).
The current standard of care after breast conserving therapy is that of whole breast irradiation (WBI) of 25 fractions followed by a boost of 5 fractions delivered over a 6 week period. This technique means, particularly for small tumours, that an area of distinctly uninvolved breast tissue will be treated, which contributes to the overall acute toxicity to the whole breast. New techniques such as accelerated partial breast irradiation (APBI) are being investigated across the world. (Vicini et al 2003). This technique offers the potential advantages of decreasing overall treatment time and potential side effects of radiotherapy to uninvolved breast tissue.

Whether the standard WBI followed by a boost or a new technique such as APBI is used, the tumour bed (the area defined as the location where the tumour resided prior to resection) must be adequately covered by radiotherapy. Hence accurate localisation of the tumour bed is essential.

**CLIPPING**

The use of clipping to aid in the localisation of breast boost volumes was investigated as far back as 1993 (Barlow et al). Medium titanium clips were placed within the tumour cavity at the time of surgery. These then become a radiographic surrogate for the resected tumour. Prior to using clips a combination of pre-operative imaging (mammograms), pathological considerations, surgical scar location and palpation have all aided in localisation. With the advent of CT radiotherapy planning localisation, radiotherapy departments have relied upon post operative seroma formation (fluid filled cavity) as the method of localisation. Landsis et al and Hukarms et al 2008 demonstrated large inter-observer variations when surgical clips alone were used for delineation. The use of clips not only aids in localisation but ultimately radiotherapy treatment verification, two of the fundamental elements for accurate radiotherapy delivery. Researchers (Weed et al 2004, Hepel et al 2010, Oh Ks et al 2006, Goldgeur et al 2005, Hasan et al 2006, and Harrington et al 1996) have demonstrated that clips are a good surrogate for the lumpectomy tumour bed.

Smith et al 2009, in the Accelerated Partial Breast Irradiation Consensus Statement from the American Society for Radiation Oncology (ASTRO) stated “you must delineate the target and verify the prescribed dose is delivered accurately.” Banca et al (2002) indicate that a precise target definition based on surgical clips and CT changes could increase local control without necessarily increasing the prescribed radiation dose to the tumour bed.

There is an important subgroup of patients who pose significant delineation issues when using CT alone without clips. These are patients who require chemotherapy prior to radiotherapy. This group experiences significant time delays from surgery to their radiotherapy planning CT and often have complete resolution of the seroma by the commencement of treatment. This subgroup therefore would most benefit from breast lumpectomy clipping at the time of surgery. The clips allow for localisation and verification of breast lumpectomy patients regardless of visible seroma (Smith et al 2000 and Coles et al 2009).

**BREAST CTV CHANGES OVER TIME**

There is a body of reported evidence indicating that breast seroma volumes do change over time. Large seromas alone are being used as surrogates for lumpectomy, leading potentially to large amounts of healthy tissue unnecessarily being treated. Current practice is to CT scan for radiotherapy two weeks post op for both the whole breast (treatment) and boost fields. A number of studies (Weed et al 2004; Jacobson et al 2006; Nichols et al 2007; Prendergast et al 2009; Hukarms et al 2008; Kader et al 2004; Oh...
et al 2000) have reported that serum volumes progressively decrease with longer times from surgery. Following on from these studies, Tersteeg et al (2009) suggest scanning a second time prior to boost treatment to potentially reduce the size of the gross tumour volume (GTV) required to be treated.

What does this all mean for the future of radiotherapy treatment of early stage breast cancer? The reduction in the amount of healthy tissue being treated by radiotherapy is an important objective. This study will develop expert standards of practice in breast tumour localisation and add to the body of knowledge related to changes in breast tumour changes post surgery and during radiotherapy.

4.0 SCHEMA

4.1 Surgery with clipping

4.2 Multidisciplinary Breast Clinic

4.3 Chemo/RT Combined

4.4 RT Alone

4.5 Radiotherapy (RT)

4.6 Chemotherapy (chemo)

4.7 Multidisciplinary Breast Clinic (MDT)

(Red double-headed arrows indicate data for within and between groups statistical analysis – see section 11)

5.0 OBJECTIVES

The addition of systematic protocol clipping to the current method of imaging utilised at Royal North Shore Hospital Radiation Oncology Cancer Centre will improve the delineation of the clinical target volume (CTV) both the areas at highest risk of recurrence and reducing the volume of healthy tissue being irradiated.

Dept of Radiation Oncology, Royal North Shore Hospital (NCCAHS)
Version 4, 8/5/10
Repeat planning CT scans for both those having chemotherapy and those not prior to commencement of boost treatment will add to the body of information to determine if we can predict at what time we should CT patients with the aim of minimizing the irradiation of healthy normal tissue.

6.0 AIMS

- To introduce a protocol for the use of breast lumpectomy clipping and CT for accurate tumour localisation for breast radiotherapy patients.
- To derive the optimal time at which to CT plan patients after breast conservative surgery in reference to minimal clinical target volume of breast boost treatment.

7.0 DESIGN

This is an investigative study assessing the feasibility of clipping breast patients to improve best practice of breast boost delineation and location. It will also aid in the decision process as to when it is best to CT breast lumpectomy patients for radiotherapy.

A convenience sample of patients who best fit the eligibility criteria for the study will be invited to participate. A total of 60 patients, 30 (cohort 1) whose routine treatment requires them to have chemotherapy prior to radiotherapy and 30 (cohort 2) of those proceeding straight from breast conserving surgery to radiotherapy will be recruited.

8.0 PATIENT ELIGIBILITY

INCLUSION CRITERIA:
Patients must fulfil all of the following criteria for admission to study:

- Histological confirmed diagnosis of early stage invasive breast cancer.
- Breast conservative surgery which requires whole breast radiotherapy and boost with +/- nodal volumes.
- Ability to tolerate protocol therapy.
- Willingness to comply with study requirements and accessible to treatment and follow up.
- Written and informed consent.
- Postmenopausal or > 40 years.

EXCLUSION CRITERIA:
Patients who fulfil any of the following criteria are not eligible for admission to study:

- Prior radiotherapy to the breast or chest or previous malignancies.
- Any patient not requiring boost treatment.
- Contraindications for radiotherapy (e.g., Gene mutations)
• Pregnant or lactating women
• Those requiring total mastectomy
• Psychiatric or addictive disorders that preclude obtaining informed consent or adherence to protocol.

9.0 TREATMENT

9.1 BREAST CONSERVATIVE SURGERY CLIPPING PROCEDURE

A minimum of 5 - 6mm titanium clips will be used and spaced around the cavity. There is no national protocol for optimal breast clipping for radiotherapy. This study will use the model as published by Coles et al (2008). It must be noted here that clips are placed inside human tissue now for localisation of nodes and for haemostasis of blood vessels.

1. One each at the medial, lateral, superior and inferior extent of the tumour bed.

2. One posteriorly, deep to the pectoralis fascia. (This fixed clip will remain stable).

3. One anteriorly within cavity

The dimensions and orientation of the surgical specimen will be recorded by the surgeon in the patient’s medical records.

Additional consent will not be required for the clipping process. Clips are placed during surgery at the discretion of specialists when required as a standard procedure for surgery. They are only being placed in standardised protocol way and thus will be covered by the patient’s usual surgical consent process.

9.2 POST OP CT SCAN IN RT TREATMENT POSITION

The patients will be seen in routine clinics and examined by the radiation oncologist prior to the CT scan to verify that there is no contraindication for postoperative radiotherapy. Study consent for extra CT scans will be obtained (see appendix 1 Patient Information sheet and informed consent form.)

The post op CT scan will be performed no more than 3 weeks post surgery. All patients going onto have chemotherapy or just radiotherapy alone will have this RT planning CT (NCTE SCHEMA 4).

The Chemotherapy Cohort will have a rescan 2 weeks prior to RT (CT b1). This repeat scan is to ensure consistency to cohort 2 who have not had chemotherapy.

All RT patients are to have a repeat CT scan at 40GY.

The RT CT scans will be performed with 3mm slice thickness. The patient is routinely positioned supine on a custom breast board with both arms up. Scans include the entire...
breast and lung fields. All scans hence will be performed in exactly the same way as current treatment protocol requires.

Image registration will take place using match points on the Eclipse Varian Medical System. The match points to use are: bony structures, mammary gland tissue, pectoral and dorsal muscle structures and the pectoralis slab.

9.3 TARGET VOLUME DELINEATION

This study follows the RTOG Breast Cancer Atlas for Radiation Therapy Planning Consensus Definitions of White et al 2009.

Breast CTV:
- Considers referenced clinical breast at time of CT
- Includes the apparent glandular breast tissue
- Incorporates consensus definitions of anatomical borders (see below)
- Includes the lumpectomy GTV

Lumpectomy GTV: Includes seroma and surgical clips

Breast chest wall boundaries
- Cranial - clinical reference second Rib intersection
- Caudal - clinical reference and loss of CT apparent breast
- Anterior - skin
- Posterior - excludes pectoralis muscles and chest wall muscles and ribs
- Lateral clinical reference and mid axillary line typically excludes (Lat) dorsi muscles
- Sternal Rib Junction

This will be outlined according to protocol with the aid of breast tissue changes apparent on each CT, pathological and radiographic information, the fluid filled cavity and surgical clips. A margin of 10 mm adjacent to breast tissue will be added to create the CTV.

PLANNING TARGET VOLUME (PTV) = CTV + 1cm

Current department protocol dictates a rescan should occur if the volume of CTV breast tissue on the original planning CT is > 100 cc. This will then be the scan used for boost voluming.

The study process requires the volume values to be recorded for all CTVs that are completed.

Each time a CT is completed one Radiation Oncologist will contour each CT and create a CTV. To eliminate bias the RO is unable to refer to the previous CT when contouring those following. Each CTV volume is recorded.

CTV CT1 at 2 wks post surgery CTV CT2 at 40 Gy
Secondly, as seroma cavity evaluation is subjective, evaluation of the use of surgical clips in aiding lumpectomy localisation will be performed in the following way, as reported by Flannery et al (2009):

The change in volume of the surgical cavity between CT1 and CT2 is calculated by assigning co-ordinates to clips and creating a box around the clips. This is to be completed on each scan. Provided the clip changes remain proportional the relative change in box volume should reflect the relative change in volume of the actual cavity.

The geometric centre of the clip volumes will be also compared to the CTV volumes to ascertain relative positional changes of treatable volumes.

The group who have had chemotherapy prior to RT will have their CTA1 CTV volumes compared to that which is outlined at 2 weeks prior to the start of radiotherapy (CTb1) and then again at 40gy (see schema 4).

10.0 ENDPOINTS

10.1 Volumetric changes between pre RT planning CT (2-3wks) post surgery and those at each subsequent CT time point.

10.2 Geometric centre changes between each outlined CTV.

10.3 Planning volumes of those having chemotherapy prior to the commencement of RT and those not having chemotherapy.

11. DATA TO BE COLLECTED

11.1 Patient and treatment details:

Age, tumour type, size and location of pathology specimen, postoperative complications, surgical technique including clips placed and Physician.
Chemotherapy before treatment and time from chemotherapy to start of Radiotherapy Planning CT. Time intervals from surgery and each RT planning CT.
Cup breast size

Calculated CTV cavity volumes (CTCV) for each CT and procedure type.

12. STATISTICAL CONSIDERATIONS
12.1 Study Design
This is a prospective investigative study designed to aid in the localisation of postoperative breast lumpectomy volumes and to analyse their changes over time from surgery to completion of radiotherapy.

12.2 Data Analysis
The SPSS V17 data package will be used to analyse data. A multi-variant analysis of patient information will be completed to analyse correlations between clinical factors affecting localisation. ANOVA and independent T TESTING within each group and across groups to compare volumetric changes of each CTV will be used (see red double-headed arrows on study schema). These tests will demonstrate changes and trends related to each data set.

13. RESPONSIBILITIES OF THE INVESTIGATOR
The investigator is responsible for the following:
- Ensuring that the written informed consent by the patient is obtained before study entry.
- Responsible for any regulatory requirements being followed
- The investigator is required to ensure compliance to the protocol.

14. REPORTING OF RESULTS
The principle investigator of this study will be responsible for the dissemination of the findings. The results may be published after the final analysis (or interim analysis if the study is terminated early) in a peer reviewed journal.
15. REFERENCES


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Romestain, P., Lehmque, Y., Carrie, C., Coquard, R., Montbarbon, X., Ardis, J. M.,
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APPENDIX D Patient Information and Consent Form

NORTHERN SYDNEY CENTRAL COAST AREA HEALTH SERVICE
ROYAL NORTH SHORE HOSPITAL

PATIENT INFORMATION & INFORMED Consent FORM
FOR THE STUDY TITLE:
Breast boost Localisation using clips after breast conserving surgery: Changes in breast boost volumes from breast surgery to the completion of radiotherapy.

INTRODUCTION
This is a study looking at the best way to plan patients' treatment for breast tumours in Radiotherapy. This study will only include patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

You are being asked if you would like to take part in this study because you have breast cancer requiring breast conservative surgery requiring radiotherapy. You will receive the normal treatment you would have received if you were not on the study. The only difference will be that you will be required to undergo one to three extra radiotherapy Computer Tomography scans (CT scans).

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to examine the imaging of tumours in postoperative patients who are to have radiotherapy for breast tumours. This research is being done because we do not know when after surgery is the best time to do the CT for radiotherapy of the breast. There has been both an evolution in radiotherapy techniques and an emergence of improved radiation delivery. Hand in hand with the improved dose delivery of radiotherapy has been the requirement for improved imaging. This has been met to some degree by CT planning alone but more recently clips placed during surgery is playing a major role. These small clips make it easier to localise the tumour. It is still unclear at what time the current imaging practices should be carried out to best define the tumour and areas at risk for recurrence.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?
A total of 80 people from Royal North Shore Hospital will take part in this study.

WHAT IS INVOLVED IN THE STUDY?
The localisation clips placed already during surgery will be used to help locate your tumour for radiotherapy. If you decide to participate you will be asked to have your routine CT performed for radiotherapy as well as an extra CT scan performed during radiotherapy. If you are to have chemotherapy prior to the commencement of radiotherapy you will have an additional CT scan 2-3 weeks post surgery as well as the additional one during radiotherapy. You will not be exposed to dangerous levels of radiation, you will however be exposed to more radiation than you will have if you were not to have the treatment.

Dept of Radiation Oncology, Royal North Shore Hospital, (NNCAHS) HREC Protocol Number: Version 3, 705/10 Patient Information Breast boost localisation study
Dr Jillian Lomasney, (02) 9926 5028
**Procedures and Medical Tests:**
Apart from the extra scans all other tests will be performed as routine treatment. Radiotherapy planning is carried out via the patient being placed in the treatment position with arms placed above their head. A radiotherapy planning CT is performed and measurements taken as part of the planning process. The patient is given two permanent tattoos that aid in treatment location on a daily basis.

**HOW LONG WILL I BE IN THE STUDY?**
If you agree to participate we will keep in contact through your Radiation Oncologist.

**WITHDRAWAL**
You can choose not to take part in this study or stop taking part at any time. If you decide to stop participating in the study we encourage you to talk to your doctor first.

**WHAT ARE THE RISKS OF THE STUDY?**
This research involves exposure to a small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millirem (mRem) per year. The effective dose from this study is about 8mSv per CT scan which is equivalent to about 3.5 CT scans of the chest. This additional radiation dose from this study is a small fraction of the radiation you will be receiving as part of your radiotherapy.

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**
If you agree to take part in this study, there will be a direct benefit to you. Your treatment will be the same way as if you had not the extra scans. The extra CT’s will be reviewed at a later date to provide information that we hope will lead to the improvement of treatment in the future for other patients benefit.

**WHAT OTHER OPTIONS ARE THERE?**
If you decide not to take part in this study you will still receive radiation treatment as normal procedure. Please talk to your doctor about these and other options. Your doctor can also discuss with you what will happen if you decide not to undertake any treatment at this time.

**WHAT ABOUT CONFIDENTIALITY?**
Every effort will be made to keep your personal information confidential. Your medical records will be utilised by the Radiation Oncology staff for data analysis only. Qualified representatives from the hospital, such as the Human Research Ethics Committee Members or hospital administrators, may also require to view the data collected to assess the results. This information may include test results, reports of operations, x-rays or other body scan reports and questionnaires.

Please be assured that your privacy will be maintained.

- Your name will not be used in any reports about the study.
- Your date of birth, which is required to confirm your age, will not be used in any reports about the study.
- You will be identified only by code and initials.
- Identifying information will be kept behind locked doors.

Dept. of Radiation Oncology, Royal North Shore Hospital, (NCAHHS) HREC Protocol Number.
Version 3, 305.41 Patient Information Breast boost Radiation Study.
Dr. Jillian Lamvar, (02) 9926 5528.

2017
WHAT ARE THE COSTS?
You will not be paid for taking part in this study. In the case of research-related side effects or injury, medical care will be provided by your doctor or you will be referred for appropriate medical care.

WHAT ARE MY RIGHTS AS A PARTICIPANT?
Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Deciding not to take part or deciding to leave the study later will not result in any penalty or any loss of benefits to which you are entitled. A Data Safety Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study.
You will be given a copy of this signed and dated consent form.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
If you have questions about taking part in this study or if you suffer a research-related injury you can talk to your doctor.

You can also meet with the doctor who is in charge of the study at the Royal North Shore Hospital, Dr Lamouy on phone number 9926-5028.

If you would like advice regarding your rights as a patient or about ethical issues related to this study, you can talk to someone who is not involved in the study at all. That person is a Patient Representative who is an independent person within the Hospital on 9926-7612.

WHAT HAPPENS IF I SUFFER INJURY OR COMPLICATIONS AS A RESULT OF THE STUDY?
If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is caused by the drugs or procedures, or by the negligence of any of the parties involved in the study. If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies.

If you are not eligible for compensation for your injury or complication under the law but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.
NORTHERN SYDNEY CENTRAL COAST AREA HEALTH SERVICE
ROYAL NORTH SHORE HOSPITAL

Consent form for the serial CT breast boost scanning study.

I, ___________________________ 
(name of participant) ___________________________ 
(surname) ___________________________ 

I have been invited to participate in a research project entitled: Breast boost localization using clips after breast conserving surgery: Changes in breast boost volumes from breast surgery to the completion of radiotherapy.

1. In relation to this project I have read the Participant Information Sheet and have been informed of the following points:

2. Approval has been given by the Human Research Ethics Committee (HREC) of Northern Sydney Central Coast Health.

3. The purpose of the study is to determine the best procedure and time to CT scan breast patients who require a boost for radiotherapy. I understand that my treatment will not be influenced by the findings of the serial CT's and that my treatment will not be altered in any way if I decide to take part in this study. This research is being done to improve breast tumour localisation for radiotherapy and to determine an optimal time to CT scan these same breast patients.

4. It has been explained to me that I will have additional radiotherapy CT scans as required by the study the number depending on if I am having chemotherapy or not. All other tests and scans I need are routine. This study has been approved by the Radiation Safety Committee of Royal North Shore Hospital. The radiation exposure involved is less than the limit set by the Australian Radiation Protection and Nuclear Safety Agency.

5. I also have had explained to me that the research study involves exposure to a small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about 8mSv per scan. The dose from this study is comparable to that received from several computed tomography x-ray (CT) procedures. The benefits from the study should be weighed against the possible detrimental effects of radiation, including an increased risk of fatal cancer. In this particular study, the risk is low and the estimated risk of such harm is equivalent to approximately 50 round trips from Sydney to London by plane per scan.

Dept of Radiation Oncology, Royal North Shore Hospital (NCCAMS) HREC Protocol Number: 407
Version 3: 705/10 Patient Information Breast boost localization study
Dr Jillian Lamont, (02) 9464 8068
6. I understand that there are some possible common adverse effects or risks related to radiotherapy and these are described in the patient information section of this document.

7. I am aware that my involvement in this project may be terminated if:
   • If my doctor wishes me to withdraw from the study for any reason
   • I wish to withdraw my consent for any reason
   • If I become pregnant

   If I develop a problem which I suspect may have resulted from my involvement in this project, I am aware that I may contact my Oncologist or Dr Lamoury on 9926-5028.

8. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the research staff, I am aware that I may contact the Patient Representative who is an independent person within the Hospital on 9926-7912.

9. I can refuse to take part in this project or withdraw from it at any time without affecting my medical care.

10. Participation in this project will not result in any extra medical and hospital costs to me.

11. I understand that my research records will be stored in a locked room in the Radiation Oncology Cancer Centre at the Royal North Shore Hospital. The research team, authorised personnel, and regulatory entities may have access to my study records to protect my safety and welfare.

12. I consent to the collection, processing, reporting of my data. All data will be de-identified, therefore not including my name, address or phone number. My information will be identified by a numerical random code and my initials only. I also acknowledge that the Government Health Department Officials, Radiation Oncologist, Physicist at Royal North Shore and the clinical trial staff directly involved in the study, may examine my medical records at this Institution and any other Institution that I may have been treated at, only as they relate to this project.

13. If the results of my tests or information regarding my medical history are published, my identity will not be revealed.

14. If I am taking part in any other study I will disclose this to the investigators.

15. If I am harmed as a result of being in this study, I understand that the Hospital has taken out an insurance policy to cover the liability of my doctor. If I would like a copy of this policy, I can ask Dr Lamoury by phoning 9926-5028.

16. I declare that I am over the age of 18 years.
17. After considering all these points, I accept the invitation to participate in this project.

18. I also state that I have/have not participated in any other research project in the past 3 months. If I have, the details are as follows:

__________________________________________________________________

Patient: __________________________________________________________
(Please print name)

Patient Signature: ___________________________ Date: ________________

Name of witness __________________________________________________
(Please print name)

Signature of Witness ____________________________________________ Date: ________________

Investigator’s confirming statement:
I have given the research subject information on the study, which in my opinion is accurate and sufficient for the subject to understand fully the nature, risks and benefits of the study, and the rights of a research subject. There has been no coercion or undue influence. I have witnessed the signing of this document by the subject.

Investigator’s Name: ________________________________

Investigator’s Signature: ___________________________ Date: ________________

Dept of Radiation Oncology, Royal North Shore Hospital, (NCCARS) HREC Protocol Number: 607
Version 3. 7/3/10 Patient Information Breast boost localisation study
Dr Jillian Larmour, (02) 9926 5038
Withdrawal of Consent:
I have decided to withdraw my consent to participate in this study.

Patient's Name: ______________________________

Patient's Signature: __________________________ Date: ________________

Investigator's Signature: ______________________ Date: ________________
APPENDIX E Satisfaction Survey Breast Radiation Oncologist

Satisfaction Survey Breast Radiation Oncologist

Intra Operative Clip Placement - Breast boost localisation using clips after breast conserving surgery: Changes in breast boost volumes from breast surgery to the completion of radiotherapy.

In May 2011 a standardized surgical clipping protocol was added to the current methods of imaging utilised at Royal North Shore Hospital Radiation Oncology Cancer Centre. This protocol was developed to improve the delineation of the clinical target volume (CTV), with the aim:

- To ensure adequate radiation dose is delivered to the areas at highest risk of recurrence.
- To reduce the volume of healthy tissue being irradiated for early stage breast cancer patients.

May 2010-Dec 2011.

- 42 patients had clips inserted around the surgical bed at the time of surgery (99 CT data sets measured).

Survey Purpose

The following questions are intended to gauge the opinions of RADIATION ONCOLOGISTS around the introduction of this protocol. These answers will be kept anonymous.
To what extent do you agree with the following statements?

<table>
<thead>
<tr>
<th>Statements</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree or disagree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to the introduction of this protocol I felt there were difficulties with voluming the breast boost target volume. Discuss below</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>When I started using this protocol I felt I had a sound understanding of the benefits of CLIP volume delineation for breast radiotherapy patients</td>
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<tr>
<td>With the clip volume protocol it is easier to outline those patients who have had seroma volume resolution after chemotherapy. Discuss below</td>
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<tr>
<td>I believe this protocol is beneficial for my patients.</td>
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</tbody>
</table>

General comments about this protocol development

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APPENDIX F Satisfaction Survey MDT Breast Clinic Surgeon

SATISFACTION SURVEY MDT BREAST CLINIC SURgeONS

Intra Operative Clip Placement - Breast boost localisation using clips after breast conserving surgery: Changes in breast boost volumes from breast surgery to the completion of radiotherapy.

In May 2011 a standardized surgical clipping protocol was added to the current methods of imaging utilised at Royal North Shore Hospital Radiation Oncology Cancer Centre. This protocol was developed to improve the delineation of the clinical target volume (CTV), with the aim:

- To ensure adequate radiation dose is delivered to the areas at highest risk of recurrence.
- To reduce the volume of healthy tissue being irradiated for early stage breast cancer patients.

May 2010- Dec 2011.

- 42 patients had clips inserted around the surgical bed at the time of surgery (99 CT data sets measured).

SURVEY PURPOSE

The following questions are intended to gauge the opinions of surgeons around the introduction of this protocol. These answers will be kept anonymous.
Northern Sydney Cancer Centre
Department of Radiation Oncology

To what extent do you agree with the following statements?

<table>
<thead>
<tr>
<th>Statements</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree or disagree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>When I started using this protocol I felt I had a sound understanding of the benefits of volume delineation for breast radiotherapy patients.</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>I believe this protocol is beneficial for my patients.</td>
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<td>I will continue with this clipping protocol for early stage breast cancer patients.</td>
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<tr>
<td>The surgical clipping procedure was easy to carry out.</td>
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</tbody>
</table>

General comments about this protocol development

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