DEVELOPMENT OF THREE-DIMENSIONAL RADIOTHERAPY
TECHNIQUES IN BREAST CANCER

Thesis submitted for the degree of Doctor of Philosophy at the University
of Leicester

by

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March 2005
This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.
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Abstract

*Development of three-dimensional radiotherapy techniques in breast cancer: Dr Charlotte Coles*

Radiotherapy following conservation surgery decreases local relapse and death from breast cancer. Currently, the challenge is to minimise the morbidity caused by this treatment without losing efficacy. Despite many advances in radiation techniques in other sites of the body, the majority of breast cancer patients are still planned and treated using 2-dimensional simple radiotherapy techniques. In addition, breast irradiation currently consumes 30% of the UK’s radiotherapy workload. Therefore, any change to more complex treatment should be of proven benefit. The primary objective of this research is to develop and evaluate novel radiotherapy techniques to decrease irradiation of normal structures and improve localisation of the tumour bed.

I have developed a forward-planned intensity modulated (IMRT) breast radiotherapy technique, which has shown improved dosimetry results compared to standard breast radiotherapy. Subsequently, I have developed and implemented a phase III randomised controlled breast IMRT trial. This National Cancer Research Network adopted trial will answer an important question regarding the clinical benefit of breast IMRT. It will provide DNA samples linked with high quality clinical outcome data, for a national translational radiogenomics study investigating variation in normal tissue toxicity. Thus, patients with significant late normal tissue side effects despite good dose homogeneity will provide the best model for finding differences due to underlying genetics.

I evaluated a novel technique using high definition free-hand 3-dimensional (3D) ultrasound in a phantom study, and the results suggested that this is an accurate and reproducible method for tumour bed localisation. I then compared recognised methods of tumour bed localisation with the 3D ultrasound method in a clinical study. The 3D ultrasound technique appeared to accurately represent the shape and spatial position of the tumour cavity. This tumour bed localisation research facilitated protocol development of a proposed national breast radiotherapy trial investigating IMRT and partial breast irradiation.
Acknowledgements

The clinical studies described here were dependent on the good will and expertise of the staff within The Oncology Centre, Addenbrooke's Hospital, Cambridge. I particularly wish to record my thanks to Dr Charles Wilson, Clinical Director of Oncology, and Professor Bruce Ponder, Professor of Oncology, and all the patients who kindly participated in the studies. In addition, the research would not have been possible without grants from the Breast Cancer Campaign and Addenbrooke's Charities.

Specific individuals, who suffered with my persistent difficulties and endless questions, include: Andrew Hoole, who helped me with my limited computing skills and developed software specifically for this research. Nikki Twyman, who patiently helped a humble doctor understand the physics of breast radiotherapy. Jenny Wilkinson, Cambridge Breast IMRT Trials radiographer, whose support and sense of humour spurred me on to complete this research. Margaret Moody who always had constructive advice as I passed through the highs and lows of clinical research, and Fiona Miller who guided me through the baffling topic of statistics.

I would particularly like to acknowledge the help and support I received from my co-investigator, Dr Charlotte Cash. Without her attention to detail and diligence, none of the joint ultrasound research would have been possible. Thanks are also due to Dr Graham Treece and the rest of the team at the University Department of Engineering, Cambridge, whose mathematical minds developed the novel imaging software. I would like to thank Mr Arnie Purushotham and the rest of the Cambridge Breast Unit Team, who always approached the research studies with enthusiasm, despite the pressures of a busy one-stop breast clinic. Also, I would like to acknowledge the support I received form Dr John Le Vay and the team at Ipswich Hospital, who facilitated with the laser camera validation study.

Special praise must go to my supervisors. Firstly, to Dr Paul Symonds my University supervisor, whose role in overseeing the 'big picture' has been extremely helpful. Secondly, to Dr Neil Burnet my local supervisor, who through his seemingly endless enthusiasm, encouragement and patience has guided me through these studies. My admiration of his qualities as a clinical researcher has inspired me to complete this thesis and continue with future research.

Finally a special word of thanks must go to my family: my long-suffering husband Jonathan, and children Eleanor and Charlie who were both born during this research period. Their love and sense of fun gave me a sense of perspective, which was a key element in completing this work.
List of publications

This is a current list of manuscripts, abstracts and presentations, which I have achieved during the course of this research.

Invited Lectures


Book Chapters


Papers: published or in-press directly related to research thesis


Review. Reduction of radiotherapy-induced late complications in early breast cancer: the role of intensity modulated radiation therapy (IMRT) and partial breast irradiation. Part II – Radiotherapy
strategies to reduce radiation-induced late effects. CE Coles, AM Moody, CB Wilson and NG Burnet. Clinical Oncology (in press).

Papers: published during research period, but not directly related to research thesis


Submitted papers directly related to research thesis


High definition three-dimensional ultrasound to localise the surgical cavity for breast radiotherapy planning: validation of a novel technique. Cash CJC, Coles CE, Treece GM, Miller FNAC, Hoole A, Gee AH, Prager RW, Burnet NG.

Abstracts directly related to research thesis
(♦ Denotes oral presentation)


Poster Presentations directly related to research thesis

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<tbody>
<tr>
<td>2D</td>
<td>2-dimensional</td>
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<tr>
<td>3D</td>
<td>3-dimensional</td>
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<tr>
<td>ALD</td>
<td>Average lung distance</td>
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<tr>
<td>APBI</td>
<td>Accelerated partial breast irradiation</td>
</tr>
<tr>
<td>ARPS</td>
<td>Addenbrooke’s radiotherapy planning system</td>
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<tr>
<td>BTE</td>
<td>Basic treatment equivalent</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CLD</td>
<td>Central lung distance</td>
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<tr>
<td>CRT</td>
<td>Conformal radiotherapy</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CTV</td>
<td>Clinical target volume</td>
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<tr>
<td>DCIS</td>
<td>Ductal carcinoma in-situ</td>
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<td>DVH</td>
<td>Dose volume histogram</td>
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<tr>
<td>EBCTCG</td>
<td>Early Breast Cancer Trialists Collaborative Group</td>
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<tr>
<td>EIC</td>
<td>Extensive intraductal component</td>
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<td>ELIOT</td>
<td>Electron intraoperative therapy</td>
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<tr>
<td>EORTC</td>
<td>European Organisation for the Research and Treatment of Cancer</td>
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<tr>
<td>HDR</td>
<td>High dose rate</td>
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<tr>
<td>HU</td>
<td>Hounsfield unit</td>
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<tr>
<td>IBTR</td>
<td>Ipsilateral breast tumour recurrence</td>
</tr>
<tr>
<td>ICRU</td>
<td>International Commission on Radiation Units and Measurements</td>
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<tr>
<td>IMC</td>
<td>Internal mammary chain</td>
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<tr>
<td>IMPORT</td>
<td>Intensity Modulated and Partial Organ Radiotherapy</td>
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<td>IMRT</td>
<td>Intensity modulated radiotherapy</td>
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<tr>
<td>IQR</td>
<td>Inter quartile range</td>
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<tr>
<td>LDR</td>
<td>Low dose rate</td>
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<td>LF</td>
<td>Limited field</td>
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<tr>
<td>MLC</td>
<td>Multi-leaf collimator</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NCRI</td>
<td>National Cancer Research Institute</td>
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<tr>
<td>NCRN</td>
<td>National Cancer Research Network</td>
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<tr>
<td>NSABP</td>
<td>National Surgical Adjuvant Breast Project</td>
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<tr>
<td>NTCP</td>
<td>Normal tissue complication probability</td>
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<td>OAR</td>
<td>Organ at risk</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>OR</td>
<td>Over reactor</td>
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<tr>
<td>PRIME</td>
<td>Post-operative Radiotherapy in Minimal Risk Elderly Patients</td>
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<tr>
<td>PTV</td>
<td>Planning target volume</td>
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<tr>
<td>RAPPER</td>
<td>Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy</td>
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<tr>
<td>RTOG</td>
<td>Radiotherapy Oncology Group</td>
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<tr>
<td>SECRAB</td>
<td>Sequencing of Chemotherapy and Radiotherapy in Adjuvant Breast Cancer</td>
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<tr>
<td>SFRT</td>
<td>Segmented field radiotherapy</td>
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<tr>
<td>SNP</td>
<td>Single nucleotide polymorphism</td>
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<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
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<td>START</td>
<td>Standardisation of Breast Radiotherapy</td>
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<tr>
<td>STV</td>
<td>Systematic treatment volume</td>
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<tr>
<td>TARGIT</td>
<td>Intra-operative targeted radiotherapy</td>
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<tr>
<td>TGF-β</td>
<td>Transforming growth factor beta</td>
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<tr>
<td>WF</td>
<td>Wide field</td>
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Chapter 1. Introduction

1.1 Why is breast radiotherapy important?
Breast cancer is the most common cancer in women in Europe, with approximately 180,000 new cases per year. The majority are detected at an early stage and are often managed with conservation surgery, post-operative radiotherapy and increasingly, systemic treatment. Breast irradiation is a major component of radiotherapy workload, and it currently utilises 30% of radiotherapy resources in the UK [1].

That radiotherapy after conservative breast surgery or mastectomy significantly reduces the risk of loco-regional recurrence compared with surgery alone, has been shown in a number of randomised-controlled trials, including the landmark National Surgical Adjuvant Breast Project (NSABP) B-06 study [2]. In addition, the Early Breast Cancer Trialists Collaborative Group (EBCTCG) systematic overview of radiotherapy confirmed that improved local control impacted on the development of distant relapse and subsequent survival from breast cancer. It found a 4-fold reduction in local recurrence risk after breast conservation surgery and reported that prevention of 4 local recurrences prevents 1 breast cancer death [3]. Two subsequent randomised trials have demonstrated an overall survival benefit of approximately 9% in node-positive women given both radiotherapy and systemic treatment following mastectomy [4,5]. In addition, 2 meta-analyses of the effects of radiotherapy in early breast cancer have demonstrated a long-term overall survival improvement in irradiated patients [6, 7].

Despite this, concerns have been raised by the results of a meta-analysis which indicated that although post-operative radiotherapy reduces the risk of death from breast cancer, this may be offset by an increase in cardiovascular mortality, resulting in equivalent survival overall [8]. A significant increase in death from vascular causes in patients receiving radiotherapy has also been reported in the EBCTCG systemic overview. However, these data were obtained from patients treated with older equipment and techniques and the long-term follow-up of patients treated with more modern techniques is likely to show considerably lower risks.

The use of systemic treatment (chemotherapy and hormonal therapy) has increased considerably in recent years. This prompted several studies to ask the question: can radiotherapy be avoided after conservative breast surgery, if systemic treatment is given? In the Scottish Trial, all patients received systemic treatment with either chemotherapy or tamoxifen. There was a loco-regional relapse rate of 24.5% in the non-irradiated group compared with 5.8% following breast irradiation and a non-significant trend towards fewer distant metastases in the radiotherapy group [9]. Another
Introduction

trial randomised high-risk patients with 10 or more positive axillary lymph nodes. All patients had standard chemotherapy, some had tamoxifen, and a few had intensification chemotherapy with autologous bone marrow transplant. It was demonstrated that radiotherapy was the most important factor influencing relapse rate, and the disease-free survival was significantly improved in the radiotherapy group, with a trend for increased overall survival [10].

Fisher et al investigated the effect of tamoxifen alone, radiotherapy and placebo, and radiotherapy plus tamoxifen on ipsilateral breast tumour recurrence (IBTR) in node-negative patients with tumours \( \leq 1 \text{cm} \) [11]. Cumulative incidence of IBTR through 8 years was 16.5% with tamoxifen alone, 9.3% with radiotherapy and placebo, and 2.8% with radiotherapy and tamoxifen. Radiotherapy reduced IBTR below the level achieved with tamoxifen alone, regardless of oestrogen receptor status.

These studies have proved that radiotherapy is essential following local breast excision for the majority of patients and cannot be substituted by systemic treatment alone. On-going studies are addressing whether radiotherapy can be avoided in low-risk patients, such as older patients with low grade, lymph node negative tumours (PRIME Trial; post-operative radiotherapy in minimal risk elderly patients). However, to date, no randomised controlled trial has identified a low risk group with invasive breast cancer where radiotherapy can be avoided following breast conservation.

1.2 What are the current problems with breast radiotherapy?

Breast radiotherapy is actually very challenging, as the anatomy and surrounding structures make this an inherently difficult site to irradiate in a homogeneous manner. It has a complex 3-dimensional (3D) shape, which may have been modified further by surgery, and it is located at the body-air interface. There are also important organs at risk in close proximity such as the lungs and heart (in the case of left-sided tumours). Single plane 2-dimensional (2D) radiotherapy breast plans can lead to substantial dose inhomogeneities, particularly in women with larger breasts [12]. An inhomogeneous dose may lead to increased normal tissue side effects and poor cosmetic results, which can cause significant psychological morbidity for patients [13]. The tumour bed is considered to be the site at highest risk of tumour recurrence, but conventional ‘clinical’ methods of localisation are inaccurate [14 – 20]. Inadequate coverage of the tumour bed could result in sub-optimal local control.

Given these problems, one would expect to see the use of 3D imaging and radiotherapy planning for this tumour type. However, despite many advances in radiation techniques in other sites of the
body, the majority of breast cancer patients are still planned using 2D data and treated with paired tangential fields. What is the reason for this discrepancy? The problem is 2-fold: firstly, lack of radiotherapy resources as many UK oncology centres have limited access to computed tomography (CT), 3D imaging and planning. Therefore, breast radiotherapy, which comprises one-third of the workload, is not seen as a priority for CT-planning. In addition, the change in practice would also require the use of expensive CT-compatible breast boards and extra resources for more time-consuming radiotherapy techniques, such as Intensity modulated radiotherapy (IMRT). Secondly, there is a lack of clinical evidence showing an improvement in outcome with 3D imaging and planning in breast cancer, which reduces the impetus to change practice.

1.3 Aim of thesis

1.3.1 Summary

Radiotherapy is clearly established in the management of breast cancer to increase both loco-regional control and survival. The challenge now is to reduce treatment-related morbidity without losing efficacy, and increase tumour control with no increase in side effects, for patients at low and high risk of recurrence respectively. The overall aim of this research, therefore, is to develop strategies to optimise the therapeutic ratio for patients receiving breast radiotherapy following conservation surgery. Specific aims are outlined below:

1.3.1.1 Reduction in normal tissue side effects

I aim to develop novel methods of 3D imaging and IMRT planning to improve dose homogeneity throughout the breast. The clinical effects of these techniques in terms of reduction in normal tissue side effects will then be assessed within a randomised clinical trial. A novel analytical method of quantifying change in breast volume following radiotherapy will be used in conjunction with conventional assessment of normal tissue changes.

1.3.1.2 Improvement in tumour control

I aim to assess a novel method of localising the tumour bed using 3D ultrasound. Accurate localisation of the tumour bed is highly desirable for whole breast irradiation, and obligatory for more ‘targeted’ radiotherapy. The latter includes partial breast irradiation for patients at lower risk of recurrence, whereby the region around the tumour bed is treated and the remaining breast is spared. In addition, patients at higher risk of recurrence could be treated with a concomitant photon boost centred on the tumour bed, with decreasing dose levels to regions more distant to the tumour bed. Clearly, success of these approaches depends on adequately localising and treating the region at highest risk of recurrence.
1.3.2 Hypotheses

**Hypothesis 1:**

3D optical data using the Minolta Vivid 700 laser camera provides an alternative to CT for 3D breast radiotherapy planning.

Given the resource constraints for CT planning, I aim to develop a novel method of obtaining 3D data using a free-standing laser camera, and utilising this for a radiotherapy dosimetry study (see hypothesis 2.1). The accuracy of this technique will be compared with CT planning.

**Hypothesis 2.1:**

A dosimetry study will show that breast radiotherapy dose homogeneity can be improved with simple forward-planned IMRT techniques compared with standard 2D radiotherapy.

Forward-planned IMRT is a relatively simple method of IMRT that does not require an inverse-planning computer. Smaller radiotherapy fields are added to the main treatment fields to improve dose inhomogeneities produced by conventional 2D breast radiotherapy. This can be achieved with standard rectangular fields, or shaped fields using a multi-leaf collimator. This simple technique could therefore be implemented without the need for complex technology.

**Hypothesis 2.2:**

A randomised controlled trial comparing standard 2D breast radiotherapy with forward-planned IMRT will demonstrate the clinical benefit for patients.

I aim to design and implement a randomised controlled trial, which will test the clinical worth of IMRT for breast cancer, in terms of cosmetic outcome. Clearly, the final results are beyond the time scale of this thesis, but I intend to review the progress of the trial to date.

**Hypothesis 3:**

3D optical data obtained with the laser camera provides an analytical assessment tool for measuring breast cosmesis following breast conservation treatment.

The conventional methods of assessing normal breast tissue changes following radiotherapy include clinical examination and photographic change over time. These methods have been validated but nevertheless are not ideal, due to coarse discontinuous classification systems and inter-observer variability. It is unlikely that post-radiation changes have been quantified uniformly in many studies to date, making comparisons between different studies extremely difficult. It is therefore essential to develop a robust analytical method for measuring these normal tissue changes so that the clinical effects of different radiotherapy techniques can be assessed accurately. I intend to develop such a method for implementation, in conjunction with conventional methods, within the setting of the randomised breast radiotherapy trial (hypothesis 2.2).
Hypothesis 4:

A 3D ultrasound method can accurately localise the tumour bed.

I aim to compare this novel method of tumour bed localisation with other techniques using 2D ultrasound, surgical clips and CT scanning. The 3D ultrasound method will be validated in a phantom study, and then investigated in the clinical setting within a radiotherapy planning study.
Chapter 2. Review of the literature

2.1 Reduction of radiotherapy-induced late complications in early breast cancer: the role of intensity modulated radiation therapy (IMRT) and partial breast irradiation. Part I - Normal tissue complications.

2.1.1 Introduction
Radiotherapy following conservation surgery has been proven to decrease local relapse and death from breast cancer and is now firmly established in the management of early breast carcinoma. Currently, the challenge is to minimise the morbidity caused by this treatment without losing its efficacy. This review will be divided into 2 parts, with Part I focusing on the radiation factors contributing to late normal tissue complications following radiotherapy for early breast cancer. Three major normal tissue side effects will be discussed: cosmetic outcome, cardiac complications and pulmonary side effects. This review is based on Medline and Pubmed literature searches using the key words 'breast neoplasms', 'radiotherapy' and 'side effects'.

2.1.2 Cosmetic outcome following breast radiotherapy
2.1.2.1 What is the nature and extent of the problem?
The principle long-term effects that impair cosmesis are fibrosis and induration of the breast. Fibrosis and atrophy are the result of specific responses of fibrocytes to irradiation. Fibrosis represents a proliferative response of the surviving fibrocytes to growth factors released by injury, and atrophy reflects both loss of fibrocytes and collagen reabsorption [21]. There is also evidence that transforming growth factor beta (TGF-β) plays a key role in the development of radiation-induced fibrosis [22]. Depending on the severity of late normal tissue changes, the clinical picture includes induration, hardening, change in shape and decrease in volume of the treated breast.

The extent of this problem is sizable, as shown by the pilot study for the START (Standardisation of breast radiotherapy) trial carried out at the Royal Marsden Hospital and Gloucestershire Oncology Centre involving 1410 patients. This suggested that the probability of observing some late radiation change by 5 years for patients receiving 50 Gy in 25 daily fractions, is approximately 40% [23]. A follow-up study of mastectomy patients post-radiotherapy showed that 90% of moderate or severe complications were present within 3.2 years and 4.7 years for fibrosis and telangiectasia respectively [24]. Although the frequencies of the complications seem to reach a stable level within 3 to 5 years, the clinical picture of damage may progress in individual patients over time [24, 25]. In addition, the time of onset and rate of progression may correlate with the final severity of the late normal tissue side effects [26].
2.1.2.2 How important is cosmetic outcome for patients?
Research has demonstrated that breast cancer patients rate cosmetic outcome as very important compared with other quality of life parameters [27]. A study of 254 patients treated with wide local excision for early breast cancer, of which 86% had post-operative radiotherapy, showed that radiotherapy negatively influences cosmesis, and that cosmetic outcome is correlated with patient satisfaction [28]. The same cohort was the subject of a parallel study, which demonstrated a strong correlation between psychological well being and cosmetic result [13]. In particular, cosmesis was related to patient satisfaction, anxiety and depression, body image, feelings of sexual attractiveness and self-esteem. There was also a strong correlation between body image and patient age, with younger women being more sensitive to body image alterations. Another study has demonstrated that the association between cosmetic result and self-reported psychosocial health was strongest in younger patients [29]. This is particularly relevant as the number of patients with early breast cancer is increasing due to screening.

2.1.2.3 Non-radiation factors contributing to a worse cosmetic outcome
Before focusing on radiotherapy, it is important to mention the other factors that may contribute to a poor cosmetic result. Patient-related factors can be divided into extrinsic and intrinsic (cellular) factors. Extrinsic factors include age, smoking, immunosuppression, cardiovascular disease and diabetes [30]. Another patient-related factor is breast size. Larger breasts correlate with worse cosmetic outcome and appear to relate to a greater dose inhomogeneity, which will be discussed in more detail below [31].

Intrinsic factors include individual variation in radiosensitivity, and from analysis of studies where the dosimetry was very well controlled, it is thought that 70-80% of normal tissue effects may be due to intrinsic factors [32] (see Figure 2.1). It must emphasised that these data were obtained using uniform dosimetry. Much work has been done to try and correlate in-vitro radiosensitivity with clinical outcome in patients, but at present there is no predictive test for individual intrinsic radiosensitivity [33 – 36]. It is likely that future studies will focus on the genetic basis of variations in radiosensitivity.
Review of the literature

Figure 2.1 Schematic representation of the frequency distribution of normal tissue responses amongst patients, which would result from identical radiotherapy treatment, based on a perfect theoretical endpoint without threshold or saturation.

The proposed nomenclature for the different categories of tissue effect is shown on an arbitrary scale, ranging from 1 to 5. There is a range of reactions seen amongst normal patients, including some which are greater than average, with an approximately Gaussian distribution. On the basis that this range is the result of differences in normal tissue sensitivity, patients in Category 5 could be designated 'highly radiosensitive' or 'HR'. They must be distinguished from patients with excessively sensitive normal tissues, so-called Over-Reactors (ORs), who are considered to be outside the normal range. The definition of an 'Over-Reactor' has been suggested as an individual whose normal tissue reaction falls outside the (sensitive end of) the normal range. Such cases are typically very obvious in clinical practice, although they are exceedingly rare. Within the category of 'Over-Reactors' there is some variation in the severity of normal tissue response, and a division is suggested, somewhat arbitrarily, into 'Severe' and 'Extreme Over-Reactors'. The term 'Severe Over-Reactor' (Severe OR) is intended to imply a patient whose early reactions forced a major change in the radiotherapy prescription or who later developed very severe normal tissue reactions and serious morbidity. The term 'Extreme Over-Reactor' (Extreme OR) is suggested for exceptionally rare cases, where extreme reactions occur with lower doses than used in conventional radical treatment, typically with fatal consequences. For further details see: Burnet NG, Johansen J, Turesson I, Nyman J, Peacock JH. Describing patients' normal tissue reactions: Concerning the possibility of individualising radiotherapy dose prescriptions based on potential predictive assays of normal tissue radiosensitivity. Steering Committee of the BioMed2 European Union Concerted Action Programme on the Development of Predictive Tests of Normal Tissue Response to Radiation Therapy. Int J Cancer 1998; 79: 606-613. Reprinted with kind permission from International Journal of Cancer.

In addition, the tumour characteristics can affect ultimate breast cosmesis. The original position of the tumour can influence post-treatment breast appearance, with the worse outcome obtained with inferiorly or medially located breast cancers [37 - 39]. The volume of tissue excised (which was often related to the T-stage) has also been shown to adversely affect the cosmetic result [38, 40 - 43]. It follows that the volume of tissue removed is reflected in the type of breast surgery, e.g. wide local excision or quadrantectomy, and more extensive surgery has also been shown to correlate with cosmetic outcome [29, 44]. Patient- and tumour-related factors are largely difficult to control. In contrast, radiation-induced normal breast tissue changes have the potential to be controllable.
2.1.2.4 Effect of total dose, dose per fraction, and 'boost' treatment on cosmesis

The pioneering work of Hopewell \textit{et al} and Withers \textit{et al} using animal models, has contributed greatly in our understanding of late skin reactions \cite{45, 46}. Turesson and others have carried out patient studies, which have clearly demonstrated the dose-response relationship with late radiation effects following mastectomy and conservation surgery \cite{25, 34, 47, 48}. Specifically, a dose in excess of 50 Gy to the whole breast, has been shown to be a significant independent factor for worse cosmetic outcome \cite{49, 50}.

Yarnold \textit{et al} used results from a randomised breast fractionation trial to estimate the $\alpha/\beta$ ratio for late normal tissue changes \cite{51}. Using a Cox model of time to change in breast appearance, the $\alpha/\beta$ ratio was estimated to be 4.2 Gy. The point estimate for a marked change in breast appearance and for palpable induration was 2.5 Gy and 3.5 Gy respectively. Given that the $\alpha/\beta$ ratio for late normal breast tissue effects is assumed to be relatively low, it follows that a larger dose per fraction may produce a worse cosmetic result. The linear-quadratic model and discussion of the $\alpha/\beta$ ratio is covered in more detail by Joiner and van der Kogel \cite{52}.

A report of 592 early breast cancer patients treated with 45 Gy, 4 times a week over 4.5 weeks at the Institut Gustave-Roussy, showed that only applied fractional dose over 3.5 Gy was associated significantly with an overall worse cosmetic result using multivariate analysis \cite{42}. This large applied dose resulted from the practice of treating each tangential field on alternate days using a Cobalt Unit. Another report of 80 patients, showed that 6 patients received fraction sizes of 2.25 or 2.50 Gy and had clinically significant fibrosis and breast retraction. However, this small number of patients were also treated to a total dose of 60 Gy compared to other patients who received 50 Gy in 2 Gy fractions \cite{47}. Subsequent evidence has indicated that providing the total dose is reduced, a moderately larger dose per fraction appears to produce equivalent cosmesis and local control to 50 Gy in 25 daily fractions. This has been demonstrated by several Canadian and UK studies reporting the experience in using 40 Gy in 15 or 16 daily fractions \cite{48 - 50, 53}. A large trial of 1234 women randomised to either 50 Gy in 25 fractions over 35 days or 42.5 Gy in 16 fractions over 22 days, has shown equivalent overall survival and no significant difference in cosmetic outcome \cite{54}. A similar UK trial, START has recently closed and its results will clarify the relationship between dose per fraction and cosmetic outcome \cite{23}.

Several studies have reported that a radiation boost to the tumour bed is adversely associated with cosmetic outcome \cite{55, 56}. However, other studies were unable to demonstrate this association \cite{47, 57}. The large multi-centre European Organisation for research and Treatment of Cancer (EORTC) 22881/10882 trial was specifically designed to investigate the effect of a boost treatment in terms
of local control and cosmesis. It randomised a total of 5318 patients with early breast cancer to a boost of 16 Gy to the primary tumour or no further treatment, following wide local excision and radiotherapy to the whole breast. The cosmetic outcome was evaluated by a panel, scoring photographs of 731 patients taken soon after surgery and 3 years later, and by digitiser measurements of nipple retraction of 1141 patients post-operatively and at 3 years. There was no difference in cosmetic outcome between the 2 groups prior to radiotherapy, but the 3-year analysis with panel evaluation and digitiser measurements showed that boost had a negative impact on cosmetic outcome [38]. However, it has also been reported that the additional 16 Gy boost to the tumour bed reduces the risk of recurrence in women less than 50 years [58]. The therapeutic ratio of improvement in local control versus possible worse cosmesis associated with a radiotherapy boost, must therefore be assessed on an individual basis.

2.1.2.5 Effects of dose inhomogeneity on cosmesis.

A particularly important radiotherapy-related factor influencing late cosmesis is dose inhomogeneity. Figure 2.2 illustrates a conventional 2D tangential plan for a woman with large breasts. This shows a typical distribution of dose inhomogeneities with the high regions of dose under the thin end of the wedges. Moody et al investigated late changes in breast appearance in 559 women after conservation surgery and radiotherapy for early breast cancer [31]. Breast size was assessed from a post-surgical photograph and annual photographs were collected for 5 years following radiotherapy. Moderate or severe changes were present in 6%, 22% and 39% of women with small, medium and large breasts respectively. This demonstrated a strong association with late changes in breast appearance and breast size (see Figure 2.3).
Review of the literature

Figure 2.2 2D tangential breast plan for a woman with large breasts.
Under the thin end of both wedges there are regions of 105% of the prescribed dose.

Figure 2.3 Percentage probability of late radiation effect for breast tissue.
The graph illustrates that the percentage probability of late radiation effect for breast tissue increases with time and is greater for patients with larger breasts. Re-drawn from Moody et al [31].
Review of the literature

It was hypothesised that the increase in late radiation effect observed in larger breasts was related to greater dose inhomogeneity. A separate group of 37 women with limited CT data of the breasts were studied. A significant correlation between breast size and dose inhomogeneity was found in this small group. This clinical finding fits with radiobiological modelling as 'hot spots' created within an inhomogeneous dose distribution lead to an increase in both total dose and dose per fraction; the so-called 'double trouble' phenomenon described by Withers [52]. 3-dimensional CT planning was carried out in a further 20 patients treated with a tangential wedged field technique [12]. This illustrated that 0.2 to 23.8% of the breast received a dose outside 95-105% of the prescribed dose, and dose variations across the target volume varied by -10% to +15% of the dose prescription. There was a significantly worse dose homogeneity with increasing breast volume as measured using the CT data. Improvement in dose homogeneity is clearly an important goal for breast radiotherapy, and techniques to improve this will be discussed in Part 2 of this review.

2.1.2.6 Effect of systemic treatment in addition to radiotherapy

Other factors, such as adjuvant systemic therapy, have been postulated to enhance the effect of late radiation normal tissue damage. There are some reports that chemotherapy increases the risk of acute and late subcutaneous fibrosis, but there are also studies where this effect is not statistically significant [21]. The large Danish DBCG-82TM breast conservation trial demonstrated that chemotherapy was associated with a worse cosmetic result, but was not the case in the multi-centre centre EORTC trial 22881/10882 'boost trial.' Other studies have looked specifically at the timing of chemotherapy in relation to radiotherapy. In the majority of studies, there appears to be a greater risk of a poor cosmetic outcome when the chemotherapy is administered concomitantly with radiation [40, 59, 60]. This question will hopefully be clarified by the on-going SECRAB study (Sequencing of chemotherapy and radiotherapy in adjuvant breast cancer), which randomises patients between sequential chemotherapy and radiotherapy and concomitant treatment. It plans to recruit a sub-study of 300 trial patients to assess differences in toxicity, quality of life and cosmesis.

It has also been hypothesised that tamoxifen may affect late cosmesis in radiotherapy patients as it induces the cellular secretion of TGF-β, which is involved in the pathogenesis of fibrosis. Wazer et al published the results of their cohort of 498 women, of which 130 received tamoxifen 1 to 6 weeks (median 2.7 weeks) following completion of radiotherapy [61]. This retrospective study found no increase in poor cosmetic outcome in the tamoxifen-treated patients. Taylor et al also reported a non-randomised series, and found no evidence of worse cosmesis, whether tamoxifen was taken concomitantly with radiotherapy or following its completion [40]. In contrast, Azria et al assessed 147 women who received breast radiotherapy, and found that those treated with
concomitant tamoxifen (n = 43) had significantly higher rates of subcutaneous fibrosis [62]. This group concluded that tamoxifen should be delayed until completion of radiotherapy. In the absence of randomised controlled trial evidence, the optimal timing of tamoxifen and radiotherapy remains unclear. However, some centres that have a substantial waiting time for radiotherapy, may develop a pragmatic approach and commence tamoxifen prior to radiotherapy, rather than delay systemic hormonal treatment.

In summary, radiation-related factors contributing to a worse cosmetic result may be easier to modify than non-radiation related factors. As well as dose and fractionation, improvement of dose inhomogeneity, the selection of patients for boost treatment and the use of concurrent systemic treatment are important issues for the oncologist to consider. In addition, a patient-centred treatment approach demands that strategies to improve cosmetic outcome are investigated and implemented to minimise psychosocial morbidity.

2.1.3 Radiation-induced cardiac toxicity

2.1.3.1 What is the nature and extent of the problem?

Evidence of radiation-induced cardiac toxicity from randomised trial data

The 1987 overview of the 10-year mortality results of mature trials of simple or radical mastectomy randomised to radiation or not, showed a significant excess among patients given radiotherapy [8]. At that time, the details of the specific causes of death were unavailable but an update in 1994 included these data. This showed that the difference in overall mortality after 10 years was not as large as previously observed and had lost statistical significance. The excess mortality was confined to heart disease and the risk appeared to be greater in the earlier trials where older radiotherapy techniques were used [63]. In the last few years, more data from randomised trials have emerged to support the role of post-operative radiotherapy as a strategy to reduce death from breast cancer. However, there have been conflicting reports as to whether radiotherapy is a cause of excess cardiovascular mortality.

The EBCTCG published their most recent meta-analysis of the 10- and 20-year results from 40 unconfounded randomised radiotherapy trials for early breast cancer in 2000 [3]. The results demonstrated that breast cancer mortality was significantly reduced in the radiation group, but vascular mortality was also increased by radiotherapy (death rate ratio 1.30; p = 0.0007). The proportional excess of vascular deaths appeared to be as great during the first decade as afterwards, but the absolute rates were 3 times as great in the latter period. The overall 20-year survival was 37.1% with radiotherapy versus 35.9% in control (p = 0.06). It must be noted that the majority of patients in this meta-analysis had both axillary and internal mammary chain (IMC) irradiation in
addition to breast/chest wall radiotherapy. Therefore, some of the vascular events may have been due to large heart volumes irradiated with certain IMC techniques, or irradiation of the great vessels following axillary nodal irradiation. Information was not collected centrally on cardiac, carotid artery or other intrathoracic exposure to radiation, so a direct relationship between site of radiation exposure and cause of vascular death is impossible to establish.

Two Danish trials and 1 Canadian trial have demonstrated an overall survival benefit, of approximately 9%, in node-positive women given both radiotherapy and systemic treatment following mastectomy [4, 5, 64]. These patients were also treated with axillary and IMC irradiation. The mortality of ischaemic heart disease in the Danish high-risk patients receiving adjuvant post mastectomy systemic treatment with or without radiotherapy was analysed in a separate paper [65]. This showed that the actuarial risk of ischaemic heart disease was not increased in the radiotherapy group after 12 years. A similar conclusion was reported in a retrospective cohort linkage study of all breast cancer patients treated with breast conservation and radiotherapy at a single institution between 1982 and 1988 [66]. However, longer follow up of these studies is required as the EBCTCG meta-analysis suggested that 10 years of follow up may be insufficient to definitely rule out late cardiac mortality after adjuvant radiotherapy for breast cancer.

Dosimetry studies and radiobiological modelling for prediction of radiation-induced cardiac toxicity

As suggested by the updated meta-analysis of breast radiotherapy trials by Cuzick et al, it appears that the older radiation techniques were associated with greater cardiovascular mortality. A study has been carried out to compare the dose and irradiated volume delivered to the heart using older and more modern radiotherapy techniques [67]. The newer megavoltage techniques were shown to reduce the total heart dose and to spare the left circumflex and right coronary artery, but the dose to the left anterior descending artery remained unchanged. More complex radiotherapy techniques would therefore be required to reduce the dose to this vessel.

Another approach has been to use radiobiological modelling to predict normal tissue complication probabilities (NTCP) for excess cardiac mortality. One study showed a significant increase of the average NTCP of excess cardiac toxicity from 0.6% when the breast alone was irradiated, to around 2% when the locoregional nodes were included in the target volume, depending on the amount of heart in the radiotherapy portals [68]. The authors also found a good correlation between NTCP values and the Maximum Heart Distance (defined as the maximum distance of the heart contour, as seen in the beam’s eye view of the medial tangential field, to the medial field edge). No
Review of the literature

NTCP values above 1% were found for a Maximum Heart Distance of 1 cm, but the NTCP values increased steeply with Maximum Heart Distances of 2 cm or more. A similar study calculated a mean excess cardiac mortality of 1.8% for 100 left-sided breast patients treated with standard tangential breast radiotherapy [69]. However, there was a subgroup of patients where the risk was increased to about 9%. The risk in this subgroup was substantially reduced using methods of cardiac shielding or in 1 case, several intensity-modulated beams.

Cardiac function studies as predictors of radiation-induced toxicity

Several studies have investigated myocardial function following breast radiotherapy rather than cardiac mortality and morbidity. A small prospective study followed 17 left-sided breast cancer patients following radiotherapy [70]. All patients had radiotherapy plans showing part of the left ventricle receiving at least 85 to 95% of the total dose. Half of the patients exhibited new fixed scintigraphic defects after a mean of 13 months following radiotherapy, which corresponded well with the irradiated left ventricular volume. However, there were no changes on echocardiography or any deterioration of left ventricular function after this short follow-up period.

Another study reported the incidence of cardiac perfusion abnormalities in left-sided breast cancer patients treated with radiotherapy either with or without doxorubicin [71]. Single photon emission computed tomography (SPECT) was performed pre-chemotherapy, pre-radiotherapy and 6 months after irradiation. Of the patients receiving chemotherapy and radiotherapy, 100% (7/7) developed new perfusion defects compared with 50% (5/10) patients receiving radiotherapy alone. There was a suggestion that the defects observed in the radiation only group were related to the volume of left ventricle in the field. In contrast, among the patients in the combination group, new perfusion defects were observed regardless of the volume of left ventricle irradiated. It was found that the pattern of perfusion defect seemed to correlate with the radiotherapy field as opposed to coronary artery blood distribution. The authors state that this suggests damage at the microvascular level. As with the previous study, no patients developed myocardial infarction or congestive heart failure, but this would not be expected with such short follow-up. It therefore remains to be seen whether perfusion changes are related to long-term cardiac morbidity and mortality.

It is difficult to determine from the existing evidence the precise pathogenesis of radiation-induced vascular toxicity, but clearly it is desirable to minimise the volume of heart and great vessels irradiated. The extent of the problem is also difficult to quantify due to improvement in radiotherapy techniques. The literature on radiation-induced cardiac toxicity suggests that there was a considerable risk of cardiovascular morbidity and mortality associated with the older radiotherapy techniques. This appeared to reduce substantially with the introduction of megavoltage techniques.
and simulator-assisted planning. However, in recent years there has been a greater use of potentially cardiotoxic drugs (anthracyclines and anti-HER-2 monoclonal antibodies). In addition, we are now treating more screening-detected patients (the UK breast screening programme starts at age 50 and is being extended to include the 64 to 70 age group). Improved survival rates for a largely good prognosis group could potentially result in more women experiencing late cardiac toxicity many years after initial therapy. Also, trials have shown that most patients who have breast conservation surgery for ductal carcinoma in-situ (DCIS) benefit from breast radiotherapy [72, 73]. Thus, patients with DCIS are particularly at risk from the long-term side effects of radiotherapy, since they have an essentially non-fatal condition. Therefore, reduction of cardiac risk to an absolute minimum still remains an important goal for the clinical oncologist.

2.1.4 Radiation-induced lung toxicity

2.1.4.1 What is the nature and extent of the problem?

Pathogenesis of pulmonary toxicity

Pulmonary toxicity is a recognised complication following radiotherapy for breast cancer and may manifest as pneumonitis and/or pulmonary fibrosis. Generally, 2 distinct pathological phases of lung injury are seen: early radiation effects which manifest between 1 and 8 months after radiotherapy (pneumonitis), and late effects, which may develop in some patients from 6 months onwards (fibrosis) [74]. Recovery from the early inflammatory response and the development of fibrosis may be seen between 3 and 18 months. Radiation pneumonitis mostly precedes fibrosis, but both processes can also progress independently of each other. This 2-phase lung response was illustrated in a study assessing lung density changes from routine follow-up chest radiographs in post mastectomy radiotherapy patients [75]. Early density changes reach a maximum around 6 months after radiation and may resolve completely or partially. Late lung changes usually reach a plateau after 1 year, but some patients may have radiological progression for 5 years or more. Data on clinical effects are discussed below.

Factors increasing the risk of radiation-induced pulmonary toxicity

Various factors have been postulated to increase the risk of radiation-induced pulmonary toxicity. These include the volume of lung irradiated, the use of additional nodal fields, chemotherapy treatment, concurrent tamoxifen medication, smoking habits, age and pre-radiotherapy performance status. Many studies reach different conclusions regarding the impact of these factors on radiation toxicity.

The amount of lung irradiated, however, is frequently quoted to contribute to lung morbidity. Measurements of the lung from the beam’s eye view of the lateral field or simulator field have been
used by several authors as a surrogate for the volume of lung irradiated. This relationship was confirmed by a study that compared the lung volume (obtained from dose-volume histograms) and the central lung distance (CLD) [76]. It was found that a quadratic relationship exists between the CLD and the percentage of the lung irradiation. This results in a large increase in the percentage of lung volume in the radiation field, when the CLD is increased only by a small amount. Dose-volume data and NTCPs have also been used to predict pulmonary toxicity. It has been reported that a maximum lung distance inside the treatment field of 2 to 2.5 cm predicts a risk of pulmonary morbidity of about 1% for breast radiotherapy using a 2-field tangential pair technique [77]. This appears to correlate well with the clinical data available.

Use of locoregional fields for nodal irradiation is also consistently associated with an increase in pulmonary side effects, which may reflect the increased amount of lung irradiated. The use of chemotherapy is variably reported as increasing the risk of lung toxicity, and this appears to be related to the type, dose and timing in relation to the radiotherapy. Volume of irradiated lung, nodal fields, and use of chemotherapy are discussed in the following reports from the literature.

Evidence of radiation-induced pulmonary toxicity from clinical data

A retrospective study reviewed the records of 613 patients irradiated for breast cancer who had been followed up for more than 6 months [78]. Overall, radiation pneumonitis developed in 15 (2.4%) of patients; of which 12 had complete resolution of symptoms and 3 had persistent shortness of breath (follow-up times for these patients were not specified). Median onset of radiation pneumonitis was 3 months. Radiation pneumonitis developed in 4.1% of patients receiving nodal irradiation compared with only 0.9% of those treated with breast radiotherapy alone. Multivariate analysis also confirmed locoregional irradiation as a risk factor for pneumonitis. Chemotherapy increased the risk of lung toxicity on univariate analysis, but this was lost on multivariate analysis. There was also a non-significant trend for increasing radiation pneumonitis as the average of the superior and inferior mid-lung distance (ALD) measured on the lateral simulator field increased. For ALD values of below 2 cm, below 3 cm, or above 3 cm, the rate of pneumonitis increased from 4%, to 6% and 14% respectively.

Another retrospective study of 1624 breast radiotherapy patients gave similar results with 17 (1%) developing radiation pneumonitis [79]. Five of these patients required outpatient steroid treatment, but all patients had complete resolution of pulmonary symptoms. Median onset of radiation pneumonitis was 7 weeks. Three percent (11/328) of patients treated with chemotherapy and a 3-field technique developed pneumonitis, compared with only 0.5% (6/1296) of all other patients. When the chemotherapy was administered concomitantly with 3-field radiotherapy, the incidence
increased to 8.8% (8/92). Five of the 17 patients had permanent scarring on chest radiograph, but no patients had late or persistent pulmonary problems.

Due to variation in the clinical definition of radiation pneumonitis, pulmonary function tests have been used to try and quantify possible pulmonary toxicity. An example is a study of 110 breast and lymphoma patients who had SPECT perfusion and ventilation scans and CT scans before and at 3, 18 and 48 months after radiotherapy [74]. For all patients, a partial recovery from early local perfusion, ventilation, and density changes was seen between 3 and 18 months after radiotherapy. After 18 months, local lung function did not improve (only lymphoma patients had scans at 48 months). The authors state that these findings are in keeping with histological reports of radiation-induced lung injury.

In summary, the literature concerning radiation-induced lung toxicity suggests that pneumonitis rarely causes a clinical problem if modern radiotherapy techniques are used and the volume of lung irradiated is limited. Radiation pneumonitis may be observed in the 6 months following radiotherapy, but this usually is mild, rarely requires steroid treatment and completely resolves in the vast majority of patients. It is seen in less than 1% of patients receiving breast only radiotherapy, but the incidence appears to increase with nodal irradiation, particularly when chemotherapy is administered concomitantly. Late pulmonary fibrosis is uncommon and is usually identified radiologically in asymptomatic patients. There is very little data regarding the long-term consequences of radiation induced pulmonary fibrosis from breast radiotherapy, suggesting that it rarely causes a clinical problem. Therefore future investigations of lung changes following breast radiotherapy are more relevant for normal tissue studies rather than clinical care. However, pulmonary toxicity must be considered when using loco-regional radiation for locally advanced tumours, especially if chemotherapy is also given. In this situation, the use of IMRT may be considered to reduce morbidity, whilst maximising chance of cure.

2.1.5 Conclusions
Breast cosmesis is an important issue for patients, and the oncologist should consider the effect of radiotherapy dose, fractionation, homogeneity and concurrent systemic treatment on this outcome. In addition, late cardiac morbidity is an important issue, especially for very good prognostic groups with early breast cancer or DCIS, who will live with the late sequelae of treatment. Pulmonary toxicity is uncommon, but may be more relevant for locoregional breast radiotherapy. A knowledge of normal tissue side effects thus enables the oncologist to advise treatment based on an individual’s likelihood of risk and benefit, i.e. application of the therapeutic ratio. More advanced
radiotherapy techniques, such as IMRT and conformal partial breast irradiation, may improve this therapeutic ratio.
2.2 Reduction of radiotherapy-induced late complications in early breast cancer: the role of intensity modulated radiation therapy (IMRT) and partial breast irradiation. Part II: Radiotherapy strategies to reduce radiation-induced late effects.

2.2.1 Introduction
The aim of part II of this review is to discuss how IMRT and partial breast irradiation may improve the therapeutic ratio for patients with early breast cancer following conservation surgery. This review is based on Medline and Pubmed literature searches using the key words 'breast neoplasms', 'radiotherapy', 'intensity-modulated radiotherapy' and 'partial breast irradiation'.

2.2.2 Intensity-modulated radiotherapy
IMRT describes the situation where the radiation fluence varies across the beam. The major value of IMRT for breast radiotherapy is reduction of dose inhomogeneity within the target volume. A secondary advantage is the reduction of high dose irradiation to some normal tissues. Three dimensional radiotherapy planning and IMRT techniques have been developed with the aim of improving dose homogeneity to the breast and reducing normal tissue side effects. Its clinical use in breast radiotherapy, however, is still very limited. Several methods of intensity modulation will now be discussed.

2.2.2.1 Intensity modulation using physical compensators
The concept of IMRT is not new: wedges and tissue compensators are both examples of techniques that alter radiation fluence, and have been used for many years. Initial IMRT dosimetry studies compared the use of metal compensators with conventional tangential field radiotherapy. The studies demonstrated improved dose homogeneity with the former method [80, 81]. One institution has developed a compensator library whereby the most appropriate compensator is selected for the patient after analysis of their breast dose volume histogram (DVH) [82]. Approximately 50% of patients were treated with compensators (46% from the library and 4% with individual compensators). The compensators reduced the variation in dose distribution in all compared with standard tangential plans and the system was reported to be simple and reliable in practice.

Compensators and multi-leaf collimator (MLC) based IMRT have also been directly compared with conventional breast radiotherapy. It was shown that all intensity modulation strategies produced improved dose homogeneity compared with standard techniques, but preparation and delivery of the MLC based IMRT plans took significantly longer than conventional or physical compensator methods [83 - 85]. However, the disadvantages of metal compensators are the time taken for production and the physical handling necessary for the radiographers. In addition, the last
few years have seen improvements in the time taken to plan and treat with IMRT (see discussion: forward-planned IMRT).

2.2.2.2 Inverse-planned breast IMRT

Inverse-planned radiotherapy describes the technique whereby the clinician selects the required dose to the target and states dose limits to the surrounding organs at risk (OAR's). A computer algorithm then creates a fluence map for the required dose distribution, which divides each field into a number of segments. This has the unique ability of delivering radiation dose to a concave volume [86]. These field segments can be delivered by either tomotherapy techniques or by MLC methods ('step and shoot' or dynamic) [86].

There have been several studies comparing inverse-planned IMRT with standard tangential field radiotherapy for breast cancer [83, 87 – 92]. All reported improvement in breast homogeneity and reduction of high-dose irradiation of surrounding OARs such as the heart and ipsilateral lung. However, the multiple beams usually necessary for the intensity modulation, could result in a substantial volume of normal tissue receiving a low radiation dose, i.e. a high integral dose [91, 92]. This may have implications for the development of second radiation-induced malignancies, particularly in young women with low-risk breast cancer or those with predisposing genes. In addition, inverse-planned IMRT is still considerably more time consuming than standard breast radiotherapy planning. Therefore, this technology may be best reserved, at present, for specific cases such as bilateral breast cancer, treatment of the internal mammary nodes in addition to the breast, and patients with pectus excavatum. Such patients have been studied with inverse-planned IMRT and the dosimetry has been found to be superior to conventional breast radiotherapy techniques [92].

2.2.2.3 Forward-planned breast IMRT

Forward-planned IMRT is a relatively simple method of IMRT that does not require an inverse-planning computer. Smaller radiotherapy fields are added to the main treatment fields to improve dose inhomogeneities produced by conventional 2D breast radiotherapy. This can be achieved with standard rectangular fields, or shaped fields using a multi-leaf collimator. This simple technique can therefore be implemented without the need for complex technology and treatment delivery is similar to standard breast radiotherapy if field autosequencing is used [93]. In addition, the quality assurance for forward-planned IMRT is usually considerably less time-consuming than inverse-planned IMRT. Forward-planned IMRT lends itself to breast radiotherapy as 80-90% of the treatment can be delivered using standard tangential fields and only a small amount of modulation is required. Several techniques will be discussed which consist of slightly different methods.
Donovan et al used calibrated intensity data from portal imaging data to calculate radiological thickness maps for 14 patients in a planning study [94]. A pseudo-CT outline set was derived from this information and used to create an ideal intensity-modulated beam map. The beams were implemented using multiple static fields added to standard wedged tangential fields. Reduction of the high dose regions of the irradiated volume was achieved in 12 of the 14 patients.

Van Asselen et al used the equivalent path length map obtained from raytracing through CT data sets from 5 patients, to create multiple static fields with 4 intensity steps [95]. Dose inhomogeneity was improved in 4 out of 5 patients and the mean lung dose was reduced by 10%. Lo et al created static MLC beam segments from radiological thickness maps based on digitally reconstructed breast images [96]. This planning study of 20 patients showed that the range of ‘hot spots’ was reduced from 7-22% to 7-15% with the IMRT method.

Several authors have used the beam’s eye view of the projected isodoses for the tangential fields to create multiple static fields to shield the area of higher dose [97 – 100]. Kestin et al displayed 5 isodose surfaces as 3D objects in 5% increments between 100 and 120% [97]. Auto-blocking was used to create an aperture to conform to a particular isodose surface. Zackrisson et al described a similar technique, but the MLCs were moved manually to cover the hot spots and typically only 1 extra modulated field was added to each tangent [98]. Richmond et al used the same method as Zackrisson and found that the mean percentage receiving over 107% of the planning target volume was 5.3% and 19.8% for the MLC technique and standard technique respectively [100]. We also developed a manual method of moving the MLC leaves using 3D planning data from an optical imaging device [99]. The resulting dose distribution could be re-calculated after addition of each segment, allowing further segments to be added if needed (see Figures 2.4 and 2.5). All methods reported improvements in dose homogeneity throughout the breast.
Review of the literature

**Figure 2.4 Forward IMRT planning using the beam’s eye view isodoses.**
The picture shows 2 beam’s eye view images of the same breast with the isodoses displayed as a colourwash. Left picture: the dose distribution for a standard 2-field plan is shown. The high dose areas equal or above 107% of the prescribed dose are shown by the deeper orange colour (outlined in red). The lower dose areas equal or below 95% of the prescribed dose are shown by the green colour (outlined in blue). Right picture: the dose distribution is improved with the addition of 2 additional MLC-shaped fields, which have the effect of decreasing the regions of higher dose and boosting the regions of lower dose.

**Figure 2.5 Comparison of D V H for standard and IMRT breast radiotherapy**
The graph compares the differential DVHs for the standard and IMRT breast plans displayed in figure 2.4. The IMRT plan is superior as the peak is sharper and shifted to the left.

Another technique has been developed by Chui et al, which used a series of pencil beams to model the required intensity modulation [101]. For each beam, a grid of pencil beam segments was created and the dose to the midpoint of each pencil beam segment in the open field was calculated. The optimum intensity for each pencil beam was proportional to the inverse of the midpoint dose. 15 patients with left-side breast cancer were planned with a standard wedged pair technique, inverse-planned IMRT and this method of forward-planned IMRT. The IMRT techniques were found to be superior to the standard treatment: both methods produced a more homogenous dose to
the breast and reduced the dose to the heart, ipsilateral lung and contralateral breast. The planning and treatment time for forward-planned IMRT, however, was significantly quicker than the inverse-planned technique.

2.2.2.4 Breast IMRT and clinical outcome

IMRT has evolved very rapidly over the last few years and the vast majority of papers concerning this subject report dosimetric analysis as opposed to clinical outcome. The early clinical experience of 10 patients with breast cancer treated with IMRT using multiple static fields, showed minimal or no acute skin reactions [97]. The same institution later reported the cosmetic results at 12 months of 95 patients treated with IMRT [102]. The cosmetic outcome was rated as excellent/good in 94 patients (99%), and no telangiectasia, significant fibrosis or persistent breast pain was noted.

To date, there has been only 1 randomised controlled trial designed to investigate late normal tissue side effects [51]. This was carried out at the Royal Marsden Hospital, UK and consisted of 305 patients with early breast cancer. Women with larger breasts were specifically selected for the trial on the basis that these patients would have the greatest dose inhomogeneities. They were randomised to either standard radiotherapy or forward-planned IMRT using either a metal compensator or multiple static fields. The primary endpoint was breast appearance following radiotherapy, measured with serial photographs. Interim analysis was completed in September 2002. A change in breast appearance was scored in 60/116 (52%) allocated standard 2D treatment and 42/117 (36%) patients allocated IMRT (p = 0.05). A further randomised controlled trial investigating the clinical relevance of IMRT for women with all breast sizes is underway at Addenbrooke’s Oncology Centre, Cambridge (see chapter 5). Two confirmatory trials would provide the impetus to adopt IMRT for breast cancer patients as standard practice in the UK with likely benefits for many women.

2.2.3 Partial breast irradiation

An alternative strategy to minimise irradiation of OARs, such as the heart and lungs, is to irradiate only part of the breast. The planned radiotherapy volume is centred on the position of the excised tumour and this requires accurate localisation of the tumour bed. The rationale for partial breast irradiation and the reported studies, methods of tumour localisation and the concept of breast radiotherapy target volumes will now be discussed.

2.2.3.1 Rationale for partial breast irradiation and reported studies

Breast cancer multifocality has been studied in a group of mastectomy patients who would have been eligible for breast conservation surgery [103]. This pathological study illustrated that the
density of tumour foci decreased with distance from the reference tumour. For invasive breast tumours less than or equal to 2 cm, 28% had non-invasive foci at a distance of greater than 2 cm from the reference tumour, and 14% had invasive tumour foci at the same distance. Randomised trials of breast conservation with or without radiotherapy have also shown that tumour recurrences usually occur close to the site of the original tumour. The NSABP B-06 trial reported that 86% of local recurrences were within or close to the reference quadrant [2]. The Milan trial had similar findings, with 79% of recurrences occurring at or close to the original tumour site [104].

These findings have raised the question whether whole breast radiotherapy is necessary for all breast cancer patients following conservation surgery, or whether just part of the breast surrounding the tumour bed could be targeted. This concept of partial breast radiotherapy is attractive, as it is likely to reduce toxicity, due to a smaller volume of normal tissue irradiated. Clearly, this strategy will only improve the therapeutic ratio, if normal tissue side effects are reduced whilst maintaining equivalent/better local control. Thus it is essential that the tumour bed is localised accurately and attention is paid to radiotherapy volumes (see later discussion: clinical target volume (CTV) and planning target volume (PTV)). One step further is to postulate that reducing the breast tissue volume requiring a tumouricidal radiation dose, may allow use of larger radiation doses per fraction (i.e. accelerating overall treatment time) without additional normal tissue toxicity [105]. The potential advantages of accelerated partial breast irradiation (APBI) can be divided into health economic, patient satisfaction and radiobiological issues. Firstly, a substantial reduction in the number of radiotherapy fractions would be welcomed by institutions, as breast irradiation constitutes a significant proportional of the workload (30% in the UK). This would impact positively on radiotherapy waiting lists. Secondly, a shorter overall treatment time is more attractive to patients and is particularly important in remote areas, where patients may opt for mastectomy rather than travel long distances over a period of weeks for radiotherapy [106]. Lastly, there is emerging evidence that the \( \alpha/\beta \) for breast tumours is \( \sim 4 \) Gy, which implies that local control may improve with a higher dose per fraction [51]. In addition, local radiotherapy could be completed prior to systemic therapy without significant delay of either treatment. However, the \( \alpha/\beta \) for late normal tissue change is also around 3-4 Gy, but the smaller volume of normal tissue irradiated may modify the potential decrease in therapeutic ratio.

To date, there is a paucity of data relating to the normal tissue consequences of partial breast irradiation. Over a decade ago, Emami stated in his seminal paper that 'there is a critical need for more accurate information about the tolerance of normal tissue to radiation. This is not only related to the time-dose parameters, but specifically to the partial volumes of normal tissue receiving variable dose levels' [107]. Unfortunately, this extensive literature review did not include any
information specifically pertaining to the breast tissue, because whole breast radiotherapy was (and
still is) the standard treatment. Probably the best evidence available is from the EORTC ‘boost
versus no boost’ randomised trial, which investigated the effect of a boost to the tumour bed in
addition to whole breast radiotherapy. This showed that a boost volume of > 200 cm³ decreased the
probability of an excellent/good global cosmetic result in the univariate analysis, but significance
was not retained in the multivariate model [108].

A number of studies have investigated the effect of partial breast irradiation and these can be
divided into brachytherapy, intra-operative radiotherapy, and external beam techniques. A
discussion of these studies follows with particular attention to the effect on normal tissue side
effects and local control, of irradiated breast volume, dose and fractionation, and patient selection
(where this information is available).

2.2.3.2 Brachytherapy techniques
A series of 27 patients at Guy’s Hospital in the UK, were treated with a low dose rate (LDR)
iridium implant to the tumour bed as sole radiation treatment [109]. The surgery consisted of
tumourectomy with no attempt to achieve wide excision. A rigid implant was inserted at this time,
with the aim of achieving a 2 cm margin of normal tissue around the tumour bed. The dose
delivered was 55 Gy to the 85% isodose continuously over 5 days. After 6 years median follow-up,
local recurrence was apparent in 6 patients (37%), which compared unfavourably with historical
controls. None of the patients developed fibrosis, but 1 patient developed telangiectasis at the site
of a superficially placed iridium wire. It was concluded that this was an ineffective method of
radiotherapy treatment. However, 15 patients had positive margins and 12 patients were node
positive, suggesting that inadequate surgery and unsuitable patient selection contributed to the
outcome.

Perera et al originally reported a series of 39 patients who were treated with high dose rate (HDR)
brachytherapy only following conservation surgery [110]. The total dose was 37.2 Gy delivered in
10 fractions, twice daily over 5 to 7 days. The median volume encompassed by the 37.2 Gy isodose
shell was 30.35 cm³ (range: 9.6 – 100.8 cm³). After a median follow-up of 20 months, 1 patient had
recurred and was salvaged with further surgery and external beam radiotherapy. Patient-rated
satisfaction was high, but 4 cases of fat necrosis were noted. An update of the same series has
recently been published at a median follow-up of 91 months [111]. They report a total of 6
recurrences (16%), which is greater than expected for whole breast radiotherapy following breast
conservation surgery. Four recurrences were outside the treated volume. An accompanying
editorial has suggested that these results may be due to a sub-optimal technique and less than ideal
set of patients, as 3 patients had an extensive intraductal component (EIC), 6 had positive lymph nodes, 2 had unknown nodal status, and 12 had less than 2 mm margins [106]. In addition, the dose was prescribed to encompass the tumour bed without a margin for sub-clinical spread, resulting in a small median implant volume with no allowance for CTV.

Other brachytherapy studies have reported more favourable results. Vicini et al at the William Beaumont Hospital in the USA, used LDR iodine-125 implant as sole radiotherapy treatment for 60 women [112]. A total of 50 Gy was delivered over 96 hours to the surgical bed plus a 2 cm margin. All 19 patients followed up for a minimum of 24 months post therapy were noted to have good to excellent cosmetic results. It was reported that 51 patients had obtained their 6 – 12 month follow-up mammogram and no local recurrences were noted at this early stage. The patient characteristics were different as EIC, infiltrating lobular features, young age, and node positivity (from 1995) were all excluded from this treatment. In addition, the negative margins required were equal to or more than 2 mm. This institution has also reported their experience of HDR brachytherapy (32 Gy in 8 fractions twice daily over 4 days) in 37 patients; the patient selection criteria remained stringent [113]. There was 1 breast recurrence after a median follow up of 31 months, and cosmetic outcome was reported as good or excellent in all patients. A more recent report of 199 patients receiving either LDR or HDR brachytherapy at William Beaumont showed a 5-year actuarial total recurrence rate of 1.2% at a median follow-up of 65 months [106].

King et al carried out a phase I/II trial of either LDR or HDR brachytherapy in a total of 50 patients (51 breasts) [114]. A dose of either 45 Gy continuously over 4 days or 32 Gy in 8 fractions, twice daily over 4 days, was given to the surgical bed (segmental mastectomy) with a 2 – 3 cm margin. Patient eligibility criteria included tumour \( \leq 4 \) cm, negative inked surgical margins and no more than 3 positive axillary nodes. After a median of 75 months follow-up, there was 1 in-field recurrence and grade II toxicities and cosmesis scores were similar to whole breast radiotherapy case-controls.

Arthur et al treated a group of 44 patients with partial breast brachytherapy (13 LDR: 45 Gy with a dose rate of 0.5 Gy/hour and 31 HDR: 34 Gy in 10 fractions over 5 days) [115]. The median implant volume for this institution has been reported to be 190 cm\(^3\) (range: 71 – 510 cm\(^3\)) [106]. Patient selection criteria were similar to King et al, but later node positive patients were excluded. After a median follow-up of 42 months, all patients remained locally controlled. The overall rate of good/excellent cosmetic outcome was 80%, but both LDR brachytherapy and subsequent doxorubicin treatment were significant predictors of an unfavourable cosmetic result on univariate analysis.
Wazer et al reported a HDR brachytherapy technique as single radiotherapy modality in 32 women followed up for a median of 33 months [116]. Selection criteria were similar to King et al and dose and fractionation was the same as Arthur et al. The target volume was defined as the surgical cavity plus a 2 cm margin. There was a 33% incidence of grade 3 to 4 subcutaneous toxicity, which appeared to be related to the implant volume. One case of ipsilateral breast tumour recurrence was diagnosed 23 months after HDR brachytherapy. This failure appeared to be a new primary tumour, because it was histologically distinct from the initial tumour and was located 9 cm from the initial tumour bed and 3 cm from the edge of the implant volume.

Polgar et al treated 45 patients with HDR brachytherapy within a phase I-II trial [117]. Eligibility criteria were tumour size \( \leq 2 \) cm, clear resection margins, N0 or pN0-1a, \(<\) grade 3. Exclusion criteria were EIC and invasive lobular carcinoma. Seven fractions of either 4.33 Gy (\( n = 8 \)) or 5.2 Gy (\( n = 37 \)) were given over 4 days, treating the tumour bed with a 2 cm margin. After a median follow up of 53 months, the local recurrence-free survival was 95.6% and the cosmetic results were judged to be excellent in 44 out of the 45 patients. This pilot study formed the basis for a randomised phase III trial comparing partial breast radiotherapy with whole breast radiotherapy. The partial breast radiotherapy arm consisted of either 7 fractions of 5.2 Gy HDR brachytherapy (\( n = 46 \)) or 50 Gy wide electron therapy (\( n = 17 \)) for those patients where there was a technical contraindication for brachytherapy. The whole breast radiotherapy arm consisted of 50 Gy in 2 Gy daily fractions, 5 times a week over 5 weeks (\( n = 63 \)). At a median of 30 months, the loco-regional control was 100% in both arms and there was no significant difference in radiation side effects.

Another method of delivering partial breast brachytherapy is the MammoSite balloon breast brachytherapy catheter, which was approved by the US Food and Drug Administration in May 2002. This can be placed in the tumour cavity either at the time of surgery, or afterwards under local anaesthetic. The balloon is inflated with saline and contrast agent and connected to a HDR brachytherapy source. Keisch et al implanted 54 patients with the MammoSite applicator, and 43 were ultimately eligible and received 34 Gy in 10 fractions over 5 days prescribed to a point 1 cm outside the tumour cavity using HDR iridium-192 [118]. The median implant volume for this series has been reported to be 112.1 (83 – 129.2 cm\(^3\)) [106]. A minimum skin to balloon distance of 5 mm was required and 2 patients were explanted because of inadequate skin spacing. Seven more were explanted because of sub-optimal conformance of the surgical cavity to the balloon. Two other patients were explanted due to node positivity and young age respectively. Side effects were mild to moderate and self-limiting. The main factors limiting use of the device were inadequate skin to balloon distance and poor balloon–cavity conformance. Shah et al described the early experience of 20 patients treated with the same dose and fractionation using this technique (median follow-up 9
months) [119]. They reported a lower rate of subcutaneous fibrosis with the MammoSite balloon compared with catheter-based HDR brachytherapy. This technique will form part of a randomised controlled trial comparing partial and whole breast irradiation (see External beam radiotherapy techniques).

2.2.3.3 Intra-operative radiotherapy techniques
The technique of intra-operative radiotherapy using a portable electron beam-driven device has the advantage of delivering partial breast irradiation at the time of surgery and avoiding out-patient visits for external beam or HDR brachytherapy. It has the disadvantage, however, that the definitive histological resection margins are unknown at the time of irradiation [120]. Veronesi et al have considerable experience of using ELIOT (electron intra-operative therapy), which consists of a mobile linear accelerator with a robotic arm [121]. A single fraction of radiotherapy is given with a Perspex applicator using 3 to 9 MeV electrons. The chest wall is shielded with an aluminium-lead disc and the skin is stretched out of the radiation field. The target volume consisted of the surgical bed plus a 1 – 3 cm margin. A series of 86 women have been treated with a single fraction of 17 – 21 Gy and has been well accepted by the patients. With a reported mean follow-up of 8 months, it is not possible to comment on late normal tissue side effects and local control. There is now an on-going trial in Milan, which randomises to either whole breast radiotherapy (60 Gy) or ELIOT (21 Gy) following quadrantectomy.

An alternative intra-operative radiotherapy device is the Intra-beam, a portable device which delivers 50 KV photons [120]. Pilot studies of intra-operative targeted radiotherapy (TARGIT) in the UK, USA, Europe and Australia have treated a total of 185 patients. In the majority of patients, whole breast radiotherapy was given and TARGIT replaced the boost to the tumour bed. At a median follow-up of 22 months, there have been 2 recurrences and satisfactory cosmetic results. A multicentre randomised trial is currently underway which randomises breast conservation patients to whole breast radiotherapy or TARGIT (20 Gy to the surface of the applicator, which falls to 5 Gy at 1 cm) [122]. Individual centres can add external beam radiotherapy to those patients deemed as ‘high risk’.

2.2.3.4 External beam radiotherapy techniques
An early trial randomised 708 breast conservation patients to limited field (LF) radiotherapy to the tumour bed or to wide field radiotherapy to the whole breast and regional nodes (WF) [123]. LF technique consisted of 40 – 42.5 Gy in 8 fractions over 10 days using 8 – 14 MeV electrons, to an average field size of 8 cm by 6 cm. WF consisted of 40 Gy in 15 fractions over 21 days. Marked fibrosis was seen in 14% of LF patients compared with 5% of WF patients. The overall survival
was 72.7% and 71.2% for the LF and WF groups respectively. The actuarial breast recurrence rate (first event) was 15% (LF) versus 11% (WF) for infiltrating ductal carcinoma, whereas, for infiltrating lobular carcinoma, the recurrence rate was 34% (LF) versus 8% (WF). A high actual recurrence rate of 21% (LF) and 14% (WF) was also found for EIC. Even when the lobular carcinoma and EIC were excluded from the analysis, there was still a worse recurrence rate in the LF group. This may have been due to a geographical tumour miss in the LF treatment arm, as radiotherapy planning was based on clinical assessment rather than using specific imaging techniques. This indicates an important potential problem with partial breast irradiation. In addition, other patient characteristics such as node positivity (nodal status was unknown in all) and positive margins (present in 56%) may have contributed to the higher recurrence rate in the LF group.

More recently, the William Beaumont Hospital, USA have used a CT planned 3D conformal radiotherapy (3D-CRT) technique for partial breast irradiation [124]. The same stringent patient selection criteria were used as per their brachytherapy studies. The prescribed dose was 34 Gy in 6 patients and 38.5 Gy in 25 patients, delivered in 10 fractions twice daily over 5 consecutive days. The median volume for CTV and PTV were 112 cm$^3$ and 240 cm$^3$ respectively (see later for discussion of CTV and PTV) [125]. Cosmetic results were rated as good/excellent in all patients at a median follow-up of 10 months. Potential advantages of this approach over brachytherapy are: elimination of a second surgical procedure and improved dose homogeneity within the target, which may improve cosmesis and decrease the risk of fat necrosis. Possible disadvantages of 3D-CRT are that additional margins must be added to the target to account for patient movement and organ motion. This may result in a larger breast volume irradiated than with brachytherapy, which could impact on the cosmetic result.

The Radiotherapy Oncology Group of the American College of Radiology has recently completed accrual for a phase I/II study (RTOG 0319) testing the feasibility and efficacy of 3D conformal radiotherapy confined to the lumpectomy cavity in women with low risk early breast cancer. This study was developed by the William Beaumont Group and consisted of 10 fractions of 3.85 Gy over 5 days to the tumour bed plus identical margins, as previously discussed. The protocol states that ideally < 25% of the whole breast should receive the prescribed dose. A proposed NSABP/RTOG randomised phase III trial using 25 fractions of whole breast radiotherapy as the control arm, with the same phase II dose and fractionation schedule as RTOG 0319 is due to open in the near future. Participating centres will be able to choose between interstitial brachytherapy, MammoSite brachytherapy and 3D conformal external beam radiotherapy for partial breast irradiation. A proposed randomised controlled study testing IMRT and partial breast radiotherapy
following breast conservation surgery for early breast cancer (IMPORT), is currently being
developed in the UK and the proposed design is outlined in Appendices 1 and 2 of the attached
published paper: Review. Reduction of radiotherapy-induced late complications in early breast
cancer: the role of intensity modulated radiation therapy (IMRT) and partial breast irradiation. Part
II – Radiotherapy strategies to reduce radiation-induced late effects.

Clinical reports of partial breast irradiation are encouraging, but there are some concerning results
with respect to local recurrence rates. Clearly, mature data from randomised trials is needed to give
more information regarding local recurrence and late normal tissue morbidity. Ultimately, we need
answers to the following questions: Firstly, which patient groups will benefit? Secondly, what is
the optimal treatment volume in terms of local control and cosmetic result? Thirdly, what is the
optimal dose/fractionation regimen? It is likely that many institutions will opt for an external beam
technique for delivering partial breast irradiation because of availability and familiarity of the
equipment. In addition, it has been shown in a modelling exercise, that brachytherapy appears to be
significantly more expensive than teletherapy [126]. Accurate localisation of the tumour cavity and
assessment of radiotherapy margins for external beam irradiation techniques, are therefore essential
for this approach. These will now be discussed in more detail.

2.2.4 Localisation of the post-operative breast tumour cavity: CTV
The “tumour bed” does not have a universally accepted definition. It can be described in surgical
terms as the defect within the breast following wide local excision. However, surgeons vary in their
technique, with some excising a cylinder of tissue down to the deep fascia and others resecting just
the tumour with a margin of normal tissue. The defect can be left open, sutured closed or re-
modelled. The tumour bed can also be described in radiological terms and this can vary depending
on the modality used. For example, the definition for CT and clips has been defined as the clips and
any architectural distortion, whereas ultrasound usually defines a seroma cavity. As a consequence
of the lack of universal definition of the tumour bed or cavity, the 2 phrases are used
interchangeably in the following discussion.

Planning of the radiotherapy boost CTV to the tumour bed requires an assessment of the location of
the post-operative tumour cavity. In general, this is done using a combination of information: pre-
operative radiological imaging, surgical annotation, clinical palpation of the surgical defect and
position of the breast scar, and patient’s recollection of the site of the mass. In the past, the position
of the scar has been relied on heavily to assist with locating the tumour bed. However, breast
surgical technique has changed, with the scar frequently being placed some distance from the site
of the tumour in order to achieve a better cosmetic result. This has prompted some institutes to compare traditional 'clinical' methods of boost planning with various imaging techniques.

2.2.4.1 Surgical clips for localisation of the tumour cavity
Several studies have reported the superiority of using surgical clips to locate the tumour bed compared with clinical methods [14, 15, 17 – 19, 127, 128]. All studies showed that the tumour cavity would have been under-dosed using traditional planning techniques. The clinical method could also result in a substantial volume of normal tissue being irradiated unnecessarily [19]. In addition, it was reported that medially and laterally located tumour cavity could also be missed by the tangential fields [18, 128].

Detailed descriptions of the planning techniques using surgical clips have been reported using both CT scanning and simulator films [129, 130]. A consistent policy of clip placement at the time of surgery is necessary. An example of this is to place a clip at the medial, lateral, superior and inferior extent of the tumour bed, and a fifth clip at the deepest extent of the tumour bed in the direction of the surgical excision [129]. There is the potential risk of surgical clips becoming dislodged and tracking away from the tumour bed. However, there have been no studies investigating this issue for breast radiotherapy planning.

2.2.4.2 Ultrasound for localisation of the tumour cavity
Breast ultrasonography has also been exploited as a method of localising the tumour bed for radiotherapy planning. A study compared clinical methods with ultrasound localisation and found that the full extent of the tumour cavity was underestimated in 87% of women, and the chest wall depth was incorrectly estimated in 90% using traditional methods [131]. Another study reached similar conclusions: conventional electron boost planning resulted in 55% of patients having areas of under-treatment and 20% of patients received significant over-treatment [16].

The location and appearance of the tumour cavity has been found to be highly reproducible on repeated scans, with a mean depth difference between scans of 2 mm [132]. There is some discrepancy as to whether the ability to localise the tumour cavity is more difficult with increasing time from surgery. This is important to consider with many women receiving up to six months of adjuvant chemotherapy prior to irradiation, and in those who do not there is the current UK problem of long waiting times for radiotherapy treatment. One study reported that it was difficult to visualise the cavity after 8 weeks from surgery [131]. This view was reflected by another study, which found that the optimal time for radiotherapy planning was within 60 days post-operation.
[133]. Other reports contradict this view, stating that the tumour cavity can be seen many months following surgery [132] (personal communication, Dr R Sinnatamby, consultant radiologist).

All reports in the literature have used 2D ultrasound scanning techniques. This is perfectly adequate for placement of a direct anterior electron boost field, as the dimensions of the cavity with a suitable margin can be marked on the patient’s skin and the electron energy can be selected from measurement of the cavity depth. However, other radiotherapy techniques such as a brachytherapy interstitial implant or a concomitant boost to the tumour bed using IMRT, require more detailed 3D information. This can be achieved by using a combination of ultrasound examination and placement of radio-opaque skin markers and measurement of cavity depth, followed by CT scanning in the same position [134].

2.2.4.3 Magnetic Resonance imaging (MRI) for localisation of the tumour cavity

MRI provides excellent definition of the breast and surrounding tissues. Its use in breast radiotherapy planning, however, has been very limited. This has largely been due to a combination of limited MRI resources and the difficulty of scanning the patient in the treatment position. The Bristol Haematology and Oncology Centre Hospital have experience in the use of a low-field open MRI scanner for breast radiotherapy planning, which allows imaging in the treatment position (see Figure 2.6) [20]. This group has demonstrated with MRI that conventional breast radiotherapy planning of the boost and sometimes the tangential fields can result in under-treatment of the target. In addition, greater sparing of surrounding organs at risk can be achieved with MRI-assisted planning. Potential problems with MRI radiotherapy planning include image distortion and coregistration with radiotherapy planning systems.

![Figure 2.6 Breast radiotherapy planning using MRI](image-url)
2.2.4.4 CT for localisation of the tumour bed

Despite the improvement with CT scanning for breast radiotherapy planning, it is still often difficult to distinguish glandular breast tissue from the surrounding anatomy, without the additional guidance of surgical clips. Clinically palpating then marking the breast tissue with radio-opaque wire prior to CT scanning has been shown to be helpful [135]. However, CT alone may be inadequate for accurate localisation of the tumour bed, as it is difficult to visualise and varies according to the CT window setting.

2.2.4.5 Patient set-up errors and organ motion: PTV

A margin should be added to the breast or tumour bed CTV, which takes into account set-up error and patient movement (including breast swelling and breathing), if external beam irradiation techniques are used [136 – 138]. This is the PTV. Several studies have used electronic portal imaging devices to quantify the extent of positional errors and patient movement for breast radiotherapy [139 – 142]. Lirette et al, Fein et al and Hector et al calculated a weighted standard deviation of the central breast distance (reflecting movement in the anterior-posterior direction) of 4.5 mm, 4.6 mm and 2.2 mm respectively for the systematic component of set-up error. Lirette et al, Fein et al, and Van Tienhoven et al calculated a weighted average standard deviation of 3.9 mm, 6.1 mm and 4.7 mm respectively for systematic variation in set-up error for the cranio-caudal distance (reflecting movement in the superior-inferior direction). Another study found that a vac-fix immobilisation device was superior to a breast board as it improved transfer of the planned set-up from the simulator to the treatment unit [143]. It was felt that implementation of the vac-fix device was not justified for standard tangential breast radiotherapy, but may be important for more complex techniques such as IMRT.

It is difficult to determine from the portal imaging studies exactly which part of the displacement was due to set-up error and which was due to patient movement. Hector et al showed that the average increase in breast volume during treatment was 5%, and this peaked between fractions 5 and 8 and then decreased back below the initial volume [142]. It has been stated that the effects of breathing motion are in general about half the size of the effects of set-up error [144]. Breathing motion may be particularly important in dynamic-MLC IMRT techniques, and a study has shown that dosimetric errors are dependent on the speed of the travelling leaves relative to the speed of the target motion [145]. Certain centres have implemented methods to limit breathing motion such as gated radiotherapy and breath-holding techniques [146].

One institution developing 3D-CRT for partial breast irradiation, measured the impact of patient set-up error and breathing motion to establish CTV to PTV margins [124]. This was then tested
clinically for adequate coverage of treatment. The CTV-PTV margin for 'breathing only' was calculated by measuring the displacement of surgical clips during 3 types of CT scan: free breathing, and breath holding at the end of normal inhalation and at the end of normal expiration using an active breathing control device. A margin of 5 mm in all directions was subsequently selected to completely account for breast motion during quiet breathing. The combined uncertainty of random patient set-up error and respiratory motion, and the distribution of systematic error across all fields and all patients, were measured. This was achieved by measuring the movement of the chest wall/ribs with portal imaging, as a surrogate for the tumour bed. A margin for set-up uncertainties of 5 mm was proposed from this data, producing a total CTV-PTV margin of 10 mm that was tested in 9 patients. Ninety-eight to 100% of the CTV was covered by the 95% isodose surface at the extremes of normal inhalation and exhalation using the 'breathing only' margin of 5 mm. The total CTV-PTV margin of 10 mm also seemed to provide coverage for most patients. The authors state that there is still uncertainty regarding the stability of the tumour cavity relative to the chest wall and that this may vary more in patients with larger breasts. Therefore, slightly larger CTV-PTV margins may be needed in this group of patients.

A slightly different approach has been taken in the recent British Institute of Radiology publication 'Geometric uncertainties in radiotherapy treatment planning' [138]. It suggests dividing the CTV-PTV margin into 2 volumes. The volume enclosing the mean position of the CTV in 90% of cases is called the systematic target volume (STV). The systematic errors (also considered treatment preparation errors) contributing to the CTV-STV volume include: clinician's delineation, phantom transfer (error accumulated by transferring image data from the CT scanner, through the treatment planning system to the linear accelerator), systematic set-up, breathing and treatment planning system beam algorithm. The second volume (STV-PTV) consists of random treatment execution errors that vary between fractions. These include daily set-up error, organ position and shape, and unblurred beam penumbra width. Mathematical modelling has produced equations that estimate the volume of uncertainly with a given set of errors. A worked example, which assumes correction of systematic errors using portal imaging, suggests total CTV-PTV margins of 21 mm, 17 mm and 24 mm in the anterior-posterior, right-left and superior-inferior directions respectively. It was noted that the clinician's delineation error was likely to be the largest single contributor to the required margins.

In summary, the concept of CTV and PTV is widely used for radiotherapy planning in many tumour types. However, it is less commonly utilised for breast radiotherapy where the whole breast is treated and planned clinically using anatomical landmarks. Partial breast radiotherapy using more complex 3D radiotherapy techniques, however, does require the use of this concept to ensure
accurate target coverage. The margins for PTV may vary between institutions depending on accuracy of localisation and set-up errors, and may be larger than initially supposed. Further work is required to determine the intra-and inter-clinician variability in target delineation.

2.2.5 Conclusions
Despite recent advances in radiation technology, the majority of centres worldwide use basic radiotherapy techniques based on 2D breast data. Incorporating new approaches to breast radiotherapy, such IMRT and partial breast irradiation may result in a reduction in morbidity. These more complex radiotherapy methods will require precise localisation of the tumour bed and application of appropriate margins. On-going and proposed randomised trials will test these concepts, and need to demonstrate the safety and efficacy of these techniques.
Chapter 3. Methods

The major techniques will be described in Part I of this chapter, additional methodological details pertaining to the individual studies will be discussed in the relevant chapters. Design of the IMRT clinical trial protocol will be discussed in Part II. All studies involving patients were approved by the Local Research Ethics Committee at Addenbrooke’s Hospital, and all patients provided informed consent.

3.1 Part I: Major research techniques

3.1.1 Use of a laser camera for 3D breast radiotherapy planning and assessment of change in breast volume

3.1.1.1 Principles of 3D laser image acquisition

The laser scanning device used was the Minolta Vivid 700 non-contact 3D digitiser (see Figure 3.1). The principle of operation is shown in Figure 3.2. A fan beam of laser light is scanned down the object surface using a galvano mirror while images are captured on the camera. Given knowledge of the angle of projection of the laser fan beam, the orientation of the laser source and the camera, the 3D profile of the laser stripe in each image is calculated using trigonometry principles. These profiles combine to give a full 3D point cloud map of the object surface. Scanning of the object takes 0.6 seconds and generates a 200 x 200 3D point data set. A colour image of the object is also saved with each data set. The co-ordinate system of the 3D data has its origin at the centre of the camera lens with the X-axis to the right, Y-axis upward and the negative Z-axis away from the camera. The 3D data set is either downloaded to a computer in real-time if a computer is attached to the camera, or at a later stage. The utility software provided with the camera enables some editing of the data and can export the 3D point data as a file of point triplets.
Methods

Figure 3.1 Acquistion of 3D breast data using the Minolta laser camera

Figure 3.2 Schematic laser camera diagrams
The diagram on the left shows the principle of how the laser camera obtains data. The diagram on the right illustrates the
directions of rotation, twist and tilt.

3.1.1.2 Acquisition of laser image
The camera was mounted on a tripod and could be moved about the patient with five degrees of
freedom. Due to the free nature of the camera relative to the patient, it was necessary place small
plastic markers on the patient in a known orientation. This enabled the data to be re-oriented at the
post processing stage to the standard patient co-ordinate system. Three markers were placed along
a central plane on the patient surface as indicated by the in-room lasers used for patient positioning,
and corresponded to the position of the medial and lateral tattoos and an additional marker in the
same plane. These markers enabled the tilt and rotation of the data set to be corrected. A
measurement of the X, Y and Z position of one of the markers relative to another enabled the twist
of the data set to be corrected as well. In most cases a further four markers were used to indicate
the corners of the surface area of interest. Although not strictly necessary they provided a quick method of checking whether the data set covered the entire area of interest.

3.1.1.3 Production of 3D data for radiotherapy planning
Once a point cloud of the surface had been generated further processing of the data was performed using Metris Base 5.0 (Metris NV, Belgium). This is a commercial 3D modelling software package that can import the 3D point cloud data and generate a closed triangulated mesh from it (see Figure 3.3). Within Metris Base, the data was edited to trim off unwanted regions of the surface and manipulated to orientate it with the patient co-ordinate system. Orientation was achieved by manually aligning the surface image with a 3D axis, based on the position of the 3 central markers. Once it had been edited and orientated the mesh was cross-sectioned in the axial X, Z plane at 5 mm intervals and the resulting outlines were exported.

![Figure 3.3 Breast contour derived from 3D laser data](image)
This picture shows the closed triangulated mesh contour of the breast in Metris Base 5.0.

This ‘manual’ method of orientating the data set in 3D was used for the dosimetry study. Later, an automated software method was developed by Dr Andrew Hoole and colleagues, Medical Physics Department, Addenbrooke’s Hospital. This method did not require the use of plastic markers to be placed over the 3 points on the central axis, and instead, fine felt tip pen marks were made. A photographic image was displayed with the software and the operator was able to simply select the 3 marks and the image was automatically orientated within the 3D co-ordinate system (see figure 3.4). This method allowed more precise localisation of the 3 points, as they were not obscured by the larger plastic markers. Following orientation, the surface image was then converted into axial outlines at 5 mm intervals using this in-house software. This automated method was used for
creation of clinical radiotherapy plans within the Cambridge Breast IMRT trial, following comparison with CT outlines as part of a validation study (see later).

![Image](image.jpg)

**Figure 3.4 3D laser breast images**
On the left, the photographic breast image obtained with the laser camera is shown. On the right, the closed triangulated mesh contour, produced from the laser camera data is shown.

3.1.1.4 Measurement of breast volume change using 3D laser data

Due the known difficulties in reliably defining breast tissue from other surrounding tissues, I developed the term “breast volume” to mean the extent of visible breast tissue with a straight posterior border to give a closed volume similar to that defined by the posterior radiotherapy field edge. Clearly, this is an over-estimate of breast volume as the surface of the chest is curved and contains other structures such as muscles and ribs. However, the volume defined in this thesis was considered to be more reproducible and would allow the detection of changes before and after radiotherapy, which was considered to be more relevant than absolute volume measurement.

The 3D laser image was acquired, as previously described. A considerable amount of time was spent trying to improve the accuracy and reproducibility of the laser camera technique of measuring volume change. Hence a variety of methods were investigated before the definitive method was implemented. The earlier methods were based on the manual and automated techniques described above, using a combination of Metris Base and in-house software. After much work, it became apparent that these techniques were not sufficiently reproducible to accurately detect relatively small changes in breast volume. The methods were dependent on the assumption that subsequent images could be aligned in an identical manner to the original image. However, it became clear following experiments consisting of repeated measurements on the same phantoms, that an error in alignment of around 1 mm could produce a sizeable erroneous change in volume.
Methods

Following collaboration with Dr Graham Treece and colleagues at the Department of Engineering, University of Cambridge, a final method was developed using in-house 'Viewsurf' software (validation of this method is discussed in Chapter 6). The principle requirement was to align breast contours of the same individuals, obtained with the laser camera before and after radiotherapy, using software that could 'distinguish' between changes in breast contour. Therefore, the program would attempt to match identical regions of the breast contour, but would disregard regions of change. The surface registration algorithm matched the breast surfaces using iterative re-weighted least-squares optimisation. At each iteration, closest-point registration was used, weighted by an estimate of how well the surfaces match at each point. This weighting was re-calculated and the process was repeated. This resulted in a good registration for those areas of the surface that are similar, without letting dissimilar areas affect the registration process. The laser images were acquired in the same way, and then imported into the 'Viewsurf' software. Initially, the entire surfaces were used for alignment followed by just the breast region, which had the effect of 'fine-tuning' the alignment. A numerical value was given for signed volume change i.e. if the 2 surfaces were raised to the same extent, but in different locations, the volumes would tend to cancel out. However, the associated colourwash depth contour map would indicate the location and degree of change over the entire breast surface. Therefore this method provided both quantitative and qualitative assessment of volume change (see Chapter 6 for examples).

3.1.2 Forward-planned IMRT techniques
The laser outlines (or CT outlines at a later date) were imported into the Addenbrooke's Planning System (ARPS) and were co-registered with the central axis simulator-CT used for conventional planning. The breast tissue was outlined as a region of interest with a 5 mm margin from the skin surface and from the posterior field edge or lung. This volume was calculated in ARPS and recorded for all patients. A standard plan consisting of paired tangents was produced for all patients. Plans were classified as having significant dose inhomogeneities if they exceeded the upper limit of International Commission on Radiation Units and Measurements (ICRU) 50 recommendations (+ 107% of the prescribed dose) [136]. This document states that an area greater than 2 cm² should not exceed this dose on a central axis 2D breast plan. As 3D data was used, a volume of 2 cm³ or more exceeding 107% was adopted as the criterion for significant dose inhomogeneity.

At the start of this research, there were no linear accelerators with MLCs at Addenbrooke's. Therefore, a simple method of planning we called 'segmented field radiotherapy' or SFRT was adopted [147]. This technique involved scrolling through the axial slices of the breast plan and noting at which level the 107% isodose covered the majority of the slice.
rectangular field segments, which terminated at this level, were constructed. These segments were typically weighted to 10% of the total dose (see Figure 3.5). All plans with significant dose inhomogeneities were re-planned with SFRT.

**Figure 3.5 Example of SFRT fields**
The 3D outline of the breast (blue) is shown with a standard field on the left, and shortened SFRT field on the right (green).

When MLCs became available, a forward-planned IMRT technique was developed using MLC-shaped fields. This was achieved by firstly viewing the isodose distribution along the beam’s eye view with standard tangential fields, as described by Zackrisson *et al* [98]. The MLCs were manipulated to cover areas of unacceptable high dose and produce 2 additional MLC-shaped fields. The dose distribution was re-calculated and 2 further MLC-shaped fields were added if necessary, giving a maximum of 6-fields (see Figure 3.6). This technique was made possible by a specific software module added to ARPS to ‘lock’ the isodose display whilst the MLCs were moved into position, written by Andrew Hoole.

**Figure 3.6 Example of MLC shaped fields**
The 3D outline of the breast (blue) is shown with 2 IMRT MLC-shaped fields (pink)
3.1.3 Use of 3D ultrasound for localisation of the tumour/tumour bed

3.1.3.1 Acquisition of the ultrasound image

The 3D ultrasound system consisted of a high-resolution ultrasound machine, Diasus (Dynamic Imaging, Livingston, Scotland, UK, http://www.dynamicimaging.co.uk) and a 12 MHz transducer. Attached to the transducer was an Adaptrax target with 15 differently orientated infrared emitters (Traxtal Technologies, http://www.traxtal.com, see Figure 3.7). A position sensor (Polaris, Northern Digital Inc, http://www.ndigital.com/) was used to continually track the position of the infrared emitting diodes on the transducer. Thus, both ultrasound image and associated transducer position data could be simultaneously recorded to an 800 MHz PC running the software Stradx (http://mi.eng.cam.ac.uk/~rwp/stradx), which was written by Cambridge University Department of Engineering. System calibration, co-registration and visualisation of the data were also performed by this software. The system had previously been demonstrated to have accuracy sufficient to locate points within 0.5 mm of their true 3D location, with 95% confidence [148].

In order to co-register the ultrasound image and transducer position data with the CT, the fiducial positions were recorded using a specially developed 3D tracked pointer (see Figure 3.8). This also had a series of infrared emitting diodes and enabled the position of point locations to be recorded within Stradx into the same coordinate system as the transducer position data. The pointer was placed over both fiducials and at a third point, also in the plane of the central CT slice. An ultrasound data set was then acquired by moving the transducer slowly and steadily over the area of the targets.
Methods

Figure 3.10 3D ultrasound and CT registration
(a) This shows the central CT image through fiducials (marked with crosses). The target (an olive) is indicated by the arrowheads. The full arrow points to the "fatty" Vaseline-filled centre of the olive. (b) This shows the reformatted ultrasound data superimposed on the CT image. (c) This shows the ultrasound data of the target superimposed over the CT image of the target.

3.1.4 Statistical methods
Statistical advice was provided by the Dr Eleanor Pinto and Dr Andrew Lynch, Centre for Applied Medical Statistics, University of Cambridge. Specific statistical support for the 3D ultrasound research was given by Dr Fiona Miller, University Department of Radiology. Design of the IMRT clinical trial protocol was assisted by the help of Dr Richard Sylvester, Statistician and Assistant Director of the EORTC Data Center. Statistical analysis was undertaken using Statview (version 5, 1998, SAS Institute Inc., Cary, North Carolina, USA), STATA version 7 (Stata Corp LP, Texas, USA) and Microsoft Excel (Microsoft Office 98). All data are expressed as mean +/- one standard deviation unless otherwise stated. All p-values are quoted after Bonferroni correction (where appropriate) and 95% confidence intervals (CI) are also quoted. Further details of the statistical methods used in these studies are described in the relevant results sections.
3.2 Part II: Development of clinical trial protocol: Investigation of radiotherapy dose inhomogeneity and clinical outcome in patients with early breast cancer.

I have designed and implemented a phase 3 randomised trial at Cambridge, which aims to prove the clinical benefit of forward-planned breast IMRT. In 2001, I developed the trial protocol at the ‘Methods in Clinical Cancer Research’ workshop in Switzerland. This was jointly organised by the Federation of European Cancer Societies, the American Association for Cancer Research, and the American Society of Clinical Oncology. It was then accepted by the UK National Cancer Research Institute (NCRI) Radiotherapy Studies Group as a portfolio trial in 2002 and adopted by the National Cancer Research Network (NCRN) in 2003. The background for the trial and summary of the protocol will be presented below (see Appendix for full protocol). The background for the need for a trial has been discussed in Chapters 1 and 2.

3.2.1 Principal research question

Does IMRT reduce the normal tissue side effects compared with conventional radiotherapy in patients with early breast cancer? See trial design Figure 3.11.

3.2.1.1 Why is a trial needed now?

There is a growing feeling within the UK that standard 2D breast radiotherapy could be improved by 3D planning and IMRT. In the next few years, more oncology centres will be able to deliver complex radiotherapy, including IMRT. The introduction of these new radiation techniques for all breast cancer patients requiring radiotherapy would have massive resource implications. The recent document ‘Development and implementation of conformal radiotherapy in the UK’, states that the clinical implementation of IMRT is at present ‘difficult, and probably high risk, unless built on the back of a well-founded research programme’. It recommends that IMRT should be introduced across the UK with centres taking part in controlled studies to provide evidence of efficacy and outcome [149].

Despite the interest in breast IM techniques and numerous dosimetry studies worldwide, there has only been 1 randomised controlled trial designed to investigate late normal tissue side effects [51]. This was carried out at the Royal Marsden Hospital, UK (see Chapters 1 and 2). It is hoped that two confirmatory trials (Royal Marsden and Cambridge) would provide the impetus to adopt IMRT for breast cancer patients as standard practice in the UK, providing clinical benefit is demonstrated.
Methods

3.2.2 Endpoints
The primary endpoint will be breast shrinkage after radiotherapy; serial photographs will be assessed using a validated scoring system. Secondary endpoints will include acute skin reactions, clinical assessment of late cosmetic effect and patient self-assessment using validated quality of life questionnaires. Information regarding local control, metastatic disease, survival and cardiac and pulmonary complications will be collected. A 3D laser camera will provide a novel objective and analytical method of assessing post-radiation breast shrinkage (see Chapter 3 – Methods) [99]. Change in breast volume following radiotherapy will be compared with the baseline pre-radiotherapy volume and will be analysed as a secondary endpoint. Endpoints will be assessed and analysed at 2 and 5 years from completion of radiotherapy.

3.2.3 Patient selection criteria
All patients will be 18 years or above, have operable unilateral breast cancer (T1-3, N0-1, M0 at presentation) or DCIS requiring radiotherapy, have a histological diagnosis and a complete macroscopic tumour excision by breast conserving surgery.

3.2.4 Randomisation
Patients with plans exceeding 107% of the prescribed dose, will be randomised to either IMRT or receive conventional radiotherapy within the standard radiotherapy control arm. Stratification will be carried out for T-stage and adjuvant systemic therapy using a random block design. This will take into account the possibility that cosmetic outcome is affected by tumour size and the necessary
extent of surgical resection, and cytotoxic or hormonal treatment. Standard breast radiotherapy will be used for all non-trial patients at Addenbrooke’s Hospital.

3.2.5 Sample size
The power calculation was performed with the help of Richard Sylvester, Statistician and Assistant Director of the EORTC Data Center, at the time of the ‘Methods in clinical research’ workshop. Pilot data from the START trial has suggested that the probability of observing late radiation change for patients receiving standard radiotherapy is approximately 40% [23]. Patients in the Cambridge Trial will all have dose inhomogeneities outside ICRU 50 recommendations, which may result in a higher probability of radiation change. This is reflected by the interim analysis from the Royal Marsden study of IMRT versus standard radiotherapy. Patients with larger breasts were selected on the basis that these would have greater dose inhomogeneities. A change in breast appearance was noted in 60/116 (52%) of patients in the standard group compared with 42/117 (36%) that received IMRT [51].

Therefore, it has been assumed that there will be a standard event rate of 40% in the control group at 2 years. The difference to be detected will be 10% and the hazard ratio will be 0.7. Assuming a minimum average follow-up of 2 years and 80% power and type I error of 0.05, 358 patients and 125 events in each arm are required. At the time of the power calculation, approximately 600 women with early breast cancer were treated with radiotherapy at Addenbrooke’s per year. The pilot dosimetry study showed that approximately 70% of patients planned with conventional 2D radiotherapy had dose inhomogeneities (see Chapter 4 - Results I). A very high patient accrual rate was expected, given the simplicity of the trial design with virtually no change in the patients’ treatment pathway compared with the standard radiotherapy offered out of trial. Therefore the expected duration of recruitment would be 3 years.

3.2.6 Future studies: Genetic variation in normal tissue radiosensitivity (Radiogenomics)
Blood samples are being collected from trial patients to create a DNA database, which will form part of a multicentre radiogenomics study: RAPPER (Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy). This will investigate an association between common genetic variation, reported by single nucleotide polymorphisms (SNPs), and individual patient variability in normal tissue radiation toxicity. The trial will provide a unique patient sub-group with minimal dose inhomogeneities. Variation in normal tissue response is therefore more likely to be due to genetic factors in these patients.
Chapter 4. Results I: Dosimetry study

4.1 Introduction
Forward-planned IMRT is a relatively simple method of IMRT that does not require an inverse-planning computer. Smaller radiotherapy fields are added to the main treatment fields to improve dose inhomogeneities produced by conventional 2D breast radiotherapy. This can be achieved with standard rectangular fields, or shaped fields using a multi-leaf collimator. This simple technique could therefore be implemented without the need for complex technology.

4.2 Methods
4.2.1 Validation study
The aim of the validation study was to compare the breast outlines obtained with the laser camera with CT outlines in the same patient. At the time, there was no access to a dedicated radiotherapy planning CT scanner at Addenbrooke's Hospital. Therefore, ethical approval was obtained to scan patients with the laser camera at Ipswich Hospital at the same time as their breast CT planning scans. Eleven patients were scanned with both imaging techniques, of which 3 laser camera datasets were excluded. The excluded cases all had incomplete laser datasets for the following reasons: 1 patient felt claustrophobic in the CT room and left before imaging was complete, a second had a dressing which distorted the laser images, and a third had a breast implant which caused considerable shadowing medially due to breast shape. The remaining laser and CT datasets were co-registered in ARPS and outlines through the breast at 5 mm intervals were produced for each paired dataset. The alignment of the laser outline with the CT outline was measured at 3 fixed points on each axial slice using a measurement tool in ARPS and the root mean squared difference was recorded (see Figure 4.1).
4.2.2 Acquisition of the 3D laser image and production of data for radiotherapy planning

46 patients attending the Oncology Centre for breast radiotherapy planning were scanned with the laser camera in the treatment position. The acquisition of the 3D laser image and production of data for radiotherapy planning are discussed in Chapter 3 – Methods.

4.2.3 Radiotherapy planning techniques

Methods for SFRT using rectangular fields, and forward-planned IMRT with MLC-shaped fields, are described in Chapter 3 – Methods. Standard (2 wedged tangential fields), SFRT and IMRT plans were compared using differential DVHs. SFRT and IMRT plans were considered better than standard plans if the improvement in volume > 107% was greater than any increase in volume < 95, i.e. there had to be a net increase in the volume between 95 and 107% of the prescribed dose.

4.2.4 Statistical analysis

The dosimetry and validation study data were summarised using mean and one standard deviation or median and inter quartile range as appropriate. Comparisons were tested using the paired or unpaired T-test as appropriate and Bonferroni correction was used for multiple comparisons. Ninety-five percent confidence intervals were quoted with all p-values.
4.3 Results

4.3.1 Validation study

The results of the alignment of CT and laser outlines are shown in Table 4.1. The mean root mean squared difference in alignment for the 240 measurements taken from 8 co-registered CT and laser scans was 1.6 mm (one standard deviation of 1.2 mm).

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Number of CT slices</th>
<th>Number of measurements</th>
<th>Root mean squared (RMS) difference in CT-laser alignment per patient (mm)</th>
<th>One standard deviation of root mean squared (RMS) difference in CT-laser alignment per patient (mm)</th>
</tr>
</thead>
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<tr>
<td>1</td>
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<td>1.4</td>
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<td>87</td>
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<td>1</td>
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<td></td>
<td></td>
<td><strong>1.6</strong></td>
<td><strong>1.2</strong></td>
</tr>
</tbody>
</table>

Table 4.1 Alignment of CT-laser outlines.

*Mean RMS difference for patient group
**Mean standard deviation of RMS difference for patient group

4.3.2 Dosimetry study

Sixteen of the 46 breast plans (35%) had acceptable dose homogeneity with the standard technique and no further planning was necessary. The mean difference in breast volume between these patients, and those with unacceptable dose homogeneities was 590 cm³ (p < 0.0001, 95% Confidence Interval 359 cm³, 821 cm³). However, there was an overlap in range of breast volumes: 231 cm³ to 1199 cm³ and 591 cm³ to 2616 cm³, for homogenous and inhomogeneous plans respectively. Therefore, breast volume alone cannot predict whether dose homogeneity will be acceptable.

The remaining 30/46 (65%) were planned with both SFRT and IMRT. SFRT decreased the volume > 107% of the prescribed dose in all cases, but only 12/30 (40%) had improvements in volumes > 107%, which were greater than any increase in volume < 95%. Table 4.2 shows the comparison of all 30 SFRT plans with standard planning. There is a statistically significant improvement in the
mean volume > 107% of 26 cm³, but also a statistically significant increase in the mean volume < 95% of 42.5 cm³.

<table>
<thead>
<tr>
<th>Type of plan</th>
<th>Mean volume &gt; 107% (cm³)</th>
<th>Mean volume &lt; 95% (cm³)</th>
<th>Mean difference compared with standard for volume &gt; 107% (cm³)</th>
<th>Mean difference compared with standard for volume &lt; 95% (cm³)</th>
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<tr>
<td>Standard</td>
<td>38 (46.4)*</td>
<td>174.9 (108.4)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFRT</td>
<td>11.7 (25.2)*</td>
<td>217.4 (122.6)*</td>
<td>26.3 (p &lt; 0.0001, 95% CI 15.8 – 37)</td>
<td>-42.5 (p &lt; 0.0001, 95% CI -59.3 – 25.7)</td>
</tr>
<tr>
<td>IMRT</td>
<td>7.8 (14.1)*</td>
<td>142.7 (72.8)*</td>
<td>30.2 (p &lt; 0.0001, 95% CI 16.9 – 43.5)</td>
<td>32.2 (p = 0.096, 95% CI 10.6 – 53.7)</td>
</tr>
</tbody>
</table>

Table 4.2 Comparison of dosimetry: standard, SFRT and IMRT plans
* One standard deviation of the mean volume.

IMRT decreased the volume > 107% of the prescribed dose in all cases, and 29/30 (97%) had improvements in volumes > 107%, which were greater than any increase in volume < 95%. Table 4.1 also displays the comparison between IMRT and standard plans, and there is a statistically significant improvement in the mean volume (38 cm³) > 107%. In contrast with SFRT, there is also a mean improvement in the volume < 95% (32 cm³), but this is not statistically significant. Table 4.3 summarises the results for the 30 IMRT plans and the improvement is shown graphically in Figure 4.2. Two or 4 additional segments were used in 16/30 (53%) and 14/30 (47%) plans respectively. The weighting of these segments ranged from 3% to 10%.
## Results I: Dosimetry study

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Breast volume (cm³)</th>
<th>Difference in Volume &gt; 107% with IMRT compared with standard (cm³)*</th>
<th>Difference in Volume &lt; 95% with IMRT compared with standard (cm³)*</th>
<th>Difference in Volume &gt; 107% + difference in Volume &lt; 95% (cm³)*</th>
<th>Number of additional IMRT segments and weighting**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>591</td>
<td>14</td>
<td>-4.7</td>
<td>9.3</td>
<td>2 segments, 5%</td>
</tr>
<tr>
<td>2</td>
<td>712</td>
<td>15</td>
<td>-10.6</td>
<td>4.4</td>
<td>2 segments, 7%</td>
</tr>
<tr>
<td>3</td>
<td>726</td>
<td>5.1</td>
<td>82</td>
<td>87.1</td>
<td>2 segments, 10%</td>
</tr>
<tr>
<td>4</td>
<td>781</td>
<td>61.7</td>
<td>-7.1</td>
<td>54.6</td>
<td>2 segments, 10%</td>
</tr>
<tr>
<td>5</td>
<td>787</td>
<td>31.4</td>
<td>12.3</td>
<td>43.7</td>
<td>4 segments, 10%, 5%</td>
</tr>
<tr>
<td>6</td>
<td>790</td>
<td>26.9</td>
<td>28.3</td>
<td>55.2</td>
<td>4 segments, 10%, 5%</td>
</tr>
<tr>
<td>7</td>
<td>805</td>
<td>4.4</td>
<td>23.5</td>
<td>27.9</td>
<td>4 segments, 10%, 5%</td>
</tr>
<tr>
<td>8</td>
<td>887</td>
<td>8</td>
<td>1.2</td>
<td>9.2</td>
<td>4 segments, 10%, 5%</td>
</tr>
<tr>
<td>9</td>
<td>892</td>
<td>6.6</td>
<td>-6.2</td>
<td>0.4</td>
<td>2 segments, 4%</td>
</tr>
<tr>
<td>10</td>
<td>959</td>
<td>25.6</td>
<td>51.5</td>
<td>77.1</td>
<td>4 segments, 10%, 5%</td>
</tr>
<tr>
<td>11</td>
<td>998</td>
<td>61.2</td>
<td>-18.1</td>
<td>43.1</td>
<td>2 segments, 10%</td>
</tr>
<tr>
<td>12</td>
<td>1031</td>
<td>5.7</td>
<td>53.6</td>
<td>59.3</td>
<td>4 segments, 5%, 5%</td>
</tr>
<tr>
<td>13</td>
<td>1045</td>
<td>16.6</td>
<td>-13.5</td>
<td>3.1</td>
<td>2 segments, 5%</td>
</tr>
<tr>
<td>14</td>
<td>1048</td>
<td>45.3</td>
<td>39.7</td>
<td>85</td>
<td>2 segments, 10%</td>
</tr>
<tr>
<td>15</td>
<td>1053</td>
<td>24.1</td>
<td>26.3</td>
<td>50.4</td>
<td>2 segments, 10%</td>
</tr>
<tr>
<td>16</td>
<td>1083</td>
<td>9.1</td>
<td>-6.7</td>
<td>2.4</td>
<td>2 segments, 5%</td>
</tr>
<tr>
<td>17</td>
<td>1126</td>
<td>3.5</td>
<td>177.2</td>
<td>180.7</td>
<td>4 segments, 10%, 5%</td>
</tr>
<tr>
<td>18</td>
<td>1134</td>
<td>14.6</td>
<td>49.6</td>
<td>64.2</td>
<td>4 segments, 10%, 5%</td>
</tr>
<tr>
<td>19</td>
<td>1152</td>
<td>121.3</td>
<td>-50.4</td>
<td>70.9</td>
<td>2 segments, 10%</td>
</tr>
<tr>
<td>20</td>
<td>1164</td>
<td>6.4</td>
<td>54.5</td>
<td>60.9</td>
<td>4 segments, 10%, 7%</td>
</tr>
<tr>
<td>21</td>
<td>1393</td>
<td>26.5</td>
<td>97.2</td>
<td>123.7</td>
<td>4 segments, 10%, 7%</td>
</tr>
<tr>
<td>22</td>
<td>1397</td>
<td>13.1</td>
<td>116.9</td>
<td>130</td>
<td>2 segments, 10%</td>
</tr>
<tr>
<td>23</td>
<td>1413</td>
<td>45.5</td>
<td>-23.9</td>
<td>21.6</td>
<td>2 segments, 10%</td>
</tr>
<tr>
<td>24</td>
<td>1419</td>
<td>13.8</td>
<td>-11.2</td>
<td>2.6</td>
<td>2 segments, 10%</td>
</tr>
<tr>
<td>25</td>
<td>1437</td>
<td>30</td>
<td>-20.5</td>
<td>9.5</td>
<td>2 segments, 5%</td>
</tr>
<tr>
<td>26</td>
<td>1482</td>
<td>1</td>
<td>-6.6</td>
<td>-5.6</td>
<td>2 segments, 3%</td>
</tr>
<tr>
<td>27</td>
<td>1546</td>
<td>19.3</td>
<td>181.6</td>
<td>200.9</td>
<td>4 segments, 10%, 5%</td>
</tr>
<tr>
<td>29</td>
<td>1900</td>
<td>54.7</td>
<td>33.8</td>
<td>88.5</td>
<td>4 segments, 10%, 5%</td>
</tr>
<tr>
<td>30</td>
<td>2616</td>
<td>165.8</td>
<td>113.4</td>
<td>279.2</td>
<td>4 segments, 10%, 5%</td>
</tr>
</tbody>
</table>

Table 4.3 IMRT plans dosimetry results
*A positive number denotes improved dosimetry and a negative number denotes worse dosimetry.

**segments are opposed and equally weighted.
4.4 Discussion

The results show that optical outlines obtained from a 3D laser camera can be used as an alternative to CT for providing a 3D surface contour, which may then be used for radiotherapy planning. In addition, the patient can be imaged in the treatment position using existing breast boards. Although there was an initial cost for the laser camera, this was considerably cheaper than the cost of a CT-simulator and CT-compatible breast boards. The disadvantage of the laser camera is the lack of internal anatomical information, which is provided by CT. Subsequently, a method was developed using 3 slices from a simulator-CT scan, taken superiorly, centrally and inferiorly through the breast, which enables interpolation of the lung position. This limited information was then co-registered with the surface breast outlines obtained using the laser camera. Breast radiotherapy planning with optical imaging using room laser (such as the Osiris system), has been described, but it appears that this is the first report of a freestanding laser camera method [82].

The dosimetry study suggests that approximately one-third of patients do not require forward-planned IMRT to improve dose homogeneity and are adequately treated with standard 2D techniques. Despite a statistically significant difference in mean breast volume between patients with homogenous and inhomogeneous plans, there was overlap in the range of breast volumes in these 2 patient groups. Therefore, it should be recommended that all patients were evaluated for IMRT using 3D imaging and DVH assessment of standard planning, rather than choosing only women with larger breasts.

Both SFRT and IMRT significantly reduced the volume > 107%, but SFRT also significantly increased the volume < 95%. This is not surprising, as SFRT is a simpler technique using
Results I: Dosimetry study

rectangular fields, whereas the IMRT used MLC-shaped fields to follow the shape of the 107% isodoses. In addition, the IMRT method enabled 'boosting' of volumes less than 95%. One out of thirty plans could not be improved with IMRT (see Table 4.3, patient 26). This patient had a very small volume > 107% (3.4 cm³) with standard planning. It was impossible to produce an improvement in volume > 107% that was greater than the increase in volume < 95% using this technique. One cannot assume, however, that improvements in dosimetry necessarily translate into \textit{clinically} significant improvements in cosmetic result. This important consideration is the topic of the next chapter.
Chapter 5. Results II: Implementation of breast IMRT via a randomised controlled trial – a report of the first year’s experience

5.1 Introduction
This chapter reports the first year experience of a single-centre randomised trial of breast IMRT versus conventional 2D radiotherapy. The trial opened in April 2003, and to date (December 2004), 370 patients have been recruited. The first year’s dosimetry results and the results of a radiotherapy process timing study will be presented. How the framework of a randomised controlled trial assisted in implementing breast IMRT at Addenbrooke's NHS Trust Oncology Centre will be discussed. Clearly, any outcome results will not be shown, as the trial is still open for recruitment.

5.2 Methods
5.2.1 Dosimetry study
Between April 2003 and April 2004, 138 patients were consented for the Cambridge Breast IMRT study. A novel method was used to produce optical outlines using a 3D laser camera (Minolta Vivid 700), as initially there was no access to a multislice CT scanner for breast radiotherapy planning [99] (see Chapter 3 – Methods). Although, this provided an alternative to CT, processing of the 3D data for planning was time consuming. At the end of 2003, a dedicated multi-slice radiotherapy CT scanner became available, and subsequently trial patients were localised with CT and the fields placed later with virtual simulation using an isocentric technique. The non-trial breast patients underwent conventional simulator-localisation with a single CT slice for 2D planning using a non-isocentric treatment technique.

A standard plan consisting of tangential fields was produced for all trial patients. The breast PTV was outlined and defined as 0.5 cm from the skin, superior and inferior field edge, and posterior field edge (or lung) [12]. Plans were classified as having significant dose inhomogeneities if they exceeded the upper limit of ICRU 50 recommendations (+ 107% of the prescribed dose) [136]. This document states that 2 cm² should not exceed this dose on a central axis 2D breast plan. As we were using 3D data, we adopted a volume of 2 cm³ or more exceeding 107% as the criterion for defining significant dose inhomogeneities.

Those patients with satisfactory dose homogeneity were not randomised and were treated with standard radiotherapy, but were followed up as per the randomised patients. Patients with significant dose inhomogeneities were randomised to either standard breast radiotherapy (control
arm) or IMRT (interventional arm). The women randomised to the interventional arm were re­planned with a forward-planned IMRT technique (see Chapter 3 – Methods) [150]. Differential DVHs were used to compare the standard and IMRT plans in the interventional group, and as a record of the dosimetry for all patients. I collated and analysed all the dosimetry data presented in the results.

5.2.2 Timing study
The study aimed to record the localisation and planning times for all patients, and treatment times for a subset, receiving breast radiotherapy at Addenbrooke’s Oncology Centre between January and March 2004. This study was undertaken after the introduction of CT planning for trial patients, so there is no specific data on the timing for laser-planned trial patients. I designed a proforma to record the localisation and planning times, and remained with the patients’ radiotherapy records until the planning process was complete. I subsequently collated and analysed all the localisation and planning timing data. Breast timing forms were classified as ‘complete’ if they contained all timing information for localisation and planning. Information about physics checks and clinician checks for virtual placement of fields (trial patients only) were regarded as desirable, but not essential for satisfactory completion.

Treatments were timed for a subset of 108 trial patients, for a total of 578 radiotherapy fractions; timing started when the patient entered the treatment room and finished when the patient left. This was undertaken as part of Basic Treatment Equivalent (BTE) research led by Mrs Donna Routsis, Research Radiographer, Addenbrooke’s Hospital Oncology Centre [151].

5.2.3 Statistical analysis
The dosimetry and timing data were summarised using mean and one standard deviation or median and inter quartile range (IQR) as appropriate. Comparisons were tested using the paired or unpaired T-tests, and 95% confidence intervals were quoted with all p-values.

5.3 Results
5.3.1 Dosimetry study
29% of trial patients had acceptable dose homogeneity using ICRU 50 criteria and received standard 2-field radiotherapy. The remaining 71% of patients were randomised (see Table 5.1). The mean breast volume and separation were significantly larger in the randomised women (see Table 5.2).
### Table 5.1 Breakdown of numbers and percentages of trial patients

* Four patients had inadequate laser data for 3D planning and were assigned to the non-randomised group. Figures in brackets show values if these patients are excluded.

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Percentage of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>138</td>
<td>100</td>
</tr>
<tr>
<td>Non-randomised*</td>
<td>44 (40)</td>
<td>32 (29)</td>
</tr>
<tr>
<td>Total randomised</td>
<td>94</td>
<td>68</td>
</tr>
<tr>
<td>Randomised IMRT</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>Randomised standard</td>
<td>49</td>
<td>35</td>
</tr>
</tbody>
</table>

### Table 5.2 Comparison of breast volumes and separation between non-randomised and randomised patients.

<table>
<thead>
<tr>
<th></th>
<th>Non-randomised patients</th>
<th>Randomised patients</th>
<th>Comparison of non- and randomised patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean breast volume on CT (cm³)</td>
<td>657</td>
<td>1251</td>
<td></td>
</tr>
<tr>
<td>One standard deviation of the mean breast volume (cm³)</td>
<td>284</td>
<td>546</td>
<td></td>
</tr>
<tr>
<td>Range of breast volume (cm³)</td>
<td>284 – 1526</td>
<td>449 – 3066</td>
<td></td>
</tr>
<tr>
<td>Mean breast separation (cm)</td>
<td>18.5</td>
<td>21.9</td>
<td></td>
</tr>
<tr>
<td>One standard deviation of the mean breast separation (cm)</td>
<td>2</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Range of breast separation (cm)</td>
<td>14 – 24</td>
<td>16 – 29</td>
<td></td>
</tr>
<tr>
<td>Mean difference in breast volume between non- and randomised patients (cm³)</td>
<td>594</td>
<td></td>
<td>(p &lt; 0.0001, 95% CI 411 – 776)</td>
</tr>
<tr>
<td>Mean difference in breast separation between non- and randomised patients (cm)</td>
<td>3.5</td>
<td></td>
<td>(p &lt; 0.0001, 95% CI 16 – 29)</td>
</tr>
</tbody>
</table>
In the randomised patients, there was a statistically significant improvement in volumes > 107% in the interventional (IMRT) group when compared to the control group (see Table 5.3). This improvement was also seen when comparing IMRT and standard plans within the interventional group (see Table 5.4). There was no statistically significant difference in the mean volume < 95% either between the interventional and control groups, but there was within the interventional group (see Tables 5.3 and 5.4). The apparent difference in improvement in volume < 95% between the interventional and control groups, and within the interventional group, is likely to be due to chance rather than some other difference between these relatively small groups.

<table>
<thead>
<tr>
<th></th>
<th>IMRT patients</th>
<th>Control patients</th>
<th>Comparison of IMRT with control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean volume &gt; 107%</td>
<td>12.0</td>
<td>49.2</td>
<td></td>
</tr>
<tr>
<td>(cm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range of volume &gt; 107%</td>
<td>0 – 103.6</td>
<td>2 – 526.9</td>
<td></td>
</tr>
<tr>
<td>Mean volume &lt; 95%</td>
<td>95.8</td>
<td>98.6</td>
<td></td>
</tr>
<tr>
<td>(cm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range of volume &lt; 95%</td>
<td>11.9 – 239.7</td>
<td>6.7 – 348.2</td>
<td></td>
</tr>
<tr>
<td>Mean difference breast volume &gt; 107% (cm³)</td>
<td>37.2* (p = 0.01, 95% CI 9.0 - 65.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference breast volume &lt; 95% (cm³)</td>
<td>2.9 (p = 0.8, 95% CI -31.5 - 25.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.3 Comparison of dosimetry between IMRT and control patients

*This is the statistically significant mean decrease in volume > 107% with IMRT compared with control.
### Results II: Implementation of breast IMRT

<table>
<thead>
<tr>
<th></th>
<th>IMRT plans</th>
<th>Standard plan</th>
<th>Comparison of IMRT with standard plans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean volume &gt; 107% (cm³)</td>
<td>12.0</td>
<td>35.8</td>
<td></td>
</tr>
<tr>
<td>Range of volume &gt; 107% (cm³)</td>
<td>0 - 103.6</td>
<td>2.7 - 280.4</td>
<td></td>
</tr>
<tr>
<td>Mean volume &lt; 95% (cm³)</td>
<td>95.8</td>
<td>117.0</td>
<td></td>
</tr>
<tr>
<td>Range of volume &lt; 95% (cm³)</td>
<td>11.9 - 239.7</td>
<td>10.2 - 471.8</td>
<td></td>
</tr>
<tr>
<td>Mean difference breast volume &gt; 107% (cm³)</td>
<td>23.7* (p &lt; 0.0001, 95% CI 13.9 - 33.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference breast volume &lt; 95% (cm³)</td>
<td>21.2 (p = 0.03, 95% CI 2.0 - 40.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table 5.4 Comparison of dosimetry between IMRT and standard plans in the interventional group*

Forty-two out of the 45 (93%) interventional patients were treated with the 4-field forward-planned IMRT technique as described. The additional MLC-shaped fields were typically weighted to 10% of the main breast tangents. Twelve patients (27%) also had wedges in the inferior/superior direction on the additional fields to decrease the volume < 95%. Two plans (4%) could not be improved with IMRT without introducing a substantial volume < 95% and the patients were treated using the standard plan because it was deemed safer. A further patient had a very atypical breast shape and was treated with 15 MV photons for the whole breast tangents, 6 MV photons for the additional fields with an inferior/superior wedge, and 0.5 cm bolus throughout treatment. All other patients (randomised and non-randomised) were treated with 6 MV photons.

#### 5.3.2 Timing study

From January to March 2004, 215 patients were planned for 2-field (breast only) radiotherapy. Fifty-three (25%) were trial patients and 162 (75%) were non-trial patients. There was a comparatively large proportion of non-trial patients, as the trial was within its first year and recruitment was deliberately limited in the early months. Breast timing forms were complete in 45/53 (85%) and 106/162 (65%) of trial and non-trial patients respectively. Table 5.5 shows the breakdown for localisation times using either conventional simulation or CT scanning. Some of the trial patients were also involved in a 3D ultrasound study, which was carried out at the same time as CT localisation. When these patients were excluded, there was little difference between the simulator and CT times (median 30 and 32 minutes respectively). In addition, the CT-localised trial patients had optical scans of both breasts using the laser camera, to provide a baseline measurement.
of breast volume. If this step were omitted, the CT-simulation would probably have been quicker than conventional simulation. However, the median time for virtual simulation of fields was 15 minutes (see Table 5.6). The time taken for the doctor to check the fields was recorded in 35/53 (57%) of the trial patients. This median time was 10 minutes with an inter quartile range of 8 minutes.

<table>
<thead>
<tr>
<th>Patient numbers</th>
<th>Simulator</th>
<th>CT (total)</th>
<th>CT (no ultrasound)</th>
<th>CT (with ultrasound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time (mins)</td>
<td>30</td>
<td>42</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>Inter-quartile range (mins)</td>
<td>15</td>
<td>20</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Range (mins)</td>
<td>20-65</td>
<td>15-65</td>
<td>15-45</td>
<td>35-65</td>
</tr>
</tbody>
</table>

Table 5.5 Timing for breast localisation

<table>
<thead>
<tr>
<th>Virtual field placement</th>
<th>Produce standard 2D plan</th>
<th>3D contouring</th>
<th>Analysis of DVH</th>
<th>Complete plan*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time (mins)</td>
<td>15</td>
<td>20</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>Inter quartile range (mins)</td>
<td>9</td>
<td>5</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Range (mins)</td>
<td>10 – 30</td>
<td>5 – 45</td>
<td>15 – 45</td>
<td>2 – 35</td>
</tr>
</tbody>
</table>

Table 5.6 Breakdown of timing for 3D planning process

n = 45. * Patients randomised to interventional arm were re-planned with IMRT.

Table 5.7 shows the differences in total planning time for the various patient groups. The shortest median time was the non-trial group at 20 minutes, whereas the longest median time was 130 minutes for the trial group randomised to intervention. The breakdown of the planning process times for the trial patients is shown in Table 5.6. Table 5.8 shows that the median physics check was twice as long for the trial patients (20 minutes as opposed to 10 minutes for the non-trial patients).
Results II: Implementation of breast IMRT

<table>
<thead>
<tr>
<th></th>
<th>2D planning:</th>
<th>3D planning:</th>
<th>3D planning:</th>
<th>3D planning:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>non-trial</td>
<td>trial patients</td>
<td>trial patients</td>
<td>trial patients</td>
</tr>
<tr>
<td></td>
<td>patients</td>
<td>(total)</td>
<td>(control-standard plan)</td>
<td>(interventional-IMRT)</td>
</tr>
<tr>
<td>Patient numbers</td>
<td>106</td>
<td>45</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>Median time (mins)</td>
<td>20</td>
<td>90</td>
<td>90</td>
<td>130</td>
</tr>
<tr>
<td>Inter quartile range (mins)</td>
<td>35</td>
<td>58</td>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>Range (mins)</td>
<td>8 – 150</td>
<td>65 – 260</td>
<td>65 – 160</td>
<td>105 – 260</td>
</tr>
</tbody>
</table>

Table 5.7 Total planning time

<table>
<thead>
<tr>
<th></th>
<th>2D planning:</th>
<th>3D planning:</th>
<th>3D planning:</th>
<th>3D planning:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>non-trial</td>
<td>trial patients</td>
<td>trial patients</td>
<td>trial patients</td>
</tr>
<tr>
<td></td>
<td>patients</td>
<td>(total)</td>
<td>(control-standard plan)</td>
<td>(interventional-IMRT)</td>
</tr>
<tr>
<td>Patient numbers</td>
<td>76</td>
<td>37</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Median time (mins)</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Inter quartile range (mins)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Range (mins)</td>
<td>5 – 25</td>
<td>10 – 45</td>
<td>10 – 45</td>
<td>15 – 40</td>
</tr>
</tbody>
</table>

Table 5.8 Timing for physics check

Table 5.9 shows the median treatment times for the IMRT and non-IMRT trial patients. It can be seen that the treatment times for the first fraction are compatible with the 20 minute designated slot for first day treatments (there is no data for IMRT incorporating a superior-inferior wedge). Subsequent treatment times for all groups are within the designated 15-minute slot.
Results II: Implementation of breast IMRT

<table>
<thead>
<tr>
<th>Median treatment times (minutes)</th>
<th>Non-IMRT treatments</th>
<th>IMRT treatments: 2 additional segments</th>
<th>IMRT treatments: 4 additional segments*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fraction</td>
<td>14.58 (n = 53)</td>
<td>16.08 (n = 22)</td>
<td>No data</td>
</tr>
<tr>
<td>Subsequent fractions</td>
<td>11.13 (n = 310)</td>
<td>12.63 (n = 135)</td>
<td>12.98 (n = 58)</td>
</tr>
</tbody>
</table>

Table 5.9 Median treatment times for Cambridge Breast IMRT Trial patients

*The 4 segments consisted of 2 MLC-shaped fields, and 2 further additional fields for the superior-inferior wedge.

Discussion

5.3.3 Dosimetry study

That mean breast volume was significantly larger in the randomised compared with the non-randomised patients is not surprising. This demonstrated the association with late changes in breast appearance and breast size reported by Moody et al, who also showed that the increase in late radiation effect observed in larger breasts was related to greater dose inhomogeneity [31]. A separate group of 37 women with limited CT data of the breasts were studied. A significant correlation between breast size and dose inhomogeneity was found in this small group.

Following this report, attempts have been made to select patients for IMRT based on measures of breast size. Neal et al showed that dose heterogeneity was most strongly correlated with breast volume (r = 0.70, 95% confidence interval (CI) 0.37 – 0.87). There was also a positive correlation for breast dose heterogeneity versus bra cup size (Spearman rank correlation rho = 0.62), breast area (r = 0.39, 95% CI -0.06 – 0.71) and chest wall separation (r = 0.31, 95% CI -0.15 – 0.66) [12]. The Cambridge IMRT Breast Trial results show that despite a significant difference in mean breast volume and separation, there is an overlap between the ranges of these parameters in randomised and non-randomised patients, i.e. it is not possible to accurately predict benefit from IMRT based on breast size alone. This may reflect that it is shape as well as size, which determine breast dose homogeneity. This finding was also shown in the pilot study of 48 patients, which prompted the use of screening for dose inhomogeneities exceeding ICRU 50 recommendations, rather than selecting women with larger breasts for our trial. As well as being more inclusive, it gives unique and valuable information on the percentage of patients without significant dose inhomogeneities. These dosimetry data to date suggests that the figure is around 30%, which is very similar to the finding of our pilot study [150]. Screening for dose inhomogeneities using CT scanning also has potential advantages for the patient even if a standard 2-field breast plan is used. It has been shown that this increased 3D information allows better coverage of breast tissue compared with simulator-planned
Results II: Implementation of breast IMRT

fields [152]. This is a particular concern for medially and laterally located tumour beds which could be missed by simulator-planned fields [18, 128]. The dosimetry results from this clinical study, show that the forward-planned IMRT technique reduced the median volume > 107% without increasing the median volume < 95%.

5.3.4 Timing study
The results of the timing study show that the process for the 3D radiotherapy planning is considerably more time consuming than conventional 2D simulator-based planning. This is not surprising given the relative increase in complexity. However, the timing study was introduced at the start of several new techniques: CT scanning in a different position, virtual simulation, and isocentric set-up for treatment. Therefore, there will undoubtedly be improvements in the time taken as techniques become more familiar. An example is the virtual simulation process, as it takes time to assimilate the large amount of radiological information available and place the fields to cover the target optimally whilst limiting inclusion of normal tissue. The technique has implications for skill mix, as the previously doctor-led simulator planning is now moving to radiographer-led CT localisation and planning. The timing study will be repeated once the radiographer-led process is established.

5.3.5 Implementation of breast IMRT via a clinical trial
A randomised trial has been a useful method of introducing changes in a controlled and methodical manner, by limiting the numbers recruited per week. It would have been impossible to change the techniques for all breast radiotherapy patients simultaneously due to lack of resources and unfamiliarity with new techniques. Consequently, there was no ethical dilemma as to which patients would receive a potentially ‘better’ treatment, by using randomisation within a trial setting.

Initially, trial recruitment was limited to 1 or 2 patients referred by 2 consultants closely involved in the trial. At this stage, the laser imaging technique was used, which proved to be effective, but was time consuming. It also lacked the complete internal anatomy information provided by multislice CT. Therefore, CT scanning was implemented when this facility became available. This was a gradual transition as the original breast boards would not fit through the bore of the CT scanner and new CT-compatible boards had to be purchased. The Addenbrooke’s Breast Radiotherapy group decided that this would be an opportune time to change to an isocentric planning technique for the CT-scanned trial patients, and I led a working party to implement this. The standard simulator-based technique was to mark the medial and lateral field entry points with tattoos and set-up to those points with the aid of a back pointer. As virtual simulation was used to place the fields, it would be unnecessary to tattoo the actual field entry points. This meant that the tattoos could be
placed away from the breast on more stable tissue. The addition of a contralateral tattoo would also contribute to a more reproducible set-up technique. The new technique was assessed with an automated electronic portal imaging matching facility (PipsPro), which was radiographer-led.

The timing study gave useful information regarding the components of the entire radiotherapy process. This gave important information for allocation of resources and training. An example is the 3D planning component, which will clearly remain more time consuming than simple 2D planning even taking into account improvements in the learning curve. Therefore, an effort has been made in training more radiographers and planning technicians in the technique and re-assessing the skill mix required for this technique. This initial report confirms that new 3D breast planning and IMRT is more time consuming and requires considerably more resources than conventional 2D techniques. It is therefore essential to investigate the clinical benefit of these new technologies.
Chapter 6. Results III: Validation of analytical assessment tool for assessing breast cosmesis following radiotherapy

6.1 Introduction

Given the importance of cosmetic outcome to women following breast-conserving treatment, there is a drive to minimise the side effects of treatment as much as possible without compromising local recurrence and cure rates. In order to assess the effect on cosmesis of new radiotherapy (and surgical) techniques, it is essential that the assessment tools are optimal. Panel assessment of photographs has been shown to be a useful method of grading breast cosmesis, and has been used in the EORTC Boost versus non boost trial and the UK START trial [23, 153]. It has been shown that breast size and shape are factors that influence this global photographic score the most [153]. This is not surprising as change in breast volume, thought to be due to fibrosis, has been shown to be the commonest post-radiation side effect [31]. Although this method of assessment is useful, it also has disadvantages: it produces a rather coarse discontinuous classification system, which is less sensitive than a continuous scale.

In view of this, attempts have been made to produce more sensitive methods of assessing breast cosmesis using a continuous scale. Many of these have focussed on assessing the effect of fibrosis on the cosmetic outcome. An example is the breast retraction assessment whereby digitiser measurements of the displacement of the nipple can be made using patient photographs [153, 154]. A similar method has measured change in symmetry between the treated and untreated breast using computer-assisted image analysis [155]. The breast retraction assessment method reduced intra- and inter observer variability compared with photographs scored by a panel, but was less good in assessing patients presenting with inferiorly located tumours, and was unable to assess skin changes. The computerised measurement of breast symmetry also showed substantial differences compared to assessment by a panel and, more importantly, the patient's own evaluation of cosmesis.

Some novel methods of measuring fibrosis after breast radiotherapy have been reported in the literature. A tissue compliance meter measures the depth of penetration of a rubber-tipped probe under the force of 1 kilogram [30]. Some women found the test painful, and some areas of the breast produced less reliable results than others. A viscoelasticity skin analyser has also been used to measure skin elasticity after breast radiotherapy, but the method is currently a research tool [156].
It has been reported that ultrasonic measurement of the dermal thickness of the breast shows significant differences between irradiated and non-irradiated breast tissue [157]. MRI has also been used to assess areas of fibrosis, but associated time constraints and expense are likely to limit their widespread introduction into clinical practice for this purpose [158].

Given these reports from the literature, it appears that the ideal cosmesis assessment tool would be quantifiable using a continuous scale, but would also identify important qualitative changes. In addition, it would be acceptable to the patient and possible to implement clinically. A novel method has been developed using a 3D laser camera appears to fulfil these criteria. The validation process of this technique prior to implementation within a clinical trial of breast IMRT is presented.

6.2 Methods

6.2.1 Acquisition of laser image and measurement of breast volume change using 3D laser data

See Chapter 3 – Methods.

6.2.2 Phantom study

The first part of this experiment was carried out with the help of Dr Graham Treece. We wished to ascertain the accuracy of the laser camera in detecting changes in volume, and a modelling clay phantom was used for this process. A piece of intact modelling clay was imaged 5 times with the laser camera. Then a piece of clay was removed (clay volume 1) with a sharp knife, taking care not to deform the clay. The remaining clay was imaged twice more with the laser camera. A second piece of clay (clay volume 2) was removed and the process was repeated. The volumes of the 2 separate pieces of clay were measured with water displacement (Archimedes’ principle), using a water-filled measuring cylinder with 2 ml gradations. The measurements were repeated twice for each piece of the clay and the total volume was calculated from the mean values. Each of the 5 original images was registered with the subsequent 4 images for clay volumes 1 and 2 using the Viewsurf software. In addition, clay volume 1 and 2 images were registered with each other. This produced multiple measurements for clay volumes 1 and 2, and the volume of the combination, which could be compared to the data obtained with water displacement.

The aim of the second part of the experiment was to ascertain the reproducibility of the system when assessing the volume of an anthropomorphic breast phantom, i.e. without the added potential problems of patient movement and breathing. A breast phantom was used, which had been constructed from a plaster of Paris mould from an actual patient. This was imaged 10 times using the laser camera, with re-positioning of the camera each time. The 10 data sets were registered with
each other using Viewsurf, producing 45 separate measurements of volume. The anthropomorphic phantom gave additional information to the clay model as it demonstrated that the laser camera was able to reproduce the surface contour of a typical breast patient, which was larger and had a greater curvature than the clay phantom.

6.2.3 Patient studies of the effect of breathing and movement
The next step was to assess the reproducibility of the laser camera method in patients where clearly movement and respiration could pose a potential problem. Firstly, the effect of breathing was investigated in 1 patient. With the patient in the radiotherapy treatment position on a breast board, 10 camera frames each were taken in deep inspiration, deep expiration, and free breathing. The camera was re-positioned between each camera frame. The 10 images produced in each phase of respiration were compared within the groups, producing 45 measurements for deep inspiration, deep expiration and free breathing respectively. In addition 45 measurements were carried out by comparing images for deep inspiration and deep expiration together.

Based on the results of this pilot data (see Results section later), a larger study of 10 patients was performed. Each patient was imaged 10 times in the radiotherapy treatment position in the same session, whilst carrying out free breathing. Again, the camera was re-positioned between each camera frame. This produced 45 measurements of breast volume, and a total of 450 measurements in total. The PTV obtained from the CT planning data set was used to compare total breast volume in each patient. This volume was based on the radiotherapy fields, and was drawn 5 mm from the skin surface and 5 mm from the posterior field/lung edge. Clearly, this was likely to be an over-estimation of the total breast volume, but it was a consistent method with which to compare patients. The total breast volume was correlated with the standard deviation of the mean change in breast volume, in order to ascertain whether there was greater variation in women with larger breasts.

6.2.4 Surgical study
Although the concept of the laser camera assessment was originally to detect changes due to radiotherapy, it would have taken at least 2 years to obtain any meaningful results from comparing pre- and post-radiotherapy laser camera images. Therefore, this small pilot study was carried out in surgical cases to ascertain if the laser camera system could detect small changes in breast volume in 13 patients pre- and post-surgery. In addition to the volume change, an assessment of the colourwash depth contour map of the co-registered images was carried out to give information about the location of the volume change. In each patient, 1 laser scan was carried out before surgery and another at the time of radiotherapy planning, with each image taken with the patient in
the radiotherapy treatment position. Additional information was collected: the surgery to radiotherapy planning time interval, the weight of the resected specimen, and the volume of the specimen created from the maximum specimen dimensions (using the formula for volume of an ellipsoid: \( \pi \) divided by 6 then multiplied by the maximum specimen dimensions).

6.2.5 Statistical methods

The mean values with one standard deviation were used where appropriate. Degree of correlation was shown, with the associated p-value.

6.3 Results

Results of the clay phantom result are shown in Table 6.1: all are within the 2 ml accuracy of the water displacement method. The one standard deviations of less than 0.5 ml suggest good reproducibility of the laser system. The 45 measurements of the anthropomorphic breast phantom gave a mean difference in volume of 0.78 ml with one standard deviation of 0.5 ml.

<table>
<thead>
<tr>
<th>Clay phantom measurements</th>
<th>Mean volume: water displacement method (cc)</th>
<th>Mean volume: laser camera method (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clay volume 1</td>
<td>17.5</td>
<td>17.66 (SD* 0.23)</td>
</tr>
<tr>
<td>Clay volume 2</td>
<td>20</td>
<td>21.66 (SD 0.40)</td>
</tr>
<tr>
<td>Clay volume 1+ 2</td>
<td>37.5</td>
<td>39.29 (SD 0.27)</td>
</tr>
</tbody>
</table>

Table 6.1 Comparison of clay phantom measurements using water displacement and laser camera methods. Volume measured in cubic centimetres (cc). * SD: 1 standard deviation of the mean.

The comparisons of differences in breast volume measurements obtained during different phases of breathing are displayed in Table 6.2.

<table>
<thead>
<tr>
<th>Difference in breast volume (cc)</th>
<th>Deep inspiration(^1) n = 45 measurements</th>
<th>Deep Expiration(^2) n = 45 measurements</th>
<th>Free Breathing(^3) n = 45 measurements</th>
<th>Inspiration and expiration(^4) n = 45 measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>4.04</td>
<td>-0.06</td>
<td>1.07</td>
<td>-8.91</td>
</tr>
<tr>
<td>1 standard deviation</td>
<td>4.28</td>
<td>2.53</td>
<td>3.13</td>
<td>5.06</td>
</tr>
</tbody>
</table>

Table 6.2 Comparison of differences in breast volume measurements obtained during different phases of respiration in the same patient. Volume measured in cubic centimetres (cc).

\(^1\)10 camera frames obtained during deep inspiration were compared with each other.

\(^2\)10 camera frames obtained during deep expiration were compared with each other.

\(^3\)10 camera frames obtained during free breathing were compared with each other.

\(^4\)10 camera frames obtained during deep inspiration and deep expiration were compared with each other.
The greatest reproducibility was found during deep expiration, and the worst when images obtained in expiration and inspiration were registered together. It was felt that imaging during free breathing was the most practical solution for future studies, as there was little difference between deep expiration, and the patients would not have to be ‘trained’ to carry out specific forms of breathing. Some patients would be better able to carry out specific breathing patterns than others, and the worst scenario would be to co-register images in deep inspiration and deep expiration in a patient who was unable to comply with specific breathing patterns.

The mean differences in breast volume measurements for 10 patients during free breathing are shown in Table 6.3. Analysis of the entire 450 measurements gave a mean difference in breast volume of 0.96 ml and mean standard deviation of 4.05 ml.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Breast volume (cc)</th>
<th>Mean breast volume change (cc)</th>
<th>Standard deviation of the mean breast volume change (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1032</td>
<td>-0.14</td>
<td>2.98</td>
</tr>
<tr>
<td>2</td>
<td>800</td>
<td>-0.98</td>
<td>6.07</td>
</tr>
<tr>
<td>3</td>
<td>2192</td>
<td>2.04</td>
<td>6.69</td>
</tr>
<tr>
<td>4</td>
<td>836</td>
<td>2.61</td>
<td>4.08</td>
</tr>
<tr>
<td>5</td>
<td>1235</td>
<td>0.85</td>
<td>2.74</td>
</tr>
<tr>
<td>6</td>
<td>615</td>
<td>1.14</td>
<td>1.11</td>
</tr>
<tr>
<td>7</td>
<td>952</td>
<td>1.13</td>
<td>1.49</td>
</tr>
<tr>
<td>8</td>
<td>232</td>
<td>0.56</td>
<td>0.70</td>
</tr>
<tr>
<td>9</td>
<td>1114</td>
<td>0.47</td>
<td>3.94</td>
</tr>
<tr>
<td>10</td>
<td>1015</td>
<td>1.9</td>
<td>4.76</td>
</tr>
</tbody>
</table>

Table 6.3 Mean differences in breast volume measurements during free breathing.

45 measurements obtained per patient, displayed in cubic centimetres (cc).

The correlation between size in breast and reproducibility of the laser camera method is shown in Figure 6.1. Clearly this is a small patient sample, but there is a suggestion that the reproducibility is worse for patients with larger breasts. This makes sense, as larger breasts are likely to be more mobile. However, patient 2 with a breast volume of only 800 ml, had a standard deviation of the mean volume difference of 6.02. Therefore, it is not simply breast size which affects movement, but other factors such as patient compliance.
Results III: Validation of breast cosmesis assessment

Fig. 6.1 Correlation between breast volume and standard deviation of the mean change in breast volume
Volume measured in cubic centimetres (cc).

\[ R^2 = 0.4534 \quad p = 0.0328 \]

**Table 6.4 Assessment of change in breast volume following surgery**

Table 6.4 displays the results of the surgical study. Two out of thirteen patients had laser data missing from their scans and therefore could not be accurately assessed. Patients 6 – 10 had volume changes less than +/- 5 ml, and patient 11 had a volume change less than +/- 10 ml. These 6 patients showed no obvious areas of volume change on qualitative assessment of the depth contour map. Patients 1 – 3 had volume loss of more than 10 ml, and this was shown to be in the region of the scar (see Figure 6.2 – 6.4, for illustration of the pre-operative, post-operative, and combined laser camera images for patient 1). Patient 4 was known to have a large seroma in the region
Results III: Validation of breast cosmesis assessment

around the scar on the radiotherapy CT planning scan. She was found to have an increase in volume of 12 ml and this was seen in the region around the scar on the depth contour map (see Figures 6.5 – 6.7). Patient 5 had almost no volume change, but had a combination of loss of volume around the scar and swelling elsewhere in the breast.

Figure 6.2 Pre-operative breast image for patient 1
The red crosses were used to co-register the 3D ultrasound and laser camera data.

Figure 6.3 Post-operative breast image for patient 1
The black arrows indicate the position of the scar, and there appears to be some loss of volume compared to the pre-operative image (Figure 6.2).
Results III: Validation of breast cosmesis assessment

Volume change from 1 to 0 is 27.97ml

Figure 6.4 Combined pre- and post-operative breast images for patient 1
The red colour indicates a loss of volume corresponding to the region around the scar. The assessment method gave a value of 28 ml as the loss of volume.

Figure 6.5 Pre-operative breast image for patient 4

Figure 6.6 Post-operative breast image for patient 4
The black arrows indicate the position of the scar.
Results III: Validation of breast cosmesis assessment

Volume change from 1 to 0 is -13.11 ml

Figure 6.7 Combined pre- and post-operative breast images for patient 4
The blue colour indicates an increase in breast volume around the region of the scar. The assessment method gave a value of 13 ml for the increase in volume.

6.4 Discussion
The laser camera technique is a novel, analytical, non-contact method for measuring change in breast volume. Bulstrode et al compared 5 different methods of measuring total breast volume [158]. They concluded that volume displacement of the breast was inaccurate, MRI was too expensive at present, volumes calculated from anatomical measurements were unreliable, volume calculated from mammograms were less acceptable to patients due to discomfort, but thermoplastic moulding of the breast showed promise. Although the direct comparison has not been made, it is likely that the laser camera method would be more acceptable to patients than thermoplastic moulding, as it a non-contact technique, which takes less than 5 minutes (actual data acquisition is less than 1 second).

Validation of the laser camera system shows that the technique is accurate and reproducible. Reproducibility may decrease with increasing breast size, but even applying 2 standard deviations of the worse result (patient 3, Table 6.3), the reproducibility would be within +/- 15 ml, i.e. less than +/-1% of the total breast volume. As well as producing an objective continuous system for measuring change in breast volume, this technique has the advantage of incorporating qualitative assessments of other factors contributing to cosmetic change. For example, the colour photographs produced enable assessment of skin changes and scars (the Viewsurf software allows magnification and 3D rotation of the image). The method also shows the position of the volume changes, for
Results III: Validation of breast cosmesis assessment

example patient 5, Table 6.4 had negligible change in net breast volume, but assessment of the colourwash depth contour map showed regions of both increased and decreased volume.

This study clearly shows the possible use of the laser camera as a post-surgery cosmetic assessment tool. However, the primary aim of the research was to develop a tool to measurement post-radiotherapy changes in the breast. A particularly appealing possible application of the technique would be to register the depth contour map with the individual radiotherapy isodose contours. This could enable the effect of dose and volume to be studied in individual patients, i.e. studying the effect of high dose volumes on fibrosis and loss of breast volume. Following this successful validation study, the laser camera technique has been incorporated as part of the assessment of a randomised controlled trial comparing the cosmetic outcome with standard breast radiotherapy and IMRT. The primary endpoint is cosmetic outcome assessed using serial photographs. Assessment with the laser camera is a secondary endpoint: patients receive pre-radiotherapy scans and post-radiotherapy scans at 2 and 5 years, with imaging of the contralateral breast acting as a control. Most importantly, the trial also assesses the patients’ view of their cosmetic result, by using serial quality of life questionnaires with specific items pertaining to breast radiotherapy. Therefore, the results of the laser camera technique will be compared with a validated photographic assessment method and patients’ subjective assessment of cosmesis.
Chapter 7. Results IV: High definition three-dimensional ultrasound to localise the surgical cavity for breast radiotherapy planning: validation of the technique

7.1 Introduction
There have been numerous reports illustrating the inferiority of ‘clinical’ methods of tumour bed localisation when compared with other imaging methods, as described in Chapter 2 – Review of the literature. Tumour bed localisation methods include surgical clips, CT, MRI and 2D ultrasound. However, all of these techniques have potential problems. In view of this, validation of a novel technique for localising the tumour bed following breast-conserving surgery, using an optically tracked high-resolution freehand 3D ultrasound system is described [148]. Volume and spatial localisation of a ‘target’ within a phantom using both 3D ultrasound and CT, is compared to determine the point location accuracy of the ultrasound technique. This study was carried out in collaboration with Dr Charlotte Cash (CJCC), radiologist.

7.2 Methods
7.2.1 Phantom construction
It was necessary to test the 3D ultrasound method using a phantom for several reasons. Firstly, a well-defined ‘target’ representing the tumour cavity, which could be visualised using both ultrasound and CT was needed. Secondly, multiple CT scans would be required, which would be ethically unacceptable in a patient. Thirdly, it was desirable to ascertain the accuracy of the 3D ultrasound system in the absence of patient movement errors (a clinical study, which therefore included patient movement errors is described in Chapter 8).

A breast phantom was required which would incorporate a target with a composition suitable for ultrasound and CT identification and represent the tumour cavity within breast tissue. A standard model used widely in ultrasound teaching and training is an olive embedded within a turkey breast. We decided against this model for the following reasons: the model was not re-useable due to health and safety reasons, and therefore not reproducible if the experiment needed to be repeated. In addition, it was felt that there could be slight movement of the olive within the turkey breast, which would invalidate the experiment. Therefore, an alternative model was chosen using an olive embedded in gelatine, which could be re-usable, less prone to movement of the olive, and was subject to compression like breast tissue. The disadvantage of this model is that the gelatine is more homogeneous than breast tissue and does not produce the differential attenuation seen with breast
tissue. However, this was not felt to be a major problem given that there is so much variation between different breasts that it would not be possible to represent a perfect "standard" breast.

Ultrasound machines assume that the velocity of sound is 1540 metres per second (ms\(^{-1}\)) as this is taken to be a good average in tissue. Our gelatine phantom was not constructed to have this exact velocity for ultrasound, but the real value lies between 1450 ms\(^{-1}\) and 1570 ms\(^{-1}\), which is the normal range for tissue. Thus, the mean depth distances measured by the ultrasound machine would be out at most by 90/1540 percent (about 6%). Likewise, the effect of inhomogeneities of ultrasound velocity in the breast tissue would be likely to have a similar small effect.

The model was constructed using a plastic bag filled with gelatine by CJCC following discussion with me. The breast target was simulated using pitted olives filled with Vaseline to avoid acoustic reflectivity on ultrasound. Two olives were used, one whole (target 1) and one in half (target 2) to allow simple identification. An empty bag was half filled with gelatine and once partially set; the two olives were dropped into the bag and covered with further liquid gelatine. This two-stage method ensured that the olives remained within the centre of the gelatine rather than floating to the surface before the gelatine had set.

7.2.2 Target imaging

A dual detector CT (HiSpeed Nxi, General Electric Company, Wisconsin) calibrated for radiotherapy CT planning was used. It was assumed to be an accurate system for comparison with 3D ultrasound. The position of the central CT slice was marked on the phantom using laser lines (LAP Laser Applikationen, http://www.LAP-LASER.com). Two radio-opaque fiducials were placed on the phantom in the plane of the central CT slice. These simulated the position of the radiotherapy tattoos and were used for co-registration of the CT and ultrasound images. The phantom was placed on the CT table and positioned so that target 1 was close to the central CT slice and target 2 was 6 cm out-of-plane. Frequently, in clinical practice the surgical cavity is found some distance away from the central CT axis and therefore the purpose of target 2 was to assess the ultrasound system's ability to locate an object away from the central CT slice. One-millimetre contiguous CT images were then acquired through the phantom. Without moving the phantom, the table was brought out of the CT gantry to enable ultrasound imaging.

Acquisition of the ultrasound image and position data using the 3D ultrasound system is described in Chapter 3 – Methods. Two data sets of each target were obtained in orthogonal planes as part of one ultrasound examination. To ensure optimal results, all scans were carried out by 1 experienced radiologist: CJCC. Each set of fiducial registrations and ultrasound examinations were repeated 16
times, moving the position sensor (and hence the co-ordinate reference frame) in between each completed set. For each ultrasound examination, there were 4 ultrasound data sets (2 for each target), giving a total of 64 ultrasound datasets. The CT was repeated after the first eight ultrasound examinations and again at the end of the ultrasound acquisition, i.e. 3 CT scans in total.

7.2.3 CT-ultrasound co-registration
The 3 CT scans were imported into Stradx and each of the 64 ultrasound data set was spatially registered to the central CT image using the fiducials, as described in Chapter 3 – Methods.

7.2.4 Volume measurement and spatial localisation
Within Stradx, the targets from all 64 ultrasound data sets were manually outlined by a single observer: CJCC. Volume measurements were produced from the target outlines for each data set using Stradx software [159, 160]. The CT data was imported into ARPS. A window width of 200 Hounsfield Units (HU) and level of 0 HU was chosen (reference CT), which optimally depicted the targets. A single observer: CEC (myself) manually outlined both targets (3 CT scans each).

To test the effect of narrowing or widening the window width, the outlining process was repeated with window widths of 100 HU and 300 HU for the 3 CT scans. Volume measurements were obtained by importing the data into commercially available software, Metris Base 5.0 (Metris NV, Belgium). I had previously applied this method for another radiotherapy planning study: Quantitative assessment of inter-clinician variability of target volume delineation for medulloblastoma: quality assurance for the SIOP PNET 4 trial protocol [161].

The target surface was interpolated from the ultrasound outlines. From this surface, a new series of outlines re-formatted into the same plane as the CT data were imported into Metris Base. It was then possible to compare spatial localisation of both the ultrasound and CT data sets by measuring the respective centre of gravity (X, Y and Z co-ordinates) for each CT and ultrasound data set [161]. The mean reference CT (window width 200 HU) centre of gravity co-ordinates were used as a comparison for all 64 ultrasound data sets.

7.2.5 Inter- and intra-observer variability
There are two important parts of the process of olive volume measurement: firstly, acquisition of an ultrasound dataset, and secondly manually outlining the olive. We wanted to ascertain how the outlining process affected the accuracy of the ultrasound system. Intra-observer variability was taken as the variation within one observer outlining the same data set at different times as a fraction of the variation within and between datasets for a single observer. Inter-observer variability was
taken as the variation between observers outlining the same data set as a fraction of the variation within and between datasets across observers). In addition, we considered it important to differentiate between a radiologist observer who was familiar with ultrasound images, and an oncologist who was unfamiliar. Prior to the exercise, I (the oncologist) received a short period of training in the use of Stradx and interpretation of ultrasound images. The radiologist and oncologist then independently outlined 5 ultrasound datasets of the same target. The exercise was repeated 10 times by the oncologist and 16 times by the radiologist.

7.2.6 Methods of Statistical Analysis
Statistical analysis was performed using STATA version 7 (Stata Corp LP, Texas, USA). The unpaired Student’s t-test was used to test the bias of ultrasound measurement of target volume by testing the hypothesis that there was no difference between the means of the volumes measured by ultrasound and the gold standard CT measurement. Inter-observer variability was assessed using the method of Bland and Altman, computing the mean difference in volumes measured by the two observers and the normal range for this value [162]. Intra-observer variability was assessed using one-way analysis of variance to compute a reliability coefficient for each observer. For both targets, ultrasound recorded centre of gravity co-ordinates were compared to the CT recorded centre of gravity co-ordinates which were taken as a gold standard. The (signed) distance between the ultrasound and CT centre of gravity was recorded in the x, y and z directions as an estimate of systematic error. The variance in this measure was used as an estimate of random error. The overall distance between the ultrasound measured centre of gravity and CT measured centre of gravity for each error group was computed using Pythagoras’ theorem: distance = square root ($X^2 + Y^2 + Z^2$). The root mean square of all distances between the ultrasound measured centre of gravity and CT measured centre of gravity was used as a summary estimate of systematic and random (total) error. Signed distances between ultrasound and CT in each direction and overall distances were compared between the two targets using the unpaired t-test.

7.3 Results
7.3.1 CT and ultrasound measurement of volumes
Three CT volume measurements were made for each target. Narrowing and widening the window widths of the CT data affected the outlining and therefore the target volumes (Figure 7.1), with a reduction in the window width resulting in bigger outlines and therefore larger volumes. The targets were identified most readily with a window width of 0 to 200 HU. This was the chosen window width used to measure the target volumes. The mean volume for target 1 was 5.8 cm$^3$ (standard deviation 0.4 cm$^3$), and the mean volume for target 2 was 3.2 cm$^3$ (standard deviation 0.2 cm$^3$). These volumes were taken as the gold standard.
Results IV: Validation of 3D ultrasound

Thirty-two ultrasound volume measurements were taken for each target. The mean volume for target 1 was 5.4 cm$^3$ (standard deviation 0.2 cm$^3$), and the mean volume for target 2 was 3.2 cm$^3$ (standard deviation 0.3 cm$^3$). Mean ultrasound volumes for target 1 and target 2 differed from the CT measured volumes by 0.4 cm$^3$ and 0 cm$^3$ respectively, showing no significant difference (unpaired t-test with unequal variances p = 0.25 for target 1 and p = 0.67 for target 2).

![Graph showing effect of CT window on target volume](image)

**Figure 7.1 Effect of CT window on target volume**

This graph shows that the estimated volume in cubic centimetres (cc) of targets 1 and 2 varied slightly according to the CT window width.

### 7.3.2 Accuracy of spatial localisation using the 3D ultrasound system

Figure 7.2 shows one of the reference CT’s co-registered with all of the ultrasound outlines.

All distances between the centres of gravity as measured by ultrasound and CT for both targets were small but significantly different from zero. The systematic and random errors in measurement of centre of gravity with ultrasound using CT as a gold standard are summarised in Table 7.1. The ultrasound determined centre of gravity for target 1 was a mean distance of 2.2 mm (standard deviation 0.6 mm) from the reference CT determined centre of gravity. The ultrasound determined centre of gravity for target 2 was a mean distance of 2.7 mm (standard deviation 0.8 mm) from the reference CT determined centre of gravity. These values correspond to the total measurement error. The systematic measurement errors were 1.6 mm and 1.9 mm for targets 1 and 2 respectively. The random errors were 1.6 and 1.8 mm for targets 1 and 2 respectively. There was no significant difference in the accuracy of ultrasound-determined centre of gravity between the two targets (p = 0.098 unpaired t-test).
Results IV: Validation of 3D ultrasound

<table>
<thead>
<tr>
<th>Systematic error: signed mean distance (mm)</th>
<th>Random error: standard deviation of signed distance (mm)</th>
<th>Total error: total root mean square distance (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TARGET 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Y</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Z</td>
<td>-0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Overall distance</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>TARGET 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Y</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Z</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Overall distance</td>
<td>1.9</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Table 7.1 Systematic, random and total errors in measurement of centre of gravity with ultrasound using CT as a gold standard.

* Overall distance for each error type was computed using Pythagoras' theorem.

Figure 7.2 3D ultrasound and CT registration
This figure shows the reference CT co-registered with the ultrasound outlines in the radiotherapy planning system for target 1 (top) and target 2 (bottom) respectively. The CT images are outlined in red and the ultrasound images are outlined in orange.
7.3.3 Intra- and inter-observer variability

Inter-observer variability was good with a mean difference of 0.25 cc (95% of differences lie between -0.25 cc and 0.65 cc) in measurements made by the two observers. The oncologist consistently recorded values approximately 5% higher than the radiologist. These data are presented as a Bland-Altman plot in Figure 7.3. Intra-observer variability was good with a reliability coefficient of 0.69 for the radiologist and 0.49 for the oncologist.

![Figure 7.3 Bland Altman plot showing inter observer variability](image)

This plots the difference between volumes in cubic centimetres (cc) measured by the oncologist (CEC) and radiologist (CJCC) against the average of the volumes measured by the two operators. Each shape (five in total) represents measurements from a particular dataset. The horizontal line represents equal measurements made by the two operators. Most of the measurements being above this line are in keeping with a systematically larger volume being recorded by the oncologist than the radiologist. The majority of the differences lie between 0 and 0.5 cc.

7.4 Discussion

The results demonstrate that the 3D ultrasound system is an accurate and reproducible technique. It is superior to 2D ultrasound as it produces 3D ultrasound images linked with position data. This means orientation of the transducer with respect to breast contour does not influence target localisation.

A gelatine phantom was chosen because of its compressibility and to enable quantification of this potential source of error. Due to the geometry of the ultrasound beam, the axial resolution should be greater than the lateral resolution. However, due to the external effect of probe pressure as seen in the clinical situation, the error in the Z-axis was not significantly different than the errors in the X- and Y-axis. Although the gelatine was compressible, its texture was generally firmer than a lot of breast tissue. Breast tissue varies considerably in its fatty/fibrous composition and therefore compressibility. Thus error induced by compression will vary from individual to individual and...
Results IV: Validation of 3D ultrasound

from quadrant to quadrant. Operator awareness of probe compression should help to minimise this error.

Although no statistical difference between spatial localisation of the in-plane target 1 versus the out-of-plane target 2 was demonstrated (p < 0.98), the results suggest that for optimal accuracy, the area of interest should lie as close as possible to the central CT image, i.e. the image to be used for co-registration. In standard radiotherapy planning set up, the tumour bed may be some distance away from the central CT image. It was therefore, important to assess the system's ability to accurately localise a target close to the registration plane, and also away from the registration plane.

There are limitations in assuming that the CT images are the gold standard. The position of the targets on the CT are dependent on firstly the image window width and secondly on operator dependent outlining. As both these variable parameters would tend to cause a uniformly larger or smaller volume, variations in the centre of gravity should be minimal. We were aware that there would also be some variability in outlining of the CT images. However, the purpose of this study was to measure accuracy of the ultrasound system and therefore the intra- and inter-observer variability in CT outlining was not studied. In addition, the target images were well defined on CT and the oncologist was experienced in CT outlining using the planning system. Therefore, it was assumed that CT outlining variation would be minimal.

The recent British Institute of Radiology document 'Geometric uncertainties in radiotherapy planning' states that target outlining is likely to produce the greatest systematic error in radiotherapy planning [138]. This study highlights several interesting points. Firstly, the difference between the radiologist's and oncologist's ultrasound volumes was very small. This was despite the fact that the oncologist was less experienced with ultrasound imaging. The training session prior to the outlining exercise may have helped, as training coupled with well-written protocols decrease inter-observer variability in target delineation [163-165]. Secondly, although the mean volume difference was small, the oncologist consistently outlined larger volumes than the radiologist. This has been shown in other studies of target delineation [166, 167]. It appears that oncologists routinely planning radiotherapy are more likely to err on the side of caution when estimating the boundaries of a lesion, whereas radiologists are more likely to describe the anatomy. Thirdly, the small variation in intra- and inter-observer variability may reflect that the targets were relatively distinct on imaging. A less distinct target would produce greater variation. This is a familiar problem in radiotherapy planning; if the imaging modality cannot be improved, greater margins of error are added to account for uncertainty.
This phantom study was unable to take into account the effects of patient movement and breathing. This is an issue with the clinical application of any radiotherapy planning technique and we will address this in a subsequent patient study (see Chapter 8).
Chapter 8. Results V: High definition three-dimensional ultrasound to localise the surgical cavity: breast radiotherapy planning study

8.1 Introduction
This study investigated the use of high definition 3D ultrasound for breast tumour cavity localisation. The specific study aims were as follows: firstly, to determine how easily a tumour cavity could be visualised with 3D ultrasound; secondly, to determine the accuracy of CT and 3D ultrasound co-registration; thirdly, to compare 3D ultrasound with other methods of localisation; lastly, to attempt to register original tumour position with the post-operative tumour bed. This study was carried out in collaboration with CJCC.

8.2 Methods
8.2.1 Localisation of tumour bed
8.2.1.1 3D ultrasound method
The method for 3D ultrasound acquisition and co-registration with CT has been discussed in detail in Chapter 3 – Methods. The patient was positioned on a breast board in the CT-simulator room, and the position of the medial and lateral tattoos on the central CT slice were marked with the aid of laser lines. The infrared emitting pointer was used to record the position of the tattoos and a third point along the same axis, to enable co-registration of the 3D ultrasound data with the CT data. An ultrasound data set was then acquired by moving the transducer over the area of the surgical cavity and a position sensor was used to continually track the position of the infrared emitting diodes on the transducer. A radiotherapy planning CT scan was then carried out using 5 mm contiguous slice spacing and then later imported into Stradx. The tattoos were visible as radio-opaque markers and enabled the ultrasound-CT registration. Using Stradx software, the surgical cavity was outlined producing a segmented data set of the cavity alone. These segmented data sets were then reformatted into the plane of the CT examination and re-aligned with the CT data. The majority of the ultrasound scans were carried out by a radiologist: CJCC, although some were performed by an oncologist: CEC, after training, towards the end of the study. All outlining of the 3D ultrasound datasets was carried out by CJCC who was more experienced with ultrasound image analysis than CEC. However, the validation study had previously demonstrated that ultrasound volumes outlined by CJCC and CEC were very similar.
8.2.1.2 2D ultrasound method
A method for defining the surgical cavity was developed, using 2D ultrasound based on a report by Vicini et al [134]. Following acquisition of the 3D ultrasound dataset, the maximum dimensions of the cavity and depth from the skin surface using 2D B-scan information only were recorded. The projected cavity image was then marked on the skin and outlined with radio-opaque wire. This marker was seen over several CT slices, and the central image was used to reconstruct a 2D ultrasound cavity volume from the recorded dimensions. These volumes were outlined in the planning system by CEC.

8.2.1.3 Surgical clip method
The method of using surgical clips to define the surgical bed was based on the technique used at the William Beaumont Hospital, USA. Following surgical resection, one titanium clip was placed on the deep fascia and 4 more were placed radially around the tumour bed (anterior, posterior, medial and lateral). At radiotherapy planning, the surgical bed was defined as the clips and architectural disruption seen on the CT scan [125]. These volumes were outlined by CEC in 17 patients.

8.2.1.4 CT method
It was apparent that the surgical clips plus architectural disruption definition of the surgical bed was subjective and open to interpretation. Thus it was felt that a direct comparison of a well-defined seroma visualised with CT might be a better assessment of the 3D ultrasound system accuracy (as both systems are visualising a cavity). Therefore, a small number of clearly defined CT images of surgical bed seromas were identified and outlined by CEC. Thus 3D ultrasound was compared with both the apparent “standard” quoted in the literature of CT plus and clips, and the possibly more representative volumes of the well-defined CT seromas.

8.2.2 Feasibility assessment of the 3D ultrasound system

8.2.2.1 Ultrasound localisation of the surgical cavity
Three-dimensional ultrasound was carried out in 40 patients and their images were reviewed in Stradx. We used a grading system described by Leonard et al to determine how easy it was to see the post-operative cavity in each: highly visible, visible, subtle, and not visible [132].

8.2.2.2 Assessment of accuracy of 3D ultrasound-CT registration
We measured movement due to breathing in 36 patients at the time of breast radiotherapy planning. This was achieved by placing the ultrasound pointer with infrared emitting diodes on the patients’ chest wall and tracking the movement with the position sensor. The mean movement as a result of breathing was 0.48 cm (standard deviation of 0.35 cm), which was in keeping with another study.
In addition to breathing, a mean value for patient movement had been reported to be 0.5 cm, giving a total margin of error of 1 cm [124]. The combination of these data was used to create the scoring system for 3D ultrasound-CT registration. Based on this data and similar reports from the literature, a system was devised for assessing 3D ultrasound-CT alignment of the skin and/or pleura in 40 patients: exact alignment (good), alignment within 1 cm (satisfactory), alignment more than 1 cm (poor).

### 8.2.3 Comparison of volume and spatial position

The volume of the resected specimen was calculated by assuming this volume to represent an ellipsoid and using pi divided by 6 then multiplied by a, b, and c, (the maximum specimen dimensions).

A subset of 14 patients had surgical bed clips, 2D ultrasound and 3D ultrasound measurements. Measurement of the surgical bed volumes were obtained by importing the data into commercially available software, Metris Base 5.0 (see Chapter 3 – Methods). Spatial localisation using these different techniques was compared by recording the X (medial-lateral), Y (superior-inferior) and Z (anterior-posterior) centre of gravity co-ordinates using Metris Base software [161]. In addition, the spatial localisation of the 5 patients with clearly defined seromas on CT, were compared with the 3D and 2D ultrasound centre of gravity co-ordinates.

It was recognised that the surgical clip volumes in particular, were subject to interpretation by the clinician outlining. Therefore, to ensure that the surgical clip volumes were representative of volumes reported in the literature, the 17 Addenbrooke’s patients were compared with the William Beaumont series.

### 8.2.4 Co-registration of pre-operative tumour with post-operative tumour bed

The pre-operative tumour was imaged with 3D ultrasound using the same method as described for the post-operative tumour bed. At the same time, the 3D laser camera was used to obtain the contour of the pre-operative breast surface (see Chapter 3 – Methods) Pre- and post-operative laser images were co-registered using the Viewsurf software described in Chapters 3 and 5. This part of the process was carried out by either CJCC or Dr Graham Treece. The merged breast surfaces and 3D ultrasound data were then co-registered with the post-operative radiotherapy planning CT. This enabled the 3D ultrasound pre-operative image of the tumour to be compared with the tumour bed images within the radiotherapy planning system. Registration of the 3D ultrasound images of the tumour and CT were graded in the same way as the tumour bed and CT.
8.2.5 Statistical methods

Statistical analysis was performed using STATA version 7 (Stata Corp LP, Texas, USA). The correlation coefficient $r$ was quoted for all analyses of correlation. The comparison of spatial position of the centre of gravity measured by the different methods was performed by measuring the pair wise distances between the X, Y and Z co-ordinates. A distance between the centres of gravity was then computed using Pythagoras’ theorem: distance = square root ($X^2 + Y^2 + Z^2$), as an overall measure of distance between the centres of gravity computed by the different methods. For the Box and Whisker plots the central line in each box denote median values, the lower and upper boundaries the 25th and 75th centile, the error bars the 10th and 90th centile, and the closed circles outlying data points.

8.3 Results

8.3.1 Feasibility assessment of 3D ultrasound system

The mean surgery to imaging interval was 44 days (range 23 to 86 days). The post-operative cavity was seen in all 40 cases using the 3D ultrasound system, and was graded as highly visible, visible and subtle in 21/40 (53%), 12/40 (30%) and 7/40 (17%) cases respectively. CT-ultrasound registration was achieved in all cases. This was graded as good, satisfactory and poor in 24/39 (62%), 9/39 (23%) and 6/39 (15%) cases respectively. In 1 patient it was not possible to grade the accuracy of registration, because this patient had very large breasts and a deep tumour, which required considerable angulation of the probe during data acquisition. This meant that the re-sliced data in the plane of the CT did not go through skin or rib/pleura.

In contrast, localisation of the 2D ultrasound image within the planning system was not possible in 8/40 (20%) cases. There was a statistically significant difference in the ability of 3D ultrasound to localise tumour compared with 2D ultrasound, using a chi-squared test. In 4 cases the maximum dimensions of the cavity were ill defined, in 3 cases the scar caused acoustic shadowing, and in 1 case the dimensions were not recorded at the time of examination. Although the same ultrasound machine was used to obtain the grey-scale images for both the 2D and 3D ultrasound data, it was found that the ability to scroll through the 3D US data set with multiplanar re-formatting, enabled definition of the cavity that had otherwise been poorly visualised with real time 2D images. Likewise, where acoustic shadowing prevented definition of the cavity from a 2D image produced by the transducer held perpendicular to the skin surface, a well-defined 3D data set of the cavity could be produced by angling the transducer under the scar.
8.3.2 Comparison of tumour bed volumes

Comparison of Addenbrooke's and William Beaumont surgical clip volumes for the tumour bed were reassuringly similar (see Table 8.1.)

<table>
<thead>
<tr>
<th>Tumour bed volume Defined with clips (cm³)</th>
<th>William Beaumont (n = 26)</th>
<th>Addenbrooke's (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Range</td>
<td>3 – 70</td>
<td>3 – 43</td>
</tr>
</tbody>
</table>

Table 8.1 Comparison of William Beaumont and Addenbrooke's breast radiotherapy volumes localised with surgical clips.

T-stage was 1 – 2 in all cases.

Mean volumes for 3D ultrasound, 2D ultrasound, surgical clips and pathological specimen volume were 5.9 cm³, 12.1 cm³, 21.4 cm³, and 37.2 cm³ respectively (see Figure 8.1). These volumes were all statistically significantly different (paired t-test p < 0.05 for all pair wise comparisons using the Wilcoxon matched paired signed rank test).

![Figure 8.1 Box and Whisker plot for tumour bed volume.](image)

Tumour bed volumes (cm³) in 14 patients localised with clips (green), 2D ultrasound (brown) and 3D ultrasound (red), and specimen volume (purple) are displayed.

From the 30 CT scans with both 3D ultrasound and 2D ultrasound surgical cavity outlines, 5/30 (17%) had well-defined seromas using CT imaging alone. A cavity was seen on some CT slices, but merged with the breast tissue in 12/30 (40%), and no obvious cavity was seen in 13/30 (43%).
For the 5 cases with well-defined seromas, the mean tumour bed volumes for 3D ultrasound, 2D ultrasound, and CT were 17.1 cm³, 28.6 cm³, and 23.2 cm³ respectively. Figures 8.2 and 8.3 suggest that the best agreement is between CT and 3D ultrasound.

![Figure 8.2 Box and Whisker plot for tumour bed volume in 5 patients with well-defined seromas](image1)

Tumour bed volumes (cm³) localised with specimen volume (green), CT (brown), 2D ultrasound (red) and 3D ultrasound (purple) are displayed. Subjectively, this shows best agreement between CT and 3D ultrasound volumes, but the numbers are small and statistical significance has not been achieved.

![Figure 8.3 Box and Whisker plot for the differences between the specimen, 2D and 3D ultrasound volumes from CT measured volumes](image2)

Volumes (cm³) for the resected specimen (green), 2D ultrasound (brown) and 3D ultrasound (red) are shown. None is significantly different from zero (small numbers), but all discrepancies are small.

Comparison of the tumour specimen volume and weight produced a correlation coefficient ($r$) of 0.83, suggesting that the assumptions for the calculated specimen volume were reasonable. However, the correlation coefficients between calculated specimen volume and tumour bed volume measured with clips, 3D ultrasound and 2D ultrasound were 0.44, -0.05, and -0.02 respectively, i.e.
poor correlation. This is not surprising, as it is assumed the cavity will change to a certain extent once the tumour has been removed. One would expect fibrosis and seroma formation, making volume and shape of the tumour cavity relate unpredictably to that of the removed specimen.

The correlation between the surgical clips and the ultrasound methods for tumour bed volume are displayed in Figures 8.4 and 8.5. At the time of data analysis, patients with subjectively widespread clips on the CT image were recorded. 4 such patients were identified. If these 4 patients were excluded from the analysis, the correlation coefficients for both 2D and 3D ultrasound increased considerably (see Table 8.2.)

**Figure 8.4 Correlation between the 2D ultrasound tumour bed volume and the clips tumour bed volume.**
Volume measured in cubic centimetres (cc). The “N” symbols represent cases where clips were not thought to be particularly widespread, whereas the “Y” symbols represent cases where clips were thought to be widespread. The “N” symbols tend to be positioned around the line of unity, whereas the “Y” symbols tend to be outliers.

**Figure 8.5 Correlation between the 3D ultrasound tumour bed volume and the clips tumour bed volume.**
Volume measured in cubic centimetres (cc). The “N” symbols tend to be positioned around the line of unity, whereas the “Y” symbols tend to be outliers.
Results V: 3D ultrasound planning study

<table>
<thead>
<tr>
<th>Ultrasound tumour bed volumes</th>
<th>All clip volumes included</th>
<th>Widespread clip volumes excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D</td>
<td>0.47</td>
<td>0.86</td>
</tr>
<tr>
<td>3D</td>
<td>-0.1</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Table 8.2 Correlation of tumour bed volumes defined with ultrasound and clips.

8.3.3 Comparison of spatial localisation of the tumour bed volumes

Pair wise comparison of the distances between the centres of gravity (using Pythagoras’ theorem) for surgical clips, 2D and 3D ultrasound, showed that no one method agreed best with another in estimating centre of gravity (see Figure 8.6).

![Box and Whisker plot](image)

Figure 8.6 Box and Whisker plot for pair wise comparison of the distances between the centres of gravity for surgical clips, 2D and 3D ultrasound. Distances between centres of gravity in millimetres. The green plot compares 3D and 2D ultrasound, the brown compares 3D ultrasound with clips and the red compares 2D ultrasound with clips.

Differences in centre of gravity measured as mean total distance from CT for 2D and 3D ultrasound were 11.1 and 5.1 mm respectively (see figure 8.7). There was no significant difference between these distances (paired t test \( p = 0.11 \)) because of the small sample. However 3D ultrasound did produce a much better estimate of CT centre of gravity than 2D ultrasound. These data therefore suggests that the 3D ultrasound technique, when compared with CT, may well give better spatial localisation than 2D ultrasound. This may be related to errors in interpretation of tumour cavity dimensions with 2D ultrasound when the transducer is held obliquely (see section 8.4 for full discussion).
Figure 8.7 Box and Whisker plot for the differences in centres of gravity measured as mean total distance from CT for 3D and 2D ultrasound. Distances between centres of gravity in millimetres. 3D and 2D ultrasound results are shown in green and brown respectively.

8.3.4 Co-registration of pre-operative tumour with post-operative tumour bed

Registration of the 3D ultrasound image of the pre-operative tumour and the radiotherapy planning CT were recorded as good, satisfactory and poor in 5/12, 4/12 and 3/12 respectively. Table 8.3 displays the results of co-registration of the pre-operative tumour with the post-operative tumour bed using ultrasound and clip methods of localisation.

<table>
<thead>
<tr>
<th>Does the tumour bed volume contain the pre-operative tumour image?</th>
<th>Tumour bed volume</th>
<th>Tumour bed + 1.5 cm CTV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clips</td>
<td>3D US</td>
<td>2D US</td>
</tr>
<tr>
<td>Completely</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Partially</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Not at all</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 8.3 Co-registration of the pre-operative tumour with the post-operative tumour bed

* Clinical target volume.

If the 3 cases with poor registration are excluded, the tumour image was either partially or completely contained within the clips and 2D ultrasound volumes. Despite the exclusion of these 3 cases, the 3D ultrasound volume did not include the tumour in 2 cases. However, these cases had poor registration of the ultrasound tumour bed with CT. Thus, this technique obviously requires good/satisfactory CT-ultrasound registration for both the tumour and the cavity. If 1.5 cm 3D margins are added to form a CTV, the tumour was completely contained in all but 1 case for 2D and 3D ultrasound, where the CT-ultrasound registration of the tumour was poor.
8.4 Discussion

The majority of centres worldwide do not use direct imaging methods for tumour bed localisation, but rely on a combination of pre-operative mammograms, operation notes, position of scar, and patient recollection of tumour position. This 'clinical' method of localisation has been shown to be inaccurate in numerous studies, particularly as the scar may be placed for optimal cosmesis and often is some distance from the tumour bed. This study has used a variety of imaging methods to localise the tumour bed and the advantages and disadvantages for each technique will be discussed.

8.4.1 Surgical clips

The most widely used direct method of localisation is assessment of tumour bed surgical clips, which has been shown to be superior to clinical localisation [14, 15, 17-19, 127]. Consequently, it has been reported to be the 'gold standard' localisation technique [168]. Clip localisation was originally carried out using orthogonal radiographs in a simulator and more recently with multi-slice CT. It provides a relatively simple and inexpensive method of tumour bed localisation at the time of surgery.

Despite being designated as gold standard by some, surgical clips are not without their problems, some of which will be illustrated by examples from the study. Firstly, there is variation in surgical practice concerning the number and orientation of clips, which could produce different volumes and spatial information. Secondly, there are difficulties with outlining, as the clips do not completely define the 3D edge of the tumour bed. Thus, the tumour bed has been defined as the clips and 'architectural distortion'; the latter may be defined differently by clinicians and is also influenced by CT windowing. For example, Figure 8.8 shows an axial CT slice with clips surrounding an apparent cavity; this is relatively easy to outline, but clinicians may vary as to whether they include all or part of the clip.
Figure 8.8 Axial CT slice of the breast with clips surrounding tumour cavity.
The arrows indicate surgical clips, which appear to be demarcating the post-surgical tumour bed cavity.

Figure 8.9, however, illustrates a case where the tumour bed is less easy to interpret, as the clips are more widespread and there is no obvious cavity.

Figure 8.9 Axial CT slice of the breast with widespread clips.
The arrows indicate surgical clips which are widespread and do not demarcate an obvious cavity.

A third potential problem is clip migration. This has not been specifically reported in the context of breast radiotherapy planning, but has been reported following vacuum-assisted stereotactic breast biopsy [169-172]. The largest series retrospectively reviewed 165 post-biopsy mammograms: in 93 evaluable cases, the mean distance the clip had moved was 13.5 mm +/- 1.6 mm standard error of the mean (95% CI = 10.3 mm to 16.7 mm)[172]. In 21.5% of patients, the clip was more than 20 mm from the targeted site. I found that a clip was located 48 mm radially from closest tumour bed clip and 35 mm inferior to the closest axillary clip in the 3D ultrasound study (see figure 8.10). Given, the distance from tumour bed and axillary clips, it is possible that clip migration had occurred. It is of course possible that clip migration had also occurred in other cases where the clips
were noted to be widespread. Serial imaging was not performed in this study, therefore the incidence of possible clip migration cannot be commented on.

Figure 8.10 Axial CT slice of the breast with possible clip migration.
A cluster of clips is shown, but the arrow indicates a solitary clip that is at 48 mm form the nearest tumour bed clip (and 35 mm form the nearest axillary clip). This may represent clip migration.

8.4.2 CT Imaging
The use of CT alone for localising the tumour bed has been reported as being useful. Messer et al compared CT (9 patients also had surgical clips) with clinical localisation of the tumour bed and concluded that CT was superior [173]. This is not surprising, given that the accuracy of clinical localisation has been reported as between 20 – 50% [168]. Smitt et al compared CT and ultrasound localisation of the tumour bed in 32 patients and reported that cavity visualisation was similar to that of ultrasound [133]. However in the discussion, difficulties in accurate delineation with CT were discussed such as dense breast tissue, subareolar location, and axillary seromas contiguous with the tumour bed. In this study, CT alone was considered to be an unreliable method for the majority of patients when compared with ultrasound and CT plus clips: it was difficult to see a cavity in most cases, and interpretation was further complicated by the effect of CT windowing. However, the 5 cases with well-defined seromas were useful for comparison with the ultrasound methods, as these techniques were detecting a cavity as opposed to clips and architectural distortion.

8.4.3 2D and 3D ultrasound
There have been several reports of the use of 2D ultrasound for localisation of the post-surgical cavity, which showed improvements compared with clinical localisation [16, 131]. There has also been a report of 2D ultrasound used in conjunction with CT, which formed the basis of this study’s 2D ultrasound technique [134]. This study showed that both the 3D and 2D ultrasound volumes are
considerably smaller than the surgical clip volumes. This has been described in 2 other studies comparing clips with 2D ultrasound. Rabinovitch et al obtained transverse, longitudinal and depth measurements of surgical cavities in 29 women using both ultrasound and clip methods [174]. The volume was assumed to be a box, as orthogonal radiographs were used instead of CT. It was concluded that 2D ultrasound significantly underestimates the volume of the surgical cavity compared to radiographic evaluation of clips, and therefore should not be used. Ringash et al also used a simulator-based method to compare 2D ultrasound and clips for tumour bed localisation in 52 women (54 examinations) [168]. The mean volumes for ultrasound and clips were 24 cm³ and 38 cm³ respectively. They defined an adequate plan as being within the field (2 cm around the ultrasound-defined cavity) with a >\(=\) 1 cm margin. A marginal plan was within the field with < 1 cm margin, and an inadequate plan was any clip outside the field. They found that 35/54 (65%), 15/54 (28%), and 4/54 (7%) were adequate, marginal and inadequate respectively. They conclude that 2D ultrasound is useful, as ‘the usual practice of adding clinical margins to a tumour cavity, regardless of how it is localised, will correct for small errors in localisation’.

Our study also gave smaller volumes for 2D and 3D ultrasound than clips. It differed from the other studies as CT was used: where a cavity was seen on CT, it was noted that the clips were often outside the edge of the cavity. This suggests that the cavity defined by ultrasound at the time of planning is frequently likely to be smaller than the volume defined by the surgical clips. This may be due to tissue changes as a result of the healing process occurring initially around the edge of the cavity. Hence, it appears that ultrasound is not inaccurate compared to clip localisation, rather that the techniques are defining slightly different volumes. This is supported by our small comparison between ultrasound volumes and well-defined CT seroma volumes. Therefore, if ultrasound is used clinically, then the clinician should consider increasing the CTV margins to ensure adequate coverage of the tumour bed as described using clips.

It has also been shown in other studies that the surgical cavity, as detected by 2D ultrasound, becomes more difficult to visualise with increasing time from surgery. DeBiose et al suggested that the cavity was difficult to visualise after 8 weeks post surgery [131]. Ringash et al reported that that the cavity could be adequately visualised in 80% of patients who were imaged less than 100 days after surgery, but only 20% in those examined after this time period [168]. Smitt et al found that both the ability to visualise and the volume of the cavity decreased with an increasing post-surgical interval [133]. Our study also showed some correlation with decreasing volume and increasing time for 2D ultrasound \((r = 0.43, p = 0.025)\), although this was non-significant for 3D ultrasound. A criticism of the study by Rabinovitch et al, was that the poor comparison with ultrasound and clips might have been due to the inclusion of post-chemotherapy patients (median
of 24 weeks post-surgery) [174]. Given these reports from the literature and our own experience with difficulty in imaging post-chemotherapy patients, we elected to exclude chemotherapy patients from this study. Therefore the mean surgery to imaging interval was 44 days (range 23 to 86 days). This comparatively short time interval may explain the high level of cavity localisation in the study. This decreased ability to visualise the cavity with time is probably due to reabsorption of seroma and organisation of tissues. In view of this problem, it may be appropriate to limit ultrasound localisation to patients who do not require chemotherapy.

A problem with 2D ultrasound is that the volume is created from maximum dimensions (width, length and depth), thus it will always form a cuboid, which may not be representative of the actual post-operative cavity. Figure 8.11 shows the larger 2D ultrasound volume and the smaller, more conformal 3D ultrasound and CT volumes. This is supported by the 2D ultrasound volume data, which was consistently larger than the 3D data.

![Figure 8.11 Tumour bed volumes using different imaging modalities](image)

The red, pink and purple outlines indicate the tumour bed volumes localised using CT, 3D ultrasound and 2D ultrasound respectively. This illustrates that the 2D ultrasound volumes are larger, as they are based on maximum dimensions.

A second difficulty is that the image obtained is affected by the angle at which the probe is held, and may therefore give inaccurate position data. Figure 8.12 illustrates this problem: the probe was angled to image this lateral tumour bed causing the spatial orientation of the 2D ultrasound volume to differ considerably from the 3D ultrasound and CT volumes. This is supported by the centre of gravity comparison with CT, which suggested that 3D ultrasound was superior to 2D ultrasound. Thus, 2D ultrasound is certainly better than clinical localisation for simple direct electron boost fields, but the problems with conformity and spatial accuracy make this technique less useful for more complex 3D conformal photon planning techniques.
This study suggests that 3D ultrasound is superior to 2D ultrasound. However, there are currently some disadvantages with this technique. At present, the method is time consuming and would require 'user-friendly' modifications of the software if adopted for widespread clinical use. Also, the technique requires the patient to lie as still as possible throughout the ultrasound examination to limit errors due to movement, and this is not possible in all patients.

8.4.4 Co-registration of the pre-operative tumour with the post-operative tumour bed

The results of the novel method of pre-operative tumour co-registration with the post-operative imaging proved to be extremely interesting. It added confidence to the methods of tumour bed localisation investigated in the study, by virtue of the close proximity of the tumour image to the post-operative volumes (see Figure 8.13). In all but 1 case with poor tumour-CT registration, all post-operative CTVs contained the image of the original tumour. This method could therefore be explored as a localisation technique in its own right in the future.
Figure 8.13 Co-registration of the pre-operative tumour with the post-operative tumour bed

The green, pink and purple outlines indicate the tumour bed volumes localised using clips, 3D ultrasound and 2D ultrasound respectively. The image of the co-registered pre-operative tumour (orange) is positioned within all the tumour bed volumes localised with different techniques.
Chapter 9. Conclusions

The conclusions from the 5 experimental chapters are summarised below:

Chapter 4
The novel laser camera technique provided a solution for 3D breast radiotherapy planning without a multi-slice CT scanner. Using this method, one-third of patients' plans had adequate dose homogeneity using standard tangential breast fields. Of those plans with dose inhomogeneities, almost all could be improved with forward-planned IMRT.

Chapter 5
Planning studies suggest that breast IMRT can significantly improve dose homogeneity, but so far there is little evidence of clinical benefit. I have designed and implemented the randomised Cambridge Breast IMRT trial, and the first year's dosimetry results show that IMRT produces superior radiotherapy plans. Analysis of the radiotherapy process has shown that the planning technique is more time consuming and requires more radiotherapy resources than standard 2D breast radiotherapy planning. In comparison, the IMRT treatment times are not significantly increased. However, with the use of appropriate skill mix and adequate training in new techniques, it is possible to successfully implement breast IMRT within clinical practice.

Chapter 6
The laser camera appears to be an accurate and reproducible method for measuring breast cosmesis. It is a simple, quick, non-contact technique and therefore acceptable to patients and highly feasible to implement into clinical practice. Objective measurement of volume change can be coupled with more qualitative assessment of skin changes and breast shape. It could be used as an assessment tool post-surgery and is currently being used within a breast radiotherapy trial.

Chapter 7
Localisation of the tumour bed is essential for optimal breast radiotherapy planning, but there are problems with currently available imaging methods. A novel technique using high definition free-hand 3D ultrasound was compared with CT in a phantom study and the results suggest that this is an accurate and reproducible method.

Chapter 8
The study has facilitated critical evaluation of recognised methods of tumour bed localisation as well as the novel 3D US method. All methods have some disadvantages, but all appear better than 'clinical' localisation, and the use of these imaging techniques should therefore be encouraged.
Protocols for surgical clip placement and tumour bed delineation are useful in aiding standardisation of clip-defined volumes. Ultrasound localisation methods produce smaller volumes than clip-based methods, therefore greater CTV margins should be considered. The 3D ultrasound technique appears to more accurately represent the shape and spatial position of the tumour cavity compared with the 2D method, but possible errors due to movement in some patients need to be considered. Pre-operative tumour and post-operative tumour bed co-registration is a promising new concept in breast radiotherapy planning, but requires further evaluation.

**Hypothesis 1:**

*3D optical data using the Minolta Vivid 700 laser camera provides an alternative to CT for 3D breast radiotherapy planning.*

This hypothesis was proven. The novel laser camera technique provided a solution for 3D breast radiotherapy planning without a multi-slice CT scanner.

**Hypothesis 2.1:**

*A dosimetry study will show that breast homogeneity can be improved with simple forward-planned IMRT techniques compared standard 2D radiotherapy.*

This hypothesis was proven. Two-third of patients' plans had inadequate dose homogeneity using standard tangential breast fields. Of those plans with dose inhomogeneities, almost all could be improved with the forward-planned IMRT technique.

**Hypothesis 2.2:**

*A randomised controlled trial comparing standard 2D breast radiotherapy with forward-planned IMRT will demonstrate the clinical benefit for patients.*

This hypothesis is still under investigation: the clinical benefit of breast IMRT is currently being tested in the NCRN-adopted randomised Cambridge Breast IMRT trial. Clearly, the final results are beyond the time scale of this thesis.

**Hypothesis 3:**

*3D optical data obtained with the laser camera provides an analytical assessment tool for measuring breast cosmesis following breast conservation treatment.*

This hypothesis has been proven. Change in breast volume and shape following breast conservation were assessed using this method. Further validation of this method for radiotherapy-induced changes, in comparison with photographic assessment and patient quality of life questionnaires, is ongoing as part of the Cambridge Breast IMRT trial.
Hypothesis 4:

A 3D ultrasound method can accurately localise the tumour bed.

This hypothesis has been proven. 3D ultrasound can accurately localise the breast tumour bed, and thus can be used as a tool to assist radiotherapy planning.

The research presented in this thesis has provided a solid basis for further development of breast radiotherapy. This subject will be addressed in the final chapter: direction of future research.
Chapter 10.  Direction of future research

10.1 Background
The ultimate goal of cancer treatment is to cure the patient without causing treatment-related normal tissue damage. Radiotherapy is the most important non-surgical modality for the treatment of cancer. Thirty to 40% of the population will develop cancer, and at least half require radiotherapy at some time. Of patients having radiotherapy, 60% are treated with curative intent, often in combination with surgery and chemotherapy. However, there is considerable variation between patients in both their tumour and normal tissue responses to radiation treatment. This observation has led to the concept of individualising radiotherapy based on the patient’s risk of death from cancer and risk of normal tissue morbidity, i.e. risk-adapted radiotherapy.

10.2 Primary objective:
To develop, implement and test individualised risk-adapted breast radiotherapy both locally and nationally. Essential requirements for individualised risk-adapted radiotherapy include:

1. Knowledge of tumour characteristics at genetic, molecular and cellular levels.
2. Knowledge of individual variation in normal tissue response to radiation at genetic, molecular and cellular levels.
3. A variety of complex radiotherapy techniques, which are ‘adaptable’ to the individual’s tumour and normal tissue characteristics.

Until recently, individualised risk-adapted radiotherapy has appeared unachievable. However, we are entering an exciting new era of radiotherapy development where this concept may become reality. Clearly, a translational approach is essential with considerable interaction between the laboratory and clinic. The interaction is synergistic: risk-adapted radiotherapy relies on tumour and tissue characteristics determined by the laboratory, which in turn requires samples linked with precise analytical clinical data. This primary objective is the central theme of my future research plans in breast and cancer, which are outlined below. Each research component will be categorised according to requirements 1 – 3 above.

10.2.1 Cambridge Breast IMRT Trial and DNA database
I have developed and implemented this NCRN-adopted phase 3 randomised trial, which will provide important information regarding the clinical value of forward-planned IMRT [93]. The aim is to complete patient accrual at the beginning of 2006 and continue follow-up for 5 years. The trial has facilitated the transition from standard simulator-based 2D breast radiotherapy, to a CT-
planned 3D technique, thus contributing to requirement 3. The trial will generate 1000 blood DNA samples linked with objective and quantitative clinical data, which will be used to investigate variation in normal tissue radiosensitivity, thus providing a database for Requirement 2 (see RAPPER trial below).

10.2.2 IMPORT (Intensity Modulated Partial Organ Radiotherapy) Trials
I am a Principal Investigator of both the proposed IMPORT Low and IMPORT High trials, for low- and high-risk patients with early breast cancer respectively. The objectives are to deliver a higher dose to the volume surrounding the tumour bed, whilst limiting or omitting irradiation to normal breast tissue distant from the index quadrant [125]. My current research regarding tumour bed localisation has contributed to the protocol development. In addition, my interest in complex 3D non-coplanar partial breast radiotherapy techniques would enable Addenbrooke’s to be among the few Oncology Centres piloting IMPORT High. Precise localisation of the tumour bed will be essential, and I propose to lead a national target volume delineation study as quality assurance prior to the start of the trial [161]. Development of forward-planned IMRT in conjunction with partial breast radiotherapy will be important for Requirement 3.

The likelihood of local recurrence may be influenced by the genetic characteristics of the tumour, which include tumour response to radiation treatment. Therefore, it is proposed to establish tissue arrays from paraffin blocks of the primary breast tumours and ipsilateral relapses from IMPORT trial patients. This large tissue database will be important for Requirement 1.

10.2.3 Inverse-planned IMRT for nodal irradiation
In contrast to forward-planned IMRT, inverse planned IMRT is more complex and requires the use of specialised computer software. In general, it has no advantage over forward-planned IMRT for breast radiotherapy alone. However, it may have applications for targeted nodal irradiation in locally advanced breast cancer, whereby irradiation to surrounding critical structures such as the heart or lung, is substantially reduced compared with existing techniques [175]. In addition, if the current EORTC trial reports that irradiation of the internal mammary chain improves outcome, inverse-planned IMRT techniques may be highly desirable. I intend to develop the application of inverse-planned IMRT for nodal irradiation in an initial dosimetry planning study and this will contribute to Requirement 3.
10.2.4 Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy (RAPPER)

This translational study proposes to test an association between common genetic variation, reported by SNPs in relevant candidate genes, and individual patient variability in normal tissue radiation toxicity. I am a study group committee member of this Cancer Research UK-funded trial, which would require the use of the Cambridge Breast IMRT blood samples to form a substantial part of the study’s DNA database. These samples will be linked with analytical data regarding post-radiation change in breast size and shape. This will be achieved using a novel assessment technique I have developed using the laser camera [176]. Results from this important study are likely to be applicable to all patients requiring radiotherapy, regardless of tumour type. Requirement 2 will be fulfilled by this trial.

10.2.5 Individualised risk-adapted breast radiotherapy

The preceding studies would pave the way for a truly individualised risk-adapted breast radiotherapy, which will need to be tested clinically. Requirement 1: knowledge of the tumour characteristics and response to radiation treatment would be obtained from genetic studies using the IMPORT Trials' tumour database. This information would facilitate selection of appropriate treatment based on risk of local recurrence. Requirement 2: knowledge of individual variation in normal tissue response to radiation would be addressed by the RAPPER study. Requirement 3: complex radiotherapy techniques would be fulfilled by the development of forward- and inverse planned IMRT and 3D conformal partial breast irradiation. The research would be applicable for all breast cancer patients requiring radiotherapy.

10.2.5.1 Early breast cancer

Due to earlier detection, the numbers of patients with very small invasive breast cancer or DCIS are increasing. Therefore the aim of treatment is to deliver effective radiotherapy with the absolute minimum morbidity. Partial breast irradiation, as outlined above, lends itself to this aim. In addition, the reduced target volume, facilitates the use of larger doses of radiation given in smaller number of treatments over a shorter total time i.e. accelerated hypofractionated radiotherapy [177]. Early clinical results from the William Beaumont’s experience of accelerated partial breast irradiation show good cosmesis and a low rate of local recurrence [125]. There would be a considerable health economic benefit in the reduced number of treatments, as breast irradiation currently consumes 30% of all radiotherapy resources. Also, fewer treatments over a shorter period are likely to increase patient compliance and satisfaction. There would be additional benefits for the sub-group of patients at higher risk of relapse (identified by tumour genomics). Firstly, local control may increase as the relatively low α/β ratio of breast tumours is more sensitive to fraction
size. Secondly, a much shorter radiotherapy course could conveniently be delivered prior to systemic treatment, thus avoiding loss of local control due to radiotherapy delay and the problems of accelerated repopulation during a longer treatment course. However, the limiting factor in determining these types of radiotherapy regimens is the late normal tissue complication of fibrosis. Thus genetic information regarding variation in normal tissue response to radiation would be essential for optimal study design.

10.2.5.2 Advanced breast cancer

The aim of treatment for locally advanced cancer is to use a combination of systemic therapy, surgery and/or radiotherapy to maximise the chance of cure. For example, there is some early data to suggest that chemoradiation with taxanes as a radiosensitiser may be beneficial [178]. However, the majority of these patients are elderly and may have co-morbidity, and are therefore less likely to tolerate potentially toxic treatment. Using inverse-planned IMRT, breast and nodal radiotherapy could be delivered whilst sparing critical normal structures. Again, genetic information regarding variation in normal tissue response to radiation would be essential for identifying patients who would potentially tolerate further intensification of treatment.

In summary, the proposed research aims to achieve individualised treatment, which maximises chance of cure and minimises risk of morbidity, for patients with breast cancer.
References


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References


References


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Appendix
Investigation of radiotherapy dose inhomogeneity and cosmetic outcome in patients with early breast cancer: a randomised controlled trial.


Addenbrooke’s Hospital Oncology Centre, Cambridge, UK.

Version 3 - 1 June 2003
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1. Background

A major aim of radiotherapy technology development has been to conform the delivered dose to the target in 3 dimensions and minimise irradiation to the surrounding tissues. This reduces normal tissue morbidity and allows higher radiation doses to be delivered safely, thus increasing local tumour control, and in some cases survival. Conformal radiotherapy (CRT), and more recently intensity-modulated radiotherapy (IMRT), are examples of this philosophy. Proof of principle for the use of CRT now exists: it has been shown to reduce serious normal tissue side effects from pelvic radiotherapy, increase local control and influence survival in dose escalation studies in prostate cancer\(^1\),\(^2\). IMRT is a complex form of CRT that usually requires sophisticated computer software for the radiotherapy planning process. The vast majority of patients treated with IMRT have been in the USA, and clinical use of IMRT in the UK is extremely limited so far.

In the next few years, more oncology centres will have the capability of delivering complex radiotherapy. At present, however, there is very little evidence available as to which patient groups will benefit from the new technology. Complex radiotherapy techniques can be more time-consuming in terms of planning, treatment delivery and quality assurance procedures. Many patients may be perfectly well treated using conventional techniques, and thus the use of complex radiotherapy should be targeted to patients who will derive benefit. It is therefore essential, given limited radiotherapy resources that the introduction of new radiation techniques is carried out in a scientific manner. The recent document ‘Development and implementation of conformal radiotherapy in the UK’, states that the clinical implementation of IMRT is at present ‘difficult, and probably high risk, unless built on the back of a well-founded research programme’. It recommends that IMRT should be introduced across the UK with centres taking part in controlled studies to provide evidence of efficacy and outcome\(^3\). The aim of this research study is to investigate whether correction of radiotherapy dose inhomogeneities using 3-D planning and more complex radiotherapy delivery techniques, improves the cosmetic outcome in patients with early breast cancer.

1.1 The need for a trial

Breast cancer is the most common cancer in women in Europe, with approximately 180,000 new cases per year. The majority are detected at an early stage and are usually managed with conservation surgery, post-operative radiotherapy and increasingly, systemic treatment.
Breast irradiation is a major component of the radiotherapy workload, and it currently utilises 30% of radiotherapy resources in the UK. The aim of conservative breast cancer treatment is to offer optimal local control and survival whilst obtaining a good cosmetic outcome; post-operative radiation technique has a major impact on this endpoint. The cosmetic outcome following radiotherapy appears worse in patients with larger breasts, with breast shrinkage being the most commonly observed problem. Conventional single plane 2-D radiotherapy breast plans can lead to substantial off-axis dose inhomogeneities, particularly in women with larger breasts, but the causal relationship between dose inhomogeneity and cosmetic outcome is as yet unproven clinically. Breast appearance following treatment has been shown to be an important patient issue, and can cause significant psychological morbidity.

Dose inhomogeneities in the breast can be improved by 3-D radiotherapy planning, which requires acquisition of 3-D patient data, usually obtained from CT scanning. There can be, however, physical constraints in scanning in the conventional treatment position using a breast board, and also serious resource implications from potentially large numbers of patients. This will be less of an issue when modern CT-simulators are available in most UK oncology departments and different treatment positions are adopted, but this is likely to be a gradual change over some years. IMRT techniques produce superior dosimetry compared with conventional techniques, but the planning, treatment time, and quality assurance measures may be time-consuming, and the equipment is not universally available.

Forward-planned IMRT is a relatively simple method of IMRT that does not require an inverse-planning computer. Smaller radiotherapy fields are added to the main treatment fields to improve dose inhomogeneities produced by conventional 2-D breast radiotherapy. This can be achieved with standard rectangular fields, or shaped fields using a multi-leaf collimator. This simple technique could therefore be implemented without the need for complex technology. Dosimetric studies using simple forward-planned IMRT have been shown to improve breast dose homogeneity. To date, there has only been 1 randomised controlled trial (RCT) designed to investigate late normal tissue side effects. This was carried out at the Royal Marsden Hospital, UK and consisted of 305 patients with early breast cancer. Women with larger breasts were specifically selected for the trial on the basis that these patients would have the greatest dose inhomogeneities. They were randomised to either standard radiotherapy or forward-planned IMRT using either a metal compensator or multiple static fields. The primary endpoint was breast appearance following radiotherapy, measured...
with serial photographs. Interim analysis was completed in September 2002. A change in breast appearance was scored in 60/116 (52%) allocated standard 2-D treatment and 42/117 (36%) patients allocated IMRT (p=0.05). A second randomised controlled trial is required to investigate the clinical relevance IMRT for women with all breast sizes. Two confirmatory trials would be impetus to adopt IMRT for breast cancer patients as standard practice in the UK.

The conventional validated methods of assessing normal breast tissue changes following radiotherapy include clinical examination and photographic change over time. These methods have been validated but nevertheless are not ideal, due to coarse discontinuous classification systems and possible inter-observer variability. It is unlikely that post-radiation changes have been quantified uniformly in many studies to date, making comparisons between different studies extremely difficult. It is therefore essential to develop a robust analytical method for measuring these normal tissue changes so that the clinical effects of different radiotherapy techniques can be assessed accurately. Such a method should be implemented in conjunction with conventional methods, ideally within the setting of a randomised breast radiotherapy trial.

2. Pilot Study

We have already compared conventional breast radiotherapy planning with a simple method of forward-planned IMRT in a pilot study of 46 patients at Addenbrooke’s Hospital. 46 patients were analysed and standard radiotherapy was deemed to be adequate in 15/46 (33%), i.e. less than 2 cm³ exceeded 107% of the prescribed dose. Standard radiotherapy was therefore inadequate in 31/46 (67%) of patients. 20 of the 31 plans (66%) were improved with the addition of rectangular ‘boost fields’, typically weighted to 10% of the tangential open fields. 6/31 (19%) were made worse with additional rectangular fields, and 5/31 (16%) were of marginal benefit. All of these 11 plans were improved with forward-planned IMRT using MLC-shaped fields. 2 were 6-field plans and the remainder were 4-field plans. The IMRT technique was more time consuming to plan than the rectangular fields, but was still relatively simple.

Based on this promising pilot data, we have designed a Phase III randomised controlled trial to investigate the clinical effects of forward-planned IMRT using MLC-shaped fields. This protocol was developed at the ‘Methods in Clinical Cancer Research’ workshop in Flims,
Switzerland, in June 2001. This was jointly organised by the Federation of European Cancer Societies (FECS), the American Association for Cancer Research (AACR), and the American Society of Clinical Oncology (ASCO). Funding has been awarded by the Breast Cancer Campaign to support a research radiographer for 3 years.

3. Main Objective
The question to be answered by the study is:
Does correction of dose homogeneity improve the cosmetic outcome following radiotherapy in patients with early breast cancer?

4. Trial Design

**Proposed Design**

- T1-3, N0-1, M0 invasive breast cancer/DCIS requiring radiotherapy.
- Breast conservation surgery with complete tumour excision
- Off-axis dose inhomogeneity outside -5% and +7% of the prescribed dose using conventional 2-D radiotherapy

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<td>Use of forward-planned IMRT to correct dose homogeneities</td>
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<tr>
<td>CONTROL ARM</td>
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<tr>
<td>Conventional 2-D radiotherapy with no correction of off-axis dose inhomogeneity</td>
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5. Endpoints

5.1 Primary endpoint
The primary endpoint will be photographic assessment of late cosmetic effects using a validated 3-point scale.¹⁵

5.2 Secondary endpoints
- Acute skin reactions measured according to the Radiation Therapy Oncology Group (RTOG) grading system.
- Clinical assessment of late cosmetic effect (including induration, telangiectasia and arm oedema, in addition to breast shrinkage) after radiotherapy assessed clinically using a 3 point scale as used in the START trial.¹⁶
- Breast shrinkage following radiotherapy measured using 3-D optical imaging (see below).
• Patient self-assessment of quality of life using the EORTC QLQ-C30 with the Breast Cancer Module, Additional Body Image items (START Trial) and the Hospital Anxiety and Depression Scale \(17, 16, 18\).

• Information regarding local control, metastatic disease, survival and cardiac and pulmonary complications will be collected prospectively.

We have a means of assessing changes in breast volume and shape that we hope will provide a novel non-invasive method of assessing post-radiation breast shrinkage, by using the 3-D optical scanner (Minolta Vivid 700). Reproducibility of this technique has been assessed by taking multiple volume measurements from an anthropomorphic phantom and patients \(19\).

Change in breast volume following radiotherapy will be compared with the baseline pre-radiotherapy volume and will be analysed as a secondary endpoint. The contralateral breast will be scanned at identical time intervals and thus act as a control for each patient. We anticipate that this will provide a more objective analytical assessment tool than conventional methods.

6. Patient selection criteria
• Age 18 years and above.
• Operable unilateral breast cancer (T1-3, N0-1, M0 at presentation) or DCIS requiring radiotherapy.
• Histological confirmation of invasive carcinoma/DCIS.
• Complete macroscopic excision of tumour by breast conserving surgery (no implants).
• No history of contralateral breast cancer. No prior malignancy in the last 5 years, except skin basal/squamous cell carcinoma or in-situ carcinoma.
• Demonstration of off-axis dose inhomogeneities outside \(-5\%\) and \(+7\%\) of the prescribed dose using conventional 2-D radiotherapy treatment plan.
• Patient consents to be part of the study and is available for follow-up.

7. Randomisation
The trial will be discussed with suitable patients at the time of their first oncology appointment and a patient information sheet will be given. This will include patients attending peripheral hospital oncology units. The patient will be given a further opportunity
for discussion with the trial radiographer when she attends her simulation visit for radiotherapy planning at Addenbrooke's Oncology Centre.

Eligible patients will be initially planned using conventional single-slice 2-D radiotherapy, and 3-D data for the whole breast obtained with the laser scanner will be utilised to identify possible off-axis dose inhomogeneities produced with this technique. Patients with dose inhomogeneities outside -5% and +7% of the prescribed dose (as per ICRU 50) will be randomised to either forward-planned IMRT or receive conventional radiotherapy within the control arm 20. Those patients willing to take part in the trial, but who are ineligible due to no significant dose inhomogeneities, will receive standard 2-D radiotherapy. They will still receive the same follow-up as the randomised patients, but will be analysed as a separate cohort from the randomised trial patients.

Stratification will be carried out for T-stage and adjuvant therapy using a random block design. This will take into account the possibility that cosmetic outcome is affected by tumour size and the necessary extent of surgical resection and that chemotherapy and hormonal treatment can influence outcome. Patients who decline to take part in the study will be treated with conventional radiotherapy regardless of any possible dose inhomogeneities.

8. Sample size

Pilot data from the START trial has suggested that the probability of observing late radiation change for patients receiving standard radiotherapy is approximately 40% 16. Our study patients will all have dose inhomogeneities outside ICRU 50 recommendations, which may result in a higher probability of radiation change. This is reflected by the interim analysis from the Royal Marsden study of IMRT versus standard radiotherapy. Patients with larger breasts were selected on the basis that these would have greater dose inhomogeneities. A change in breast appearance was noted in 60/116 (52%) of patients in the standard group compared with 42/117 (36%) that received IMRT 13.

We are therefore assuming a standard event rate of 40% in the control group at 2 years. The difference to be detected will be 10% and the hazard ratio will be 0.7. Assuming a minimum average follow-up of 2 years and 80% power and type I error of 0.05, we would require 358 patients and 125 events in each arm. We currently treat approximately 600 women with early breast cancer with radiotherapy per year. Our pilot studies have shown that approximately 70% of patients planned with conventional 2-dimensional radiotherapy have dose
inhomogeneities. We expect a very high patient accrual rate given the simplicity of the trial design with virtually no change in the patients' treatment pathway compared with the standard radiotherapy offered out of trial. Therefore the expected duration of recruitment would be 2 to 3 years.

9. Methodology

9.1 3-D optical imaging device

The laser-scanning device is the Minolta Vivid 700 non-contact 3-D digitiser. A fan beam of laser light is scanned down the object surface using a galvano mirror while images are captured on the close circuit device (CCD) camera. From knowledge of the angle of projection of the laser fan beam, the orientation of the laser source and the CCD camera, the 3-D profile of the laser stripe in each image can be calculated using trigonometry. These profiles combine to give a full 3-D point cloud map of the object surface. Scanning of the object takes 0.6 seconds and generates a 200 x 200 3-D point data set.

Patients will be imaged at the pre-planning simulation stage in the treatment position. The camera is mounted on a tripod and can be moved around the patient. Due to the free nature of the camera relative to the patient, it is necessary place markers on the patient in a known orientation to enable the data to be re-oriented at the post processing stage to the standard patient co-ordinate system. If the patient has significant dose inhomogeneities with standard radiotherapy and is therefore eligible for the trial, the contralateral breast will be scanned during radiotherapy treatment to avoid extra hospital visits for the study patients. This will require 1 tiny additional radiotherapy tattoo being made near the contralateral axilla. Thus baseline volume measurements will be obtained for both breasts, with the untreated breast acting as a control (for factors such as hormonal treatment).

At the time of simulation, 3 simulator-CT outlines will be taken at fixed intervals (central, superior and inferior) through the breast intended for treatment. These CT data will be co-registered with the optical breast surface data to enable localisation of the lung. Such limited CT information has shown to be acceptable when compared with multi-slice CT data.21

Further processing of the data is performed using a commercial 3-D modelling software package, Metris Base 5.0 (Metris NV, Belgium), that can import the 3-D point cloud data and display it as a closed triangulated mesh. Once it has been edited and orientated, the mesh is
cross-sectioned in the axial plane at 5mm intervals thus producing multiple outlines. This is than imported with the CT data in our in-house Addenbrookes Radiotherapy Planning System (ARPS). Multislice CT scanning will be introduced when a dedicated Crscanner becomes available.

9.2 Forward-planned IMRT
In the planning system, the breast tissue is outlined as a region of interest with a 5mm margin inside the breast and field edges. The doses delivered to the entire breast volume using standard tangential radiotherapy fields are calculated and dose volume histograms of the breast tissue are constructed. Patients with more than 2 cm³ of the breast exceeding 107% of the prescribed dose are identified as eligible for the trial.

Those patients who are subsequently randomised to the interventional arm are re-planned using forward-planned IMRT. This is achieved by firstly viewing the isodose distribution along the beam’s eye view with standard tangential fields. The multileaf collimators (MLCs) are manipulated to cover areas of unacceptable high dose and produce 2 additional MLC-shaped fields. The dose distribution is re-calculated and 2 further MLC-shaped fields were added if necessary, giving a maximum of 6-fields. The new dose distribution is calculated enabling comparison of the dose volume histograms of the standard 2-field and IMRT plans.

9.3 Radiotherapy delivery
Radiotherapy will be delivered to the breast only, or breast and local lymph nodes according to the Addenbrooke’s Oncology Centre protocol. The internal mammary chain will not be treated. Patient position, clinical and planning target volume, field arrangement and verification will be carried out in accordance with the START Trial recommendations. 40 Gy in 15 fractions will be delivered over 3 weeks, treating all fields daily and using 6 MV photons. This dose and fractionation regimen is standard for our centre and its efficacy is based on several Canadian and UK studies showing similar local and control and cosmetic outcome compared with 2 Gy per fraction regimens, and is 1 arm of Trial B in the START trial. Dose will be prescribed to the ICRU reference point. A tumour bed boost will be given according to our local protocol, using appropriate electron energy.
The simple design of this study makes it possible to use more than 1 method of acquiring 3-D breast data (e.g. using a 3-D laser scanner or CT scanner) dose inhomogeneities can be corrected by several methods of forward-planned IMRT. This flexibility lends itself to multicentre participation whereby oncology departments can use a range of radiotherapy techniques and accepted fractionation schedules depending on available resources, as the primary research question remains the same. Therefore, it would be feasible to recruit other interested centres at a later date. Each radiotherapy planning and delivery technique, however, will require prior approval by a central Quality Assurance team.

9.4 Quality assurance

The entire radiotherapy treatment process will be carried out in accordance with the Addenbrooke’s Oncology Centre Quality Assurance Procedures which are recognised by ISO9001.

10. Trial evaluation

10.1 Normal tissue effects

10.1.1 Acute radiotherapy effects

Patients will be assessed weekly during treatment, on completion of radiotherapy and 16 weeks from the end of treatment, i.e. at routine clinic appointments. Acute skin reactions will be assessed and recorded according to the Radiation Therapy Oncology group (RTOG) grading system (see appendix for acute radiotherapy reaction forms). Details of unusually severe acute radiotherapy reactions will be recorded separately (see appendix for severe radiotherapy reaction forms).

10.1.2 Late cosmetic changes

These will be assessed at 2 years and 5 years following radiotherapy. The following methods will be used and each assessment will be carried out during the same visit to Addenbrooke’s Oncology Centre (see appendix for late radiotherapy reaction forms):
Photographic assessment

Colour print photographs (2 frontal views with hands on hips and arms above head) will be taken prior to radiotherapy as a baseline, then following radiotherapy as outlined above. The photographs will be taken under standard conditions by the Addenbrooke’s Medical Photography Department and therefore subject to the Trust’s data protection criteria. These will be assessed blindly and scored according to a recognised 3-point scoring system.

Clinical examination

The development of breast shrinkage, induration, telangiectasia, breast and arm oedema will be recorded using a similar format to that used in the START Trial. This will be carried out by either a clinician, or appropriately trained nurse/radiographer.

Breast volume assessment

The irradiated breast and contralateral breast volumes will be measured using the optical camera (as described previously) at baseline and at the stated intervals following radiotherapy. Changes in volume in the treated breast will provide an objective measurement of radiation-induced fibrosis and shrinkage. The contralateral breast will act as a control, as there may be confounding factors such as age-related changes and hormonal changes due to adjuvant systemic therapy.

10.2 Quality of life

Patient self-assessment questionnaires will be carried out at 6, 24 and 60 months following completion of radiotherapy. The questionnaires will be posted to the patients and therefore will not require any additional visits. The EORTC QLO-C30 with the Breast Cancer Module and the Additional Body Image Items (START trial) will be used in conjunction with the Hospital Anxiety and Depression Scale - HADS (see appendix)\. The questionnaires will address changes in body image, breast pain, arm swelling, satisfaction with treatment outcome, sexual and psychological functioning and impact on daily living. The HADS scores will be checked around the time of completion by the patient, as a score of 19 or above is an indicator of clinical anxiety/depression. If this occurs, the patient’s consultant will be informed.
10.3 Late complications, loco-regional recurrence, overall survival and disease-free survival.

Cardiac and pulmonary complications, loco-regional recurrence, development of metastases and death will be recorded.

10.4 Other data collection

A baseline data set will be recorded for each patient. This will include tumour details and co-morbid conditions, which may influence normal tissue radiotherapy effects such as diabetes, cardiovascular disease and smoking. All treatment details will also be recorded including surgery, radiotherapy and systemic treatment (see appendix for data collection forms).

10.5 DNA data-base

One blood sample (one 9 ml sarstedt monovette containing EDTA), will be obtained and from each patient before the start of radiotherapy, for extraction of DNA at a later date. The blood samples will be identified by trial number only. A separate consent form will be used for this purpose. Blood DNA samples will also be obtained from the consenting patients with non-significant dose inhomogeneities, which will be followed-up as a separate cohort from the randomised trial patients.

The samples will be frozen to -80 degrees centigrade and stored at Strangeways Research Laboratories, Cambridge. The DNA will be extracted at a later date in to provide a large DNA database. This will be utilised in the future to correlate genetic causes of individual variations in normal tissue radiosensitivity with the objective measures of late normal tissue changes from the trial. The details of this translational research will be the subject of a separate study protocol.

11. Statistical considerations

11.1 Statistical design

Justifications for sample size and randomisation have previously been discussed (see ‘study design’).
11.2 Analysis

Clinical and photographic endpoints will be assessed using time to event analysis based on an expected improvement in cosmetic outcome of 10% in the IMRT radiotherapy arm at 2 years. Kaplan-Meier curves will be constructed for each endpoint and analysed using the Log-Rank test. The quality of life questionnaires will be analysed according to their standard scoring and analysis procedures. The change in breast volumes as measured by the 3-D optical camera will be subject to exploratory analysis as the use of this method is presently unvalidated. The cohort of patients with non-significant dose inhomogenities will be analysed separately.

12. Stopping rule

There will be no formal stopping rule, but loco-regional control and survival will be monitored. In the unlikely event that either of these is suspected to be significantly worse in the interventional radiotherapy arm, the data will be submitted to the Independent Data Monitoring Committee (Chair, Dr Pippa Corrie, consultant medical oncologist).

13. Trial management team

Dr Margaret Moody, consultant oncologist, will act as the Principal Investigator for the Addenbrooke’s study, and the project co-ordinator will be Dr Charlotte Coles, specialist registrar in clinical oncology. Professor B J Ponder, Dr C B Wilson and Dr N G Burnet will be Co-investigators. The Steering Committee will consist of all the above people with the addition of Ms Jenny Wilkinson, trial radiographer and Dr Andrew Hoole and Mrs Nicola Twyman, physicists.

14. Data management

Data will be collected using the case report forms (see appendix) and a computerised database. The data will be stored at Addenbrooke’s Oncology Centre Clinical Trials Office, Cambridge and subject to the data protection requirements of the Trust. The study co-ordinator, Dr Charlotte Coles, will be responsible for reviewing all case report forms, and answering clinical questions concerning eligibility, treatment and the evaluation of patients. Statistical support has been available during the design of the trial and will be on going.
A trial radiographer, Jenny Wilkinson (funded for 3 years by the Breast Cancer Campaign) will be responsible for analysis of the 3-D laser data with assistance from the Physics Department. She will assist the physicians with data collection, including the quality of life questionnaires. Radiographers trained in the use of the 3-D laser will be responsible for acquisition of the 3-D breast data, under supervision of the trial radiographer. We do not envisage that simulator time and treatment time will increase greatly, and therefore the costs will be absorbed into the system.

15. Economic considerations

A formal economic evaluation of the study will not be undertaken, but the study radiographer will also be responsible for assessing the times taken for simulation, treatment planning and irradiation in both arms of the trial.

16. Ethical considerations

This study will be submitted to the Local Ethics Committee for approval prior to clinical implementation.

17. Future Studies: Genetic variation in normal tissue radiosensitivity

Blood DNA samples will be prospectively collected during the clinical trial. This DNA database will be utilised in a separate study, in conjunction with the comprehensive clinical data collected on late radiation normal tissue effects, to investigate the genetic aspects of individual variations in normal tissue radiosensitivity. This trial will provide an almost unique group of patients in whom variations in radiotherapy dose has been removed. In addition, blood DNA samples will also be obtained from the cohort of patients with non-significant dose inhomogeneities who will be followed-up separately from the randomised trial patients. Variation in normal tissue response is therefore likely to be due to underlying genetic factors. Blood will be taken, with appropriate consent, for future analysis of polymorphisms in DNA damage repair genes. This will be investigated in a separate study.

This protocol was developed at the ‘Methods in Clinical Cancer Research’ workshop in Flims, Switzerland, 23 – 28 June 2001. This was jointly organised by the Federation of European Cancer Societies (FECS), the American Association for Cancer Research
(AACR), and the American Society of Clinical Oncology (ASCO). The protocol was accepted by the NCRI Radiotherapy Studies Group as a portfolio trial in April 2002.

18. References


15. Evaluation of a time related, 3 point, ordered, 'soft' endpoint where missing data is present and censoring may be informative: analysis of late tissue response in a randomised trial comparing 3 radiotherapy fraction schedules after local surgery for early breast cancer. Proc. of 14th meeting of the international society for clinical biostatistics; 1993; Cambridge.


Patient Information: Intensity modulated radiotherapy (IMRT) for breast cancer

We would like to invite you to participate in our research study. Please take your time to make your decision.

What is the purpose of this study?
Radiotherapy (x-ray treatment) is an important part of the treatment for early breast cancer, but this can be difficult due to varying breast shapes and sizes. This means that current methods of breast radiotherapy can cause uneven delivery of X-rays to the breast. These uneven areas are more likely to produce side effects in the months and first few years following radiotherapy. Typical side effects include fibrosis (like scar tissue) which can cause shrinkage of the breast. The aim of this study is to see if a different radiotherapy technique, called intensity modulated radiotherapy (IMRT), can smooth out the delivery of radiotherapy to the breast and prevent side effects.

Why have I been chosen?
You have been told that you have early breast cancer, which will benefit from radiotherapy. We are inviting all women like you to take part in our study.

Who is organising the study?
The study is being organised by Dr Margaret Moody and Dr Charlotte Coles at Addenbrooke’s Oncology Centre, Cambridge.

What will happen to me if I take part?
You will either receive standard radiotherapy, or IMRT radiotherapy. Your oncology doctor will have discussed your radiotherapy visit to the Simulator for radiotherapy planning. This routinely includes having 3 or more tiny permanent ink marks (tattoos) near the breast so that your position is the same during each treatment. At this time, patients willing to take part in the study will have a picture taken of their breast with a 3-D camera to help plan the radiotherapy. The information from the 3-D picture will predict if you are likely to have uneven delivery of X-rays with conventional radiotherapy treatment.

If you are in the group of women likely to have uneven areas, you will be able to take part in this study. In order to prevent bias of the results, neither you nor us can chose the treatment you receive within the study. A process called randomisation chooses this by chance. You will have an equal chance of receiving either IMRT radiotherapy or conventional radiotherapy. Those patients in the study will have a 3-D picture taken of the untreated breast when they come for radiotherapy treatment so that we can compare any radiotherapy changes. All women in the study will be asked to come back to Addenbrooke’s Hospital after
2 years and 5 years (the end of the study) to assess the effects of radiotherapy. This will be done by examining and taking further 3-D pictures and ordinary photographs of both breasts. Study patients will be asked to complete a questionnaire to complete about quality of life at 6, 24 and 60 months following radiotherapy.

All women in the study will be asked to provide a blood DNA sample at the start of radiotherapy, which will be completely anonymous and a separate consent form will be signed. These blood samples will form a large DNA database to help us study possible genetic causes of radiation side effects and help answer why some people are affected more than others.

If you are in the group of women who are unlikely to have uneven areas, you will receive standard radiotherapy as it is unlikely that your treatment can be further improved with IMRT. We would like you to be followed in the same way as the women with uneven areas in the study and provide a blood DNA sample, as your breast appearance following standard radiotherapy is still important to us (see above).

**What are the possible risks of taking part?**

There is no known increased risk of IMRT compared to standard radiotherapy.

**What are the possible benefits of taking part?**

If you are randomised to the IMRT group this treatment may decrease your risk of radiotherapy side effects, such as fibrosis and breast shrinkage.

**Confidentiality – who will have access to the data?**

Your medical records and data obtained from the study will be confidential and only members of the research study team will have access to this information.

**What will happen to the study results?**

The data will be analysed when the study is complete. If we show that IMRT is beneficial, this may be adopted as standard practice for breast radiotherapy at Addenbrooke's Oncology Centre and other centres in the UK and abroad.

Your participation in this research study is entirely voluntary. You are free to decide at all times without giving a reason that you no longer wish to participate in the study. Withdrawal from the study will not affect your current or future treatment in any way.

**Further information**

If you have further questions, please contact Dr Charlotte Coles, Tel. 01223 245151 bleep 152 671 or Jenny Wilkinson Tel. 01223 245151 bleep 152 867.

Your patient has agreed to participate in the following study, which will be carried out at Addenbrooke's Hospital Oncology Centre.

Background
Breast cancer is the most common cancer in women in Europe. The majority are detected at an early stage and are managed with conservation surgery, post-operative radiotherapy and increasingly, systemic treatment. Breast irradiation currently utilises 30% of radiotherapy resources in the UK and it aims to offer optimal local control and survival whilst obtaining a good cosmetic outcome; post-operative radiation technique has a major impact on this endpoint. Cosmetic outcome following radiotherapy appears worse in patients with larger breasts, with breast shrinkage being the most commonly observed problem. Conventional 2-D radiotherapy breast plans can lead to substantial off-axis dose inhomogeneities, particularly in women with larger breasts. Breast appearance following treatment has been shown to be an important patient issue, and can cause significant psychological morbidity.

Dose inhomogeneities in the breast can be improved by 3-D radiotherapy planning, which requires acquisition of 3-D patient data, usually obtained from CT scanning. There can be, however, physical constraints in scanning in the conventional treatment position using a breast board and also serious resource implications from scanning potentially large numbers of patients. We have developed an innovative method of 3-D breast planning using optical imaging (Minolta Vivid 700 digitizer) and forward-planned intensity modulated radiotherapy (IMRT). This relatively simple IMRT technique consists of smaller MLC-shaped fields being added to the main treatment fields to improve the dose distribution. Promising pilot data has been obtained.

Main objective
The question to be answered by the study is:

Does correction of dose homogeneity improve the cosmetic outcome following radiotherapy in patients with early breast cancer?

Proposed Design

T1-3, N0-1, M0 invasive breast cancer.
Breast conservation surgery with complete tumour excision
Off-axis dose inhomogeneity outside -5% and +7% of the prescribed dose
using conventional 2-D radiotherapy

RANDOMISE 1:1 ratio

INTERVENTIONAL ARM
Use of forward-planned IMRT to correct dose inhomogeneities

CONTROL ARM
Conventional 2-D radiotherapy with no correction of off-axis dose inhomogeneity

Endpoints
The primary endpoint will be breast shrinkage after radiotherapy; serial photographs will be assessed using a validated scoring system as used in the UK Standardisation of Breast Radiotherapy (START) trial. Secondary endpoints will include acute skin reactions, clinical assessment of late cosmetic effect and patient self-assessment using validated quality of life questionnaires. Information regarding local control, metastatic disease, survival and cardiac and pulmonary complications will be collected prospectively. We have a means of assessing changes in breast volume and shape that we hope will provide a novel non-invasive method of assessing post-radiation breast shrinkage, by using the 3-D optical scanner. Change in breast volume following radiotherapy will be compared with the baseline pre-radiotherapy volume and will be analysed as a secondary endpoint. The contralateral breast will be scanned at identical time intervals and thus act as a control for each patient. We anticipate that this will provide a more objective analytical assessment tool than conventional methods.

Patient selection criteria
All patients will be 18 years or above, have operable unilateral breast cancer (T1-3, N0-1, M0 at presentation), have a histological diagnosis and a complete macroscopic tumour excision by breast conserving surgery. Off-
axis dose inhomogeneities outside -5% and +7% of the prescribed dose, using conventional radiotherapy planning, must be present.

Randomisation
Eligible patients will be randomised to either more complex radiotherapy or receive conventional radiotherapy within the standard radiotherapy control arm. Stratification will be carried out for T-stage and adjuvant systemic therapy using a random block design. This will take into account the possibility that cosmetic outcome is affected by tumour size and the necessary extent of surgical resection, and cytotoxic or hormonal treatment. Patients who decline to take part in the study will be treated with conventional radiotherapy regardless of any possible dose inhomogeneities.

Sample size
Pilot data from the UK Standardisation of Breast Radiotherapy (START) trial has suggested that the probability of observing late radiation change for patients receiving standard radiotherapy is approximately 40%. We are therefore assuming a standard event rate of 40% in the control group at 2 years. The difference to be detected will be 10% and the hazard ratio will be 0.7. Assuming a minimum average follow-up of 2 years and 80% power and type I error of 0.05, we would require 358 patients and 125 events in each arm. We currently treat approximately 600 women with early breast cancer with radiotherapy per year. Our pilot studies have shown that approximately 70% of patients planned with conventional 2-dimensional radiotherapy have dose inhomogeneities. We expect a very high patient accrual rate given the simplicity of the trial design with virtually no change in the patients' treatment pathway compared with the standard radiotherapy offered out of trial. Therefore the expected recruitment duration would be 3 years. Assessment of cosmetic outcome will be carried out at 2 years post radiotherapy, but there will be on-going follow-up to assess cardiac and pulmonary morbidity, local control and survival.

Future studies: Genetic variation in normal tissue radiosensitivity
Blood DNA samples will be prospectively collected during the clinical trial for future analysis of polymorphisms in DNA damage repair genes. This DNA database will be utilised in a separate study, in conjunction with the comprehensive clinical data collected on late radiation normal tissue effects, to investigate the genetic aspects of individual variations in normal tissue radiosensitivity. This trial will provide an almost unique group of patients in whom variations in radiotherapy dose has been removed. Variation in normal tissue response is therefore likely to be due to underlying genetic factors.

Preliminary project development team
Dr Margaret Moody, consultant oncologist, will act as the Principal Investigator for the Addenbrooke’s study, and the project co-ordinator will be Dr Charlotte Coles, specialist registrar in clinical oncology. Professor BAJ Ponder, Dr C B Wilson and Dr N G Burnet will be Co-investigators. Physics support will be provided by Nicola Twyman and Andrew Hoole and radiographer input will be given by a research radiographer funded by a 3-year grant from the Breast Cancer Campaign (to be appointed December 2002).

This protocol was developed at the ‘Methods in Clinical Cancer Research’ workshop in Flims, Switzerland, in June 2001 (organised by the Federation of European Cancer Societie, the American Association for Cancer Research, and the American Society of Clinical Oncology. The protocol was accepted by the NCRI Radiotherapy Studies Group as a portfolio trial in April 2002.

References

Further information
If you have further questions, please contact: Dr Charlotte Coles, Research Registrar in Oncology, Tel. 01223 245151 bleep 152 671.
LREC Reference Number:

Title of Project: Intensity modulated radiotherapy (IMRT) for breast cancer.

Name of Lead Investigator: Dr Margaret Moody

Please initial box

1. I confirm that I have read and understand the information sheet dated ....29/01/03...............
   (version .2..........) for the above study and have had the opportunity to ask questions. □

2. I understand that my participation is voluntary and that I am free to withdraw at any time,
   without giving any reason, without my medical care or legal rights being affected. □

3. I understand that sections of any of my medical notes may be looked at by responsible
   individuals from the trial team or from regulatory authorities where it is relevant to my
   taking part in research. I give permission for these individuals to have access to my records. □

4. I am willing that my general practitioner is notified of my participation in this research. □

5. I agree to take part in the above study. □

Name of Research Subject Date Signature
(Please print)

Name of Witness to Signature Date Signature
(Must not be member of research team)
(Please print)

Name of Research Team member Date Signature
(Please print)

3 copies required: top copy for researcher; one copy for patient; one copy to be kept with research subject’s notes.

Version No: ...1... / Dated: ...19/12/2002.....................
Cambridgeshire Health Authority

CONSENT FORM

LREC Reference Number:

Title of Project: Intensity modulated radiotherapy (IMRT) for breast cancer: consent for DNA blood sample.

Name of Lead Investigator: Dr Margaret Moody

Please initial box

6. I confirm that I have read and understand the information sheet dated ....29/01/03................... (version .2............) for the above study and have had the opportunity to ask questions.

7. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

8. I understand that sections of any of my medical notes may be looked at by responsible individuals from the trial team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

9. I am willing that my general practitioner is notified of my participation in this research.

10. I agree to take part in the above study.

Name of Research Subject Date Signature
(Please print)

Name of Witness to Signature Date Signature
(Must not be member of research team)
(Please print)

Name of Research Team member Date Signature
(Please print)

3 copies required: top copy for researcher; one copy for patient; one copy to be kept with research subject’s notes.

Version No: ...1... / Dated: ...19/12/2002.......................
IMRT Breast Radiotherapy Trial: Randomisation Checklist

Patient's name: ________________________________
Patient's address: ________________________________
Hospital number: ____________________ DOB: _____/____/____

PRIMAR Y SURGERY AND TUMOUR PATHOLOGY

Date of surgery: _____/_____/____ Side of primary: left □ right □
Pathological tumour size (mm): _______ Grade: 1 □ 2 □ 3 □
Specimen weight (g): _______
Histological type: infiltrating ductal □ infiltrating lobular □ other (specify) □
Was axillary surgery performed? Yes □ No □
If Yes:
sentinel node biopsy □ axillary clearance □ axillary sampling □
Pathological nodal status: positive □ negative □ not known □
Number of nodes involved: _______ Number of nodes examined: _______
ER/PR status: positive □ negative □ not known □
HER2 status: positive □ negative □ not known □

PATIENT FACTORS

History of:
Cardio/peripheral vascular disease? Yes □ No □
Diabetes? Yes □ No □
Smoker? Yes □ No □
Post-op breast infection/haematoma? Yes □ No □
Height (cm) _______ Weight (kg) _______ BMI _______

ADJUVANT TREATMENT

Adjuvant systemic treatment? Yes □ No □
If yes, specify: Tamoxifen □ Aromatase Inhibitor □ Chemotherapy □ specify below:
AC X 4 □ AC X 6 □ FEC □
Docetaxel □ Paclitaxel □
E-CMF □ Other □ specify _______

ALLOCATED TREATMENT

Interventional arm □ Control arm □
(Radiotherapy and chemotherapy must be separated by a minimum of 2 weeks)
which fields do you intend to treat? (tick those that apply)
Breast □ Breast boost □ Axilla □ Supraclavicular fossa □
Trial number: _______ Date of randomisation: _____/____/____
Blood sample taken (DNA database) □
Baseline quality of life questionnaire completed (before randomisation) □

25
IMRT Breast Radiotherapy Trial - Acute Radiotherapy Reactions

**PATIENT DETAILS**

Patient's name: ___________________________ Trial number: _______________________

Hospital number: ___________________________ DOB: _____________________________

**RADIOThERAPY (RT) DETAILS**

Interventional arm □ Control arm □

RT start: [ ] [ ] [ ] [ ] [ ]

RT finish: [ ] [ ] [ ] [ ] [ ]

40 Gy/ 15 fractions/ 3 weeks? Yes □ No □ If No, specify: _______________________

Which fields were treated? (tick those that apply)

- Breast □
- Axilla □
- SCF □
- Boost □

Which breast was treated? Right □ Left □

Breast volume (cm$^3$) Right: [ ] [ ] [ ] [ ] Left: [ ] [ ] [ ] [ ]

**RADIOThERAPY ACUTE SKIN REACTIONS**

RTOG grading system

- RTOG 0: no visible change to skin
- RTOG 1: faint or dull erythema
- RTOG 2a: tender or bright erythema
- RTOG 2b: patchy moist desquamation
- RTOG 3: confluent moist desquamation

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NB week 5 & 6 allow for multicentre involvement with different fractionation schedules

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Other acute radiotherapy reactions (specify): _______________________

26
IMRT Breast Radiotherapy Trial - Late Radiotherapy Effects

PATIENT DETAILS

Patient's name: ___________________________ Trial number: ________________

Hospital number: ___________________________ DOB: _______________________

Month of follow-up: 24[ ] 60[ ]

CLINICAL ASSESSMENT

Has the patient had any of the following adverse effects? Yes[ ] No[ ]

Please grade the following features (0-none, 1-a little, 2-quite a bit, 3-very much) in boxes below. Where relevant, compare with the contralateral breast/arm.

- Breast shrinkage [ ]
- Telangiectasia [ ]
- Breast induration (tumour bed) [ ]
- Breast oedema [ ]
- Breast induration (on central axis) [ ]
- Arm oedema [ ]
- Other: specify _______________________

Has there been specialist referral for any adverse treatment effect since last assessment? Yes[ ] No[ ]

If yes, specify _________________________

LASER BREAST VOLUME ASSESSMENT

Right breast volume (cm3) ________________

Left breast volume (cm3) ________________

CURRENT STATUS

Loco-regional recurrence? No[ ] Yes[ ] Date: ________________

Metastases? No[ ] Yes[ ] Date: ________________

Patient died? No[ ] Yes[ ] Date: ________________

Photographic assessments done [ ]

Quality of life questionnaires completed [ ]
SPECIAL NOTE

THE FOLLOWING IMAGE IS OF POOR QUALITY DUE TO THE ORIGINAL DOCUMENT. THE BEST AVAILABLE IMAGE HAS BEEN ACHIEVED.
IMRT Breast Radiotherapy Trial - Unusual Severe Radiotherapy Reactions

**PATIENT DETAILS**

Patient's name: ___________________________ Trial number: [ ]

Hospital number: ___________________________ DOB: [ ]

**DETAILS OF SEVERE ACUTE REACTIONS**

Date of starting radiotherapy: [ ]

Date of start of severe reaction: [ ]

Type of reaction (please give details): __________________________________________

Was any chemotherapy (CT) given? Yes [ ] No [ ]

If yes, please name schedule: __________________________________________

If CT given before RT, date of last exposure to drug: [ ]

If CT given after RT, date of last exposure to drug: [ ]

Was the patient taking any other medication? Yes [ ] No [ ]

If yes, please list: __________________________________________

Is the patient a smoker? Yes [ ] No [ ]

If yes, how many cigarettes smoked per day: [ ]

**PAST MEDICAL HISTORY**

Does the patient have any of the following illnesses?

Cardio/peripheral vascular disease Yes [ ] No [ ]

Diabetes Yes [ ] No [ ]

Collagen vascular disease Yes [ ] No [ ]

Any other significant medical condition? Yes [ ] No [ ]

If yes, please specify: __________________________________________

**FAMILY HISTORY**

Is there a family history of cancer in a 1st or 2nd degree relative? Yes [ ] No [ ]

Is there a family history of any severe RT reactions? Yes [ ] No [ ]
We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no “right” or “wrong” answers. The information that you provide will remain strictly confidential.

1. Do you have any trouble doing strenuous activities like carrying a heavy shopping bag or suitcase?  
   - No 1  
   - Yes 2

2. Do you have any trouble taking a long walk?  
   - No 1  
   - Yes 2

3. Do you have any trouble taking a short walk outside of the house?  
   - No 1  
   - Yes 2

4. Do you have to stay in a bed or a chair for most of the day?  
   - No 1  
   - Yes 2

5. Do you need help with eating, dressing, washing yourself or using the toilet?  
   - No 1  
   - Yes 2

During the past week:

6. Were you limited in doing either your work or other daily activities?  
   - Not at all 1  
   - A little 2  
   - Quite a bit 3  
   - Very much 4

7. Were you limited in pursuing your hobbies or other leisure time activities?  
   - Not at all 1  
   - A little 2  
   - Quite a bit 3  
   - Very much 4

8. Were you short of breath?  
   - Not at all 1  
   - A little 2  
   - Quite a bit 3  
   - Very much 4

9. Have you had pain?  
   - Not at all 1  
   - A little 2  
   - Quite a bit 3  
   - Very much 4

10. Did you need to rest?  
    - Not at all 1  
    - A little 2  
    - Quite a bit 3  
    - Very much 4

11. Have you had trouble sleeping?  
    - Not at all 1  
    - A little 2  
    - Quite a bit 3  
    - Very much 4

12. Have you felt weak?  
    - Not at all 1  
    - A little 2  
    - Quite a bit 3  
    - Very much 4
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Have you had diarrhoea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>newspaper or watching television?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>your family life?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>your social activities?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>financial difficulties?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

   Very poor   1  2  3  4  5  6  7  Excellent

30. How would you rate your overall quality of life during the past week?

   Very poor   1  2  3  4  5  6  7  Excellent
EORTC QLQ – BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

### During the past week:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Did you have a dry mouth?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32</td>
<td>Did food and drink taste different than usual?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33</td>
<td>Were your eyes painful, irritated or watery?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34</td>
<td>Have you lost any hair?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35</td>
<td>Answer this question only if you had any hair loss: Were you upset by the loss of your hair?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36</td>
<td>Did you feel ill or unwell?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37</td>
<td>Did you have hot flushes?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38</td>
<td>Did you have headaches?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39</td>
<td>Have you felt physically less attractive as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40</td>
<td>Have you been feeling less feminine as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41</td>
<td>Did you find it difficult to look at yourself naked?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42</td>
<td>Have you been dissatisfied with your body?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43</td>
<td>Were you worried about your health in the future?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### During the past four weeks:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>To what extent were you interested in sex?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45</td>
<td>To what extent were you sexually active? (with or without intercourse)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46</td>
<td>Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*Please go on to the next page*
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>47. Did you have any pain in your arm or shoulder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. Did you have a swollen arm or hand?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Was it difficult to raise your arm or to move it sideways?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50. Have you had any pain in the area of your affected breast?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>51. Was the area of your affected breast swollen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>52. Was the area of your affected breast oversensitive?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
**Additional Body Image Items**

**During the past week:**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite A Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.</td>
<td>Have you been self conscious about your appearance?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>55.</td>
<td>Have you been dissatisfied with your appearance when dressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>56.</td>
<td>Have you been feeling less sexually attractive as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>57.</td>
<td>Did you avoid people because of the way you felt about your appearance?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>58.</td>
<td>Have you been feeling the disease or treatment has left your body less whole?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>59.</td>
<td>Did you have any stiffness in your shoulder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>60.</td>
<td>Have you been dissatisfied with the appearance of your scar?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Since your breast radiotherapy**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite A Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>61.</td>
<td>Has the appearance of the skin in the area of your affected breast changed since your radiotherapy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please complete the following questions if you have had a lumpectomy or breast conserving surgery (but not if you have had a mastectomy).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite A Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>62.</td>
<td>Has the overall appearance of your affected breast changed, compared with the other side, as a result of your radiotherapy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>63.</td>
<td>Has your affected breast become smaller as a result of your radiotherapy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>64.</td>
<td>Has your affected breast become harder/firmer to the touch since your radiotherapy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more. This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don’t take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

**Tick only one box in each section**

### I feel tense or ‘wound up’
- Most of the time
- A lot of the time
- Time to time, Occasionally
- Not at all

### I still enjoy the things I used to enjoy:
- Definitely as much
- Not quite so much
- Only a little
- Hardly at all

### I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly
- Yes, but not too badly
- A little, but it doesn’t worry me
- Not at all

### I can laugh and see the funny side of things:
- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not at all

### Worrying thoughts go through my mind:
- A great deal of the time
- A lot of the time
- From time to time but not too often
- Only occasionally

### I feel cheerful:
- Not at all
- Not often
- Sometimes
- Most of the time

### I can sit at ease and feel relaxed:
- Definitely
- Usually
- Not often
- Not at all

### I feel as if I am slowed down:
- Nearly all the time
- Very often
- Sometimes
- Not at all

### I get a sort of frightened feeling like ‘butterflies’ in the stomach:
- Not at all
- Occasionally
- Quite often
- Very often

### I have lost interest in my appearance:
- Definitely
- I don’t take so much care as I should
- I may not take quite as much care
- I take just as much care as ever

### I feel restless as if I have to be on the move:
- Very much indeed
- Quite a lot
- Not very much
- Not at all

### I look forward with enjoyment to things:
- As much as ever I did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

### I get sudden feelings of panic:
- Very often indeed
- Quite Often
- Not very often
- Not at all

### I can enjoy a good book or radio or TV programme:
- Often
- Sometimes
- Not often
- Very seldom
Overview

Reduction of Radiotherapy-induced Late Complications in Early Breast Cancer: The Role of Intensity-modulated Radiation Therapy and Partial Breast Irradiation

Part I — Normal Tissue Complications

C. E. Coles, A. M. Moody, C. B. Wilson, N. G. Burnet

Addenbrooke's Hospital, Cambridge, UK

Abstract:
Radiotherapy after conservation surgery has been proven to decrease local relapse and death from breast cancer, and is now firmly established in the management of early breast carcinoma. Currently, the challenge is to minimise the morbidity caused by this treatment without losing its efficacy. This review will be divided into two parts, with Part I focusing on the radiation factors contributing to late normal tissue complications after radiotherapy for early breast cancer. Three major normal tissue side-effects will be discussed: cosmetic outcome, cardiac complications and pulmonary side-effects.

Introduction

What is the Rationale for Radiotherapy after Breast-conserving Surgery?

Breast cancer is the most common cancer in women in Europe, with about 180,000 new cases a year. Most are detected at an early stage and are often managed with conservation surgery, postoperative radiotherapy and, increasingly, systemic treatment. Breast irradiation is a major component of radiotherapy workload, and it currently uses 30% of radiotherapy resources in the UK [1].

A number of randomised-controlled trials, including the landmark NSABP B-06 study [2], have shown that radiotherapy after conservative breast surgery or mastectomy significantly reduces the risk of locoregional recurrence compared with surgery alone. In addition, the Early Breast Cancer Trialsists’ Collaborative Group (EBCTCG) [3] systematic overview of radiotherapy confirmed that improved local control affected the development of distant relapse and subsequent survival from breast cancer. It found a four-fold reduction in local recurrence risk after breast-conservation surgery, and reported that prevention of four local recurrences prevents one breast cancer death. Two subsequent randomised trials using more modern radiotherapy methods have shown an overall survival benefit of about 9% in node-positive women given radiotherapy and systemic treatment after mastectomy [4,5]. In addition, two meta-analyses of the effects of radiotherapy in early breast cancer have shown long-term overall survival improvement in patients receiving radiotherapy [6,7]. However, concerns were raised by the results of a meta-analysis indicating that, although postoperative radiotherapy reduces the risk of death from breast cancer, this may be offset by an increase in cardiovascular mortality, resulting in equivalent survival overall [8]. These data were obtained from patients treated with older equipment and techniques.

The use of systemic treatment (chemotherapy and hormonal therapy) has increased considerably in recent years. This prompted several studies to ask the question: can radiotherapy be avoided after conservative breast surgery if systemic treatment is given? In the Scottish Trial, all patients received systemic treatment with either chemotherapy or tamoxifen. Locoregional relapse rate was 24.5% in the non-irradiated group compared with 5.8% after breast irradiation. A non-significant trend towards fewer distant metastases was observed in the radiotherapy group [9]. Another trial randomised high-risk patients with 10 or more positive axillary lymph nodes. All patients had...
standard chemotherapy, some had tamoxifen and a few had intensification chemotherapy with autologous bone marrow transplant. It was shown that radiotherapy was the most important factor influencing relapse rate, and the disease-free survival was significantly improved in the radiotherapy group, with a trend for increased overall survival [10]. Fisher et al. [11] investigated the effect of tamoxifen alone, radiotherapy and placebo, and radiotherapy plus tamoxifen on ipsilateral breast tumour recurrence (IBTR) in node-negative patients with tumours 1 cm or less in diameter. Cumulative incidence of IBTR through 8 years was 16.5% with tamoxifen alone, 9.3% with radiotherapy and placebo and 2.8% with radiotherapy and tamoxifen. Radiotherapy reduced IBTR below the level achieved with tamoxifen alone, regardless of oestrogen receptor status.

These studies have proved that radiotherapy is essential after local breast excision for most patients, and cannot be substituted by systemic treatment alone. Ongoing studies are addressing whether radiotherapy can be avoided in low-risk patients, such as older patients with low-grade, lymph-node-negative tumours (PRIME Trial; postoperative radiotherapy in minimal-risk elderly patients). However, to date, no randomised-controlled trial has identified a low-risk group with invasive breast cancer in which radiotherapy can be avoided after breast conservation.

In summary, radiotherapy is clearly established in the management of breast cancer to increase both locoregional control and survival. Therefore, the challenge for this century, as breast radiotherapy continues its evolution, is to minimise the morbidity caused by this treatment without losing its efficacy. However, despite many advances in radiation techniques in other sites of the body, most patients with breast cancer are still planned using two-dimensional data, and treated with paired tangential fields. In addition, the breast is actually challenging to irradiate, as its anatomy and surrounding structures make this an inherently difficult site to irradiate in a homogeneous manner. It has a complex three-dimensional shape, which may have been modified further by surgery, and it is located at the body–air interface. There are also important organs at risk in close proximity, such as the lungs and heart (in the case of left-sided tumours).

This review will be divided into two parts, with Part I focusing on the radiation factors contributing to late normal tissue complications after radiotherapy for early breast cancer. Three major normal tissue side-effects will be discussed: cosmetic outcome, cardiac complications and pulmonary side-effects.

Methods

This review is based on Medline and PubMed literature searches using the key words 'breast neoplasms', 'radiotherapy', 'side effects', and the authors' clinical experience.

Cosmetic Outcome after Breast Radiotherapy

*What is the Nature and Extent of the Problem?*

The principal long-term effects that impair cosmesis are fibrosis and induration of the breast. Fibrosis and atrophy are the result of specific responses of fibrocytes to irradiation. Fibrosis represents a proliferative response of the surviving fibrocytes to growth factors released by injury, and atrophy reflects both loss of fibrocytes and collagen reabsorption [12]. There is also evidence that transforming growth factor beta plays a key role in the development of radiation-induced fibrosis [13]. Depending on the severity of late normal tissue changes, the clinical picture includes induration, hardening, change in shape and decrease in volume of the treated breast.

The extent of this problem is sizable, as shown by the pilot study for the START (Standardisation of Breast Radiotherapy) trial, which was carried out at the Royal Marsden Hospital and Gloucestershire Oncology Centre, involving 1410 patients. This suggested that the probability of observing some late radiation change by 5 years for patients receiving 50 Gy in 25 daily fractions, is about 40% [14]. A follow-up study of mastectomy patients after radiotherapy showed that 90% of moderate or severe complications were present within 3.2 years and 4.7 years for fibrosis and telangiectasia, respectively [15]. Although the frequencies of the complications seem to reach a stable level within 3–5 years, the clinical picture of damage may progress in individual patients over time [15,16]. In addition, the time of onset and rate of progression may correlate with the final severity of the late normal tissue side-effects [17].

*How Important is Cosmetic Outcome for Patients?*

Research has shown that women with breast cancer rate cosmetic outcome as very important compared with other quality-of-life parameters [18]. A study of 254 patients treated with wide local excision for early breast cancer, of which 86% had postoperative radiotherapy, showed that radiotherapy negatively influences cosmesis, and that cosmetic outcome is correlated with patient satisfaction [19]. The same cohort was the subject of a parallel study, which showed a strong correlation between psychological well-being and cosmetic result [20]. In particular, cosmesis was related to patient satisfaction, anxiety and depression, body image, feelings of sexual attractiveness and self-esteem. There was also a strong correlation between body image and patient age, with younger women being more sensitive to alterations in body image. Another study has shown that the association between cosmetic result and self-reported psychosocial health was strongest in younger patients [21]. This is particularly relevant as the number of women with early breast cancer is increasing as a result of screening.

*Non-radiation Factors Contributing to a Worse Cosmetic Outcome*

Before focusing on radiotherapy, it is important to mention the other factors that may contribute to a poor cosmetic result. Patient-related factors can be divided into extrinsic and intrinsic (cellular) factors. Extrinsic factors include age, smoking, immunosuppression, cardiovascular disease...
and diabetes [22]. Another patient-related factor is breast size. Larger breasts correlate with worse cosmetic outcome and seem to relate to a greater dose inhomogeneity, which will be discussed in more detail below [23].

Intrinsic factors include individual variation in radiosensitivity and, from analysis of studies in which the dosimetry was well controlled, it is thought that 70–80% of normal tissue effects may be due to intrinsic factors [24] (Fig. 1). It must be emphasised that these data were obtained using uniform dosimetry. Much work has been done to try and correlate in vitro radiosensitivity with clinical outcome in patients but, at present, there is no predictive test for individual intrinsic radiosensitivity [25–28]. It is likely that future studies will focus on the genetic basis of variations in radiosensitivity.

In addition, the tumour characteristics can affect ultimate breast cosmesis. The original position of the tumour can influence post-treatment breast appearance, with the worse outcome obtained with inferiorly or medially located breast cancers [29–31]. The volume of tissue excised (which was often related to the T-stage) has also been shown to adversely affect the cosmetic result [30,32–35]. It follows that the volume of tissue removed is reflected in the type of breast surgery (e.g. wide local excision or quadrantectomy), and more extensive surgery has also been shown to correlate with cosmetic outcome [21,36]. Not surprisingly, the number of lymph nodes removed has been shown to influence the severity of arm oedema [37]. Patient- and tumour-related factors are largely difficult to control. In contrast, radiation-induced normal breast tissue changes have the potential to be controllable.

**Effect of Total Dose, Dose per Fraction and Boost Treatment on Cosmesis**

The pioneering work of Hopewell et al. [38] and Withers et al. [39], using animal models, has contributed greatly to our understanding of late skin reactions. Turesson [16] and others [26,40,41] have carried out patient studies, which have clearly demonstrated the dose–response relationship with late radiation effects after mastectomy and conservative surgery. Specifically, a dose in excess of 50 Gy to the whole breast has been shown to be a significant independent factor for worse cosmetic outcome [42,43].

Given that the alpha/beta ratio for late normal breast tissue effects is assumed to be 3.0 Gy, it follows that a larger dose per fraction may produce a worse cosmetic result [44]. A report of 592 women with early breast cancer treated with 45 Gy four times a week over 4.5 weeks at the Institut Gustave-Roussy, France, showed that only applied fractional dose over 3.5 Gy was associated significantly with an overall worse cosmetic result using multivariate methods [45]. The frequency distribution of normal tissue responses among patients, which would result from identical radiotherapy treatment, is based on a perfect theoretical end point without threshold or saturation. The proposed nomenclature for the different categories of tissue effect is shown on an arbitrary scale, ranging from 1 to 5. There is a range of reactions seen among normal patients, including some that are greater than average, with an approximately Gaussian distribution. On the basis that this range is the result of differences in normal tissue sensitivity, patients in Category 5 could be designated ‘highly radiosensitive’ or ‘HR’. They must be distinguished from patients with some variation in the severity of normal tissue response, and a division is suggested, somewhat arbitrarily, into ‘severe’ and ‘extreme over-reactors’. The term ‘severe over-reactor’ (severe OR) is intended to imply a patient whose early reactions forced a major change in the radiotherapy prescription or who later developed severe normal tissue reactions and serious morbidity. The term ‘extreme over-reactor’ (extreme OR) is suggested for exceptionally rare cases, in which extreme reactions occur with lower doses than used in conventional radical treatment, typically with fatal consequences. For further details see: Bumet NG, Johansen J, Turesson I, Nyman J, Peacock JH. Describing patients’ normal tissue reactions: concerning the possibility of individualising radiotherapy dose prescriptions based on potential predictive assays of normal tissue radiosensitivity. Steering Committee of the BioMed2 European Union Concerted Action Programme on the Development of Predictive Tests of Normal Tissue Response to Radiation Therapy. Int J Cancer 1998;79:606–613. Reprinted with kind permission from the International Journal of Cancer.
Effects of Dose Inhomogeneity on Cosmesis

A particularly important radiotherapy-related factor influencing late cosmetics is dose inhomogeneity. Moody et al. [23] investigated late changes in breast appearance in 559 women after conservation surgery and radiotherapy for early breast cancer. Breast size was assessed from a postsurgical photograph, and annual photographs were collected for 5 years after radiotherapy. Moderate or severe changes were present in 6%, 22% and 39% of women with small, medium and large breasts, respectively. This demonstrated a strong association with late changes in breast appearance and breast size (Fig. 2). It was hypothesised that the increase in late radiation effect observed in larger breasts was related to greater dose inhomogeneity. A separate group of 37 women with limited computer tomography (CT) data of the breasts were studied. A significant correlation between breast size and dose inhomogeneity was found in this small group. This clinical finding fits with radiobiological modelling, as ‘hot spots’ created within an inhomogeneous dose distribution lead to an increase in both total dose and dose per fraction, the so-called ‘double trouble’ phenomenon described by Withers et al. [39]. Three-dimensional CT planning was carried out in a further 20 patients treated with a tangential-wedged field technique [51]. This illustrated that 0.2–23.8% of the breast received a dose outside 95–105% of the prescribed dose, and dose variations across the target volume varied by −10% to +15% of the dose prescription. There was a significantly worse dose homogeneity with increasing breast volume measured using the CT data. Improvement in dose homogeneity is clearly an important goal for breast radiotherapy, and techniques to improve this will be discussed in Part 2 of this review.

Effect of Systemic Treatment in Addition to Radiotherapy

Other factors, such as adjuvant systemic therapy, have been postulated to enhance the effect of late radiation normal tissue damage. There are some reports that chemotherapy increases the risk of acute and late subcutaneous fibrosis, but there are also studies where this effect is not statistically significant [12]. The large Danish DBCG-82TM breast conservation trial showed that chemotherapy was associated with a worse cosmetic result, but this was not the case in the multi-centre EORTC trial 22881/10882 ‘boost trial’ [30]. Other studies have looked specifically at the timing of chemotherapy in relation to radiotherapy. In most studies, there seems to be a greater risk of a poor cosmetic outcome when the chemotherapy is given concomitantly with radiation [32,52,53]. This question will hopefully be clarified by the ongoing SECRAB study [50] (sequencing analysis [34]. This large applied dose resulted from the practice of treating each tangential field on alternate days using a Cobalt Unit. Another report of 80 patients showed that six patients received fraction sizes of 2.25 or 2.50 Gy, and had clinically significant fibrosis and breast retraction. However, this small number of patients who received 50 Gy in 2 Gy fractions [40]. Subsequent evidence has indicated that providing the total dose is reduced, a moderately larger dose per fraction seems to produce equivalent cosmesis and local control to 50 Gy in 25 daily fractions. This has been demonstrated by several Canadian and UK studies reporting the experience in using 40 Gy in 15 or 16 daily fractions [41–43,45]. A large trial of 1234 women, randomised to either 50 Gy in 25 fractions over 35 days or 42.5 Gy in 16 fractions over 22 days, has shown equivalent overall survival and no significant difference in cosmetic outcome [46]. A similar UK trial, START (Standardisation of Breast Radiotherapy Trial) [14] has recently closed, and its results will clarify the relationship between dose per fraction and cosmetic outcome.

Several studies have reported that a radiation boost to the tumour bed is adversely associated with cosmetic outcome [37,47]. However, other studies were unable to demonstrate this association [40,48]. The large multi-centre EORTC trial 22881/10882 trial was specifically designed to investigate the effect of a boost treatment in terms of local control and cosmesis. It randomised a total of 5318 patients with early breast cancer to a boost of 16 Gy to the primary tumour or no further treatment, following wide local excision and radiotherapy to the whole breast. The cosmetic outcome was evaluated by a panel, scoring photographs of 731 patients taken soon after surgery and 3 years later, and by digitiser measurements of nipple retraction of 1141 patients postoperatively and at 3 years. There was no difference in cosmetic outcome between the two groups before radiotherapy, but the 3-year analysis, the panel evaluation and the digitiser measurements showed that boost had a negative effect on cosmetic outcome [30]. However, it has also been reported that the additional 16 Gy boost to the tumour bed reduces the risk of recurrence in women younger than 50 years [49]. The therapeutic ratio of improvement in local control, compared with possible worse cosmesis associated with a radiotherapy boost, must therefore be assessed on an individual basis.
of chemotherapy and radiotherapy in adjuvant breast cancer), which randomises patients between sequential chemotherapy and radiotherapy and concomitant treatment. It plans to recruit a sub-study of 300 trial patients to assess differences in toxicity, quality of life and cosmesis.

It has also been hypothesised that tamoxifen may affect late cosmesis in patients undergoing radiotherapy, as it induces the cellular secretion of transforming growth factor beta, which is involved in the pathogenesis of fibrosis. Wazer et al. [54] published the results of their cohort of 498 women, of which 130 received tamoxifen 1–6 weeks (median 2.7 weeks) after completing radiotherapy. This retrospective study found no increase in poor cosmetic outcome in the patients treated with tamoxifen. Taylor et al. [32] also reported a non-randomised series, and found no evidence of worse cosmesis, whether tamoxifen was taken concomitantly with radiotherapy or after its completion [32]. In contrast, Azria et al. [55] assessed 147 women who received breast radiotherapy, and found that those treated with concomitant tamoxifen (n = 43) had significantly higher rates of subcutaneous fibrosis. This group concluded that tamoxifen should be delayed until completion of radiotherapy. In the absence of evidence from randomised-controlled trials, the optimal timing of tamoxifen and radiotherapy remains unclear. However, some centres with a substantial waiting time for radiotherapy may develop a pragmatic approach and commence tamoxifen before radiotherapy, rather than delay systemic hormonal treatment.

In summary, radiation-related factors contributing to a worse cosmetic result may be easier to modify than non-radiation-related factors. In addition to dose and fractionation, improvement of dose inhomogeneity, the selection of patients for boost treatment and the use of concurrent systemic treatment are important issues for the oncologist to consider. Also, a patient-centred treatment approach demands that strategies to improve cosmetic outcome be investigated and implemented to minimise psychosocial morbidity.

Radiation-induced Cardiac Toxicity

What is the Nature and Extent of the Problem?

Evidence of radiation-induced cardiac toxicity from randomised trial data

The 1987 overview of the 10-year mortality results of mature trials of simple or radical mastectomy randomised to radiation or not, showed a significant excess among patients given radiotherapy [8]. At that time, the details of the specific causes of death were unavailable, but an update in 1994 included these data. This showed that the difference in overall mortality after 10 years was not as large as previously observed, and had lost statistical significance. The excess mortality was confined to heart disease and the risk seemed to be greater in the earlier trials in which older radiotherapy techniques were used [56]. In the last few years, more data from randomised trials have emerged to support the role of postoperative radiotherapy as a strategy to reduce death from breast cancer. However, there have been conflicting reports as to whether radiotherapy is a cause of excess cardiovascular mortality.

The Early Breast Cancer Trialists’ Collaborative Group published their most recent meta-analysis of the 10- and 20-year results from 40 unconfounded randomised radiotherapy trials for early breast cancer in 2000 [3]. The results showed that mortality from breast cancer was significantly reduced in the radiation group, but vascular mortality was also increased by radiotherapy (death rate ratio 1.30; P = 0.0007). The proportional excess of vascular deaths seemed to be as great during the first decade as afterwards, but the absolute rates were three times as great in the latter period. The overall 20-year survival was 37.1% with radiotherapy compared with 35.9% with controls (P = 0.06). It must be noted that most patients in this meta-analysis had both axillary and internal mammary chain (IMC) irradiation in addition to breast/chest wall radiotherapy. Therefore, some of the vascular events may have been caused by large heart volumes irradiated with certain IMC techniques, or irradiation of the great vessels after axillary nodal irradiation. Information was not collected centrally on cardiac, carotid artery or other intrathoracic exposure to radiation, so a direct relationship between site of radiation exposure and cause of vascular death is impossible to establish.

Two Danish trials and one Canadian trial have demonstrated an overall survival benefit, of about 9%, in node-positive women given both radiotherapy and systemic treatment after mastectomy [4,5,72]. These patients were also treated with axillary and IMC irradiation. The mortality of ischaemic heart disease in the Danish high-risk patients receiving adjuvant postmastectomy systemic treatment with or without radiotherapy was analysed in a separate paper [57]. This showed that the actuarial risk of ischaemic heart disease was not increased in the radiotherapy group after 12 years. A similar conclusion was reported in a retrospective cohort linkage study of all breast cancer patients treated with breast conservation and radiotherapy at a single institution between 1982 and 1988 [58]. However, longer follow-up of these studies is required, as the EBCTCG meta-analysis suggested that 10 years of follow-up may be insufficient to definitely rule out late cardiac mortality after adjuvant radiotherapy for breast cancer [3].

Dosimetry studies and radiobiological modelling for prediction of radiation-induced cardiac toxicity

As suggested by the updated meta-analysis of breast radiotherapy trials by Cuzick et al. [56], it seems that the older radiation techniques were associated with greater cardiovascular mortality. A study has been carried out to compare the dose and irradiated volume delivered to the heart using older and more modern radiotherapy techniques [59]. The newer megavoltage techniques were shown to reduce the total heart dose and to spare the left circumflex and right coronary artery, but the dose to the left anterior descending artery remained unchanged. More complex radiotherapy techniques would therefore be required to reduce the dose to this vessel.
Another approach has been to use radiobiological modelling to predict normal tissue complication probabilities (NTCP) for excess cardiac mortality. One study showed a significant increase of the average NTCP of excess cardiac toxicity from 0.6% when the breast alone was irradiated, to around 2% when the locoregional nodes were included in the target volume, depending on the amount of heart in the radiotherapy portals [60]. The authors also found a good correlation between NTCP values and the maximum heart distance (defined as the maximum distance of the heart contour, as seen in the beam’s eye view of the medial tangential field, to the medial field edge). No NTCP values above 1% were found for a maximum heart distance of 1 cm, but the NTCP values increased steeply with maximum heart distances of 2 cm or more. A similar study calculated a mean excess cardiac mortality of 1.8% for 100 left-sided breast cancer patients treated with standard tangential breast radiotherapy [61]. However, there was a subgroup of patients in which the risk was increased to about 9%. The risk in this subgroup was substantially reduced using methods of cardiac shielding or, in one case, several intensity-modulated beams.

Cardiac function studies as predictors of radiation-induced toxicity

Several studies have investigated myocardial function after breast radiotherapy rather than cardiac mortality and morbidity. A small prospective study followed 17 left-sided breast cancer patients after radiotherapy [62]. All patients had radiotherapy plans showing part of the left ventricle receiving at least 85–95% of the total dose. Half of the patients showed new fixed scintigraphic abnormalities in left-sided breast cancer patients treated with radiotherapy either with or without doxorubicin [63]. Single photon emission computed tomography was carried out before chemotherapy, before radiotherapy and 6 months after irradiation. Of the patients receiving chemotherapy and radiotherapy, 100% (7/7) developed new perfusion defects compared with 50% (5/10) patients receiving radiotherapy alone. There was a suggestion that the defects observed in the radiation only group were related to the volume of left ventricle in the field. In contrast, among the patients in the combination group, new perfusion defects were observed regardless of the volume of left ventricle irradiated. It was found that the pattern of perfusion defect seemed to correlate with the radiotherapy field compared with the coronary artery blood distribution. The authors state that this suggests damage at the microvascular level. As with the previous study, no patients developed myocardial infarction or congestive heart failure, but this would not be expected with such short follow-up. It therefore remains to be seen whether perfusion changes are related to long-term cardiac morbidity and mortality.

It is difficult to determine from the existing evidence the precise pathogenesis of radiation-induced vascular toxicity, but clearly it is desirable to minimise the volume of heart and great vessels irradiated. The extent of the problem is also difficult to quantify because of improvements in radiotherapy techniques. Published data on radiation-induced cardiac toxicity suggest that there was a considerable risk of cardiovascular morbidity and mortality associated with the older radiotherapy techniques. This seemed to reduce substantially with the introduction of megavoltage techniques and simulator-assisted planning. However, in recent years, there has been a greater use of potentially cardiotoxic drugs (anthracyclines and anti-HER-2 monoclonal antibodies). In addition, we are now treating more screening-detected patients (the UK breast screening programme starts at age 50 years and is being extended to include the 64–70-year age group). Improved survival rates for largely good prognosis groups could potentially result in more women experiencing late cardiac toxicity many years after initial therapy. Also, trials have shown that most patients who have breast-conservation surgery for ductal carcinoma in situ (DCIS) benefit from breast radiotherapy [64,65]. Thus, patients with DCIS are particularly at risk from the long-term side-effects of radiotherapy, as they have an essentially non-fatal condition. Therefore, reduction of cardiac risk to an absolute minimum still remains an important goal for the clinical oncologist.

Radiation-induced Lung Toxicity

What is the Nature and Extent of the Problem?

Pathogenesis of pulmonary toxicity

Pulmonary toxicity is a recognised complication after radiotherapy for breast cancer, and may manifest as pneumonitis, pulmonary fibrosis, or both. Generally, two distinct pathological phases of lung injury are seen: early radiation effects, which manifest between 1 and 8 months after radiotherapy (pneumonitis), and late effects, which may develop in some patients from 6 months onwards (fibrosis) [66]. Recovery from the early inflammatory response and the development of fibrosis may be seen between 3 and 18 months. Radiation pneumonitis mostly precedes fibrosis, but both processes can also progress independently of each other. This two-phase lung response was illustrated in a study assessing lung density changes from routine follow-up chest radiographs in postmastectomy radiotherapy patients [67]. Early density changes reach a maximum around 6 months after radiation, and may resolve completely or partially. Late lung changes usually reach a plateau after 1 year, but some patients may have radiological progression for 5 years or more. Data on clinical effects are discussed below.

Factors increasing the risk of radiation-induced pulmonary toxicity

Various factors have been postulated to increase the risk of radiation-induced pulmonary toxicity. These include the volume of lung irradiated, the use of additional nodal fields,
chemotherapy treatment, concurrent tamoxifen medication, smoking habits, age and pre-radiotherapy performance status. Many studies reach different conclusions regarding the impact of these factors on radiation toxicity.

The amount of lung irradiated, however, is frequently quoted to contribute to lung morbidity. Measurements of the lung from the beam’s eye view of the lateral field or simulator field have been used by several authors as a surrogate for the volume of lung irradiated. This relationship was confirmed by a study that compared the lung volume (obtained from dose-volume histograms) and the central lung distance [68]. It was found that a quadratic relationship exists between the central lung distance (CLD) and the percentage of the lung irradiated. This results in a large increase in the percentage of lung volume in the radiation field, when the CLD is increased only by a small amount. Dose-volume data and NTCP have also been used to predict pulmonary toxicity. It has been reported that a maximum lung distance inside the treatment field of 2-2.5 cm predicts a risk of pulmonary morbidity of about 1% for breast radiotherapy using a two-field tangential pair technique [69]. This seems to correlate well with the clinical data available.

Use of locoregional fields for nodal irradiation is also consistently associated with an increase in pulmonary side-effects, which may reflect the increased amount of lung irradiated. The use of chemotherapy is variably reported as increasing the risk of lung toxicity, and this seems to be related to the type, dose and timing in relation to the radiotherapy. Volume of irradiated lung, nodal fields, and use of chemotherapy are discussed in the following reports from the literature.

Evidence of radiation-induced pulmonary toxicity from clinical data

A retrospective study reviewed the records of 613 patients irradiated for breast cancer who had been followed up for more than 6 months [70]. Overall, radiation pneumonitis developed in 15 (2.4%) patients, of which 12 had complete resolution of symptoms and three had persistent shortness of breath (follow-up times for these patients were not specified). Median onset of radiation pneumonitis was 3 months. Radiation pneumonitis developed in 4.1% of patients receiving nodal irradiation compared with only 0.9% of those treated with breast radiotherapy alone. Multivariate analysis also confirmed locoregional irradiation as a risk factor for pneumonitis. Chemotherapy increased the risk of lung toxicity on univariate analysis, but this was lost on multivariate analysis. There was also a non-significant trend for increasing radiation pneumonitis, as the average of the superior and inferior mid-lung distance (ALD) measured on the lateral simulator field increased. For ALD values of below 2 cm, below 3 cm, or above 3 cm, the rate of pneumonitis increased from 4-6% and 14%, respectively.

Another retrospective study of 1624 breast radiotherapy patients gave similar results with 17 (1%) developing radiation pneumonitis [71]. Five of these patients required outpatient steroid treatment, but all patients had complete resolution of pulmonary symptoms. Median onset of radiation pneumonitis was 7 weeks. Three per cent (11/328) of patients treated with chemotherapy and a three-field technique developed pneumonitis, compared with only 0.5% (6/1296) of all other patients. When the chemotherapy was given concomitantly with three-field radiotherapy, the incidence increased to 8.8% (8/92). Five of the 17 patients had permanent scarring on chest radiograph, but no patients had late or persistent pulmonary problems.

Because of variation in the clinical definition of radiation pneumonitis, pulmonary function tests have been used to try and quantify possible pulmonary toxicity. An example is a study of 110 breast and lymphoma patients who had single photon emission computed tomography perfusion and ventilation scans, and CT scans, before and at 3, 18 and 48 months after radiotherapy [66]. For all patients, a partial recovery from early local perfusion, ventilation and density changes was seen between 3 and 18 months after radiotherapy. After 18 months, local lung function did not improve (only lymphoma patients had scans at 48 months). The authors state that these findings are in keeping with histological reports of radiation-induced lung injury.

In summary, published research on radiation-induced lung toxicity suggests that pneumonitis rarely causes a clinical problem if modern radiotherapy techniques are used, and the volume of lung irradiated is limited. Radiation pneumonitis may be observed in the 6 months after radiotherapy, but is usually mild, rarely requires steroid treatment and completely resolves in most patients. It is seen in less than 1% of patients receiving breast only radiotherapy, but the incidence seems to increase with nodal irradiation, particularly when chemotherapy is given concomitantly. Late pulmonary fibrosis is uncommon, and is usually identified radiologically in asymptomatic patients. Few data are available on the long-term consequences of radiation-induced pulmonary fibrosis from breast radiotherapy, suggesting that it rarely causes a clinical problem. Therefore, future investigations of lung changes after breast radiotherapy only are more relevant for normal tissue studies rather than clinical care. However, pulmonary toxicity must be considered when using locoregional radiation for locally advanced tumours, especially if chemotherapy is also given. In this situation, the use of intensity-modulated radiotherapy may be considered to reduce morbidity, while maximising chance of cure.

Conclusions

Breast cosmesis is an important issue for patients, and the oncologist should consider the effect of radiotherapy dose, fractionation, homogeneity and concurrent systemic treatment on this outcome. In addition, late cardiac morbidity is an important issue, especially for good prognostic groups with early breast cancer or DCIS, who will live with the late sequelae of treatment. Pulmonary toxicity is uncommon, but may be more relevant for locoregional breast radiotherapy. A knowledge of normal tissue side-effects thus enables the oncologist to advise treatment on the
basis of an individual’s likelihood of risk and benefit (i.e. application of the therapeutic ratio). More advanced radiotherapy techniques, such as intensity-modulated radiotherapy and conformal partial breast irradiation, may improve this therapeutic ratio.

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Overview

Reduction of Radiotherapy-induced Late Complications in Early Breast Cancer: The Role of Intensity-modulated Radiation Therapy and Partial Breast Irradiation

Part II — Radiotherapy Strategies to Reduce Radiation-induced Late Effects

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ABSTRACT:
Radiotherapy after conservation surgery has been proven to decrease local relapse and death from breast cancer, and is now firmly established in the management of early breast carcinoma. Currently, the challenge is to optimise the therapeutic ratio by minimising treatment-related morbidity, while maintaining or improving local control and survival. The second part of this review examines the role of two approaches: intensity-modulated radiation therapy (IMRT) and partial breast irradiation, as means of improving the therapeutic ratio. Discussion of IMRT includes both inverse- and forward-planned methods: the breast usually requires minimal modulation to improve dose homogeneity, and therefore lends itself to simpler forward-planned IMRT techniques; whereas inverse-planned IMRT may be useful in selected cases. There are many dosimetry studies reporting the superiority of IMRT over conventional breast radiotherapy, but there is still a paucity of clinical data regarding patient benefit from these techniques. A critical literature review of clinical partial breast radiotherapy studies focuses on the influence of irradiated breast volume, dose and fractionation, and patient selection on normal tissue side-effects and local control. Clinical reports of partial breast irradiation show several encouraging, but some concerning results about local recurrence rates. Therefore, mature results from randomised trials comparing partial breast irradiation with whole-breast radiotherapy are required. Accurate localisation of the tumour bed and application of appropriate clinical target volumes and planning target volumes are discussed in detail, as these concepts are fundamental for partial breast irradiation. Coles, C. E. et al. (2005). Clinical Oncology 17, 98-110

Keywords: Breast cancer, IMRT, partial breast irradiation

Introduction

What are the Current Problems with Breast Radiotherapy?

As discussed in Part 1 of this review, breast radiotherapy is challenging, as the anatomy and surrounding structures make this an inherently difficult site to irradiate in a homogeneous manner. It has a complex three-dimensional shape, which may have been modified further by surgery, and it is located at the body-air interface. There are also important organs at risk (OARs) in close proximity, such as the lungs and heart (in the case of left-sided tumours). Single plane two-dimensional radiotherapy breast plans can lead to substantial dose inhomogeneities, particularly in women with larger breasts [1]. An inhomogenous dose may lead to increased normal tissue side-effects and poor cosmetic results, which can cause significant psychological morbidity for patients [2]. The tumour bed is considered to be the site at highest risk of tumour recurrence, but conventional 'clinical' methods of localisation are inaccurate, which may affect local control. Thus, the aim of this review is to discuss how intensity-modulated radiotherapy (IMRT) and partial breast
irradiation may improve the therapeutic ratio for patients with early breast cancer after conservation surgery.

Methods

This review is based on Medline and PubMed literature searches using the key words 'breast neoplasms', 'radiation therapy', 'intensity-modulated radiotherapy' and 'partial breast irradiation', and the authors' clinical experience.

Intensity-modulated Radiotherapy

Intensity-modulated radiotherapy (IMRT) describes the situation in which the radiation fluence varies across the beam. The major value of IMRT for breast radiotherapy is reduction of dose inhomogeneity within the target volume. A secondary advantage is the reduction of high-dose irradiation to some normal tissues. Three-dimensional radiotherapy planning and IMRT techniques have been developed with the aim of improving dose homogeneity to the breast and reducing normal tissue side-effects. Its clinical use in breast radiotherapy, however, is still limited. Several methods of intensity modulation will now be discussed.

Intensity Modulation Using Physical Compensators

The concept of IMRT is not new: wedges and tissue compensators are both examples of techniques that alter radiation fluence, and have been used for many years. Initial IMRT dosimetry studies compared the use of metal compensators with conventional tangential field radiotherapy. The studies showed improved dose homogeneity with the former method [3,4]. One institution has developed a compensator library, whereby the most appropriate compensator is selected for the patient after analysis of their breast dose-volume histogram [5]. About 50% of patients were treated with compensators (46% from the library and 4% with individual compensators). The compensators reduced the variation in dose distribution in all compared with standard tangential plans, and the system was reported to be simple and reliable in practice.

Compensators and multileaf collimator (MLC)-based IMRT have also been directly compared with conventional breast radiotherapy. It was shown that all intensity modulation strategies produced improved dose homogeneity compared with standard techniques, but preparation and delivery of the MLC-based IMRT plans took significantly longer than conventional or physical compensator methods [6-8]. However, the disadvantages of metal compensators are the time taken for production and the physical handling necessary for the radiographers. In addition, the last few years have seen improvements in the time taken to plan and treat with IMRT (see discussion: forward-planned IMRT).

Inverse-planned Breast Intensity-modulated Radiotherapy

Inverse-planned radiotherapy describes the technique whereby the clinician selects the required dose to the target and states dose limits to the surrounding OARs. A computer algorithm then creates a fluence map for the required dose distribution, which divides each field into a number of segments. This has the unique ability of delivering radiation dose to a concave volume [9]. These field segments can be delivered by either tomotherapy techniques or by MLC methods ('step and shoot' or dynamic).

Several studies have compared inverse-planned IMRT with standard tangential field radiotherapy for breast cancer [6,10-15]. All reported improvement in breast homogeneity and reduction of high-dose irradiation of surrounding OAR, such as the heart and ipsilateral lung. However, the multiple beams usually necessary for the intensity modulation could result in a substantial volume of normal tissue receiving a low radiation dose [14,15]. This may have implications for the development of second radiation-induced malignancies, particularly in young women with low-risk breast cancer or those with predisposing genes. In addition, inverse-planned IMRT is still considerably more time consuming than standard breast radiotherapy planning. Therefore, this technology may be best reserved, at present, for specific cases such as bilateral breast cancer, treatment of the internal mammary nodes in addition to the breast and patients with pectus excavatum. Such patients have been studied with inverse-planned IMRT, and the dosimetry has been found to be superior to conventional breast radiotherapy techniques [15].

Forward-planned Breast Intensity-modulated Radiotherapy

Forward-planned IMRT is a relatively simple method of IMRT, which does not require an inverse-planning computer. Smaller radiotherapy fields are added to the main treatment fields to improve dose inhomogeneities produced by conventional two-dimensional breast radiotherapy. This can be achieved with standard rectangular fields, or shaped fields using an MLC. This simple technique can, therefore, be implemented without the need for complex technology, and treatment delivery time is similar to standard breast radiotherapy if field autosequencing is used. In addition, the quality assurance for forward-planned IMRT is usually much less time-consuming than inverse-planned IMRT. Forward-planned IMRT lends itself to breast radiotherapy, as 80–90% of the treatment can be delivered using standard tangential fields and only a small amount of modulation is required. Several techniques will be discussed, which consist of slightly different methods.

Donovan et al. [16] used calibrated intensity data from portal imaging data to calculate radiological thickness maps for 14 patients in a planning study. A pseudo-CT outline set was derived from this information and used to create an
ideal intensity-modulated beam map. The beams were implemented using multiple static fields added to standard-wedged tangential fields. Reduction of the high-dose regions of the irradiated volume was achieved in 12 of the 14 patients.

van Asselen et al. [17] used the equivalent path length map obtained from raytracing through CT data sets from five patients to create multiple static fields with four intensity steps. Dose inhomogeneity was improved in four out of five patients, and the mean lung dose was reduced by 10%. Lo et al. [18] created static MLC beam segments from radiological thickness maps based on digitally reconstructed breast images. This planning study of 20 patients showed that the range of 'hot spots' was reduced from 7–22% to 7–15% with the IMRT method.

Several investigators have used the beam's eye view of the projected isodoses for the tangential fields to create multiple static fields to shield the area of higher dose [19–22]. Kestin et al. [19] displayed five isodose surfaces as three-dimensional objects in 5% increments between 100 and 120%. Auto-blocking was used to create an aperture to conform to a particular isodose surface. Zackrisson et al. [20] described a similar technique, but the MLCs were moved manually to cover the hot spots, and typically only one extra modulated field was added to each tangent [20]. Richmond et al. [22] used the same method as Zackrisson et al. [20], and found that the mean percentage volume receiving over 107% of the planning target volume (PTV) was 5.3% and 19.8% for the MLC technique and standard technique, respectively [22]. Coles et al. [21] also developed a manual method of moving the MLC leaves using three-dimensional planning data from an optical imaging device. The resulting dose distribution could be recalculated after addition of each segment, allowing further segments to be added if needed (Figs. 1 and 2). All methods reported improvements in dose homogeneity throughout the breast.

Another technique has been developed by Chui et al. [23], which used a series of pencil beams to model the required intensity modulation. For each beam, a grid of pencil beam segments was created, and the dose to the midpoint of each pencil beam segment in the open field was calculated. The optimum intensity for each pencil beam was proportional to the inverse of the midpoint dose. Fifteen patients with left-side breast cancer were planned with a standard-wedged pair technique, inverse-planned IMRT and this method of forward-planned IMRT. The IMRT techniques were found to be superior to the standard treatment: both methods produced a more homogenous dose to the breast and reduced the dose to the heart, ipsilateral lung and contralateral breast. The planning and treatment time for forward-planned IMRT, however, was significantly quicker than the inverse-planned technique.

Breast Intensity-modulated Radiotherapy and Clinical Outcome

IMRT has evolved rapidly over the last few years, and most papers concerning this subject report dosimetric analysis as

![Fig. 2 — A comparison of the differential dose-volume histograms for the standard and intensity-modulated radiotherapy (IMRT) breast plans displayed in Fig. 3. The IMRT plan is superior, as the peak is sharper and shifted to the left.](image-url)
opposed to clinical outcome. Early clinical experience of 10 patients with breast cancer treated with IMRT using multiple static fields showed minimal or no acute skin reactions [19]. The same institution later reported the cosmetic results at 12 months of 95 patients treated with IMRT [24]. The cosmetic outcome was rated as excellent or good in 94 patients (99%), and no telangiectasia, significant fibrosis or persistent breast pain was noted.

To date, only one randomised-controlled trial (RCT) has investigated late normal tissue side-effects [25]. This was carried out at the Royal Marsden Hospital, UK, and consisted of 305 patients with early breast cancer. Women with larger breasts were specifically selected for the trial on the basis that they would have the greatest dose inhomogeneities. They were randomised to either standard radiotherapy or forward-planned IMRT, using either a metal compensator or multiple static fields. The primary end point was breast appearance after radiotherapy, measured with serial photographs. Interim analysis was completed in September 2002. A change in breast appearance was scored in 60/116 patients (52%) allocated standard two-dimensional treatment and 42/117 (36%) patients allocated IMRT (P = 0.05). A further RCT investigating the clinical relevance of IMRT for women with all breast sizes is under way at Addenbrooke’s Oncology Centre, Cambridge. Two confirmatory trials would provide the impetus to adopt IMRT for breast cancer patients as standard practice in the UK with likely benefits for many women.

Partial Breast Irradiation

An alternative strategy to minimise irradiation of OAR, such as the heart and lungs, is to only irradiate part of the breast. The planned radiotherapy volume is centred on the position of the excised tumour, and this requires accurate localisation of the tumour bed. The rationale for partial breast irradiation and the reported studies, methods of tumour localisation and the concept of breast radiotherapy target volumes will now be discussed.

Rationale for Partial Breast Irradiation and Reported Studies

Breast cancer multifocality has been studied in a group of mastectomy patients who would have been eligible for breast-conservation surgery [26]. This pathological study showed that the density of tumour foci decreased with distance from the reference tumour. For invasive breast tumours less than or equal to 2 cm, 28% had non-invasive foci at a distance of greater than 2 cm from the reference tumour, and 14% had invasive tumour foci at the same distance. Randomised trials of breast conservation, with or without radiotherapy, have also shown that tumour recurrences usually occur close to the site of the original tumour. The NSABP B-06 trial reported that 86% of local recurrences were within or close to the reference quadrant [27]. The Milan trial had similar findings, with 79% of recurrences occurring at or close to the original tumour site [28].

These findings have raised the question whether whole-breast radiotherapy is necessary for all women with breast cancer after conservation surgery, or whether just part of the breast surrounding the tumour bed could be targeted. This concept of partial breast radiotherapy is attractive, as it is likely to reduce toxicity, owing to a smaller volume of normal tissue irradiated. Clearly, this strategy will only improve the therapeutic ratio if normal tissue side-effects are reduced while maintaining equivalent or better local control. Thus, it is essential that the tumour bed is localised accurately and attention is paid to radiotherapy volumes (see later discussion: clinical target volume [CTV] and PTV). One step further is to postulate that reducing the breast-tissue volume requiring a tumourcidal radiation dose may allow use of larger radiation doses per fraction (i.e. accelerating overall treatment time) without additional normal tissue toxicity [29]. The potential advantages of accelerated partial breast irradiation can be divided into health economic, patient satisfaction and radiobiological issues. First, a substantial reduction in the number of radiotherapy fractions would be welcomed by institutions, as breast irradiation constitutes a significant proportion of the workload (30% in the UK). This would positively affect radiotherapy waiting lists. Second, a shorter overall treatment time is more attractive to patients, and is particularly important in remote areas, where patients may opt for mastectomy rather than travel long distances over a period of weeks for radiotherapy [30]. Finally, there is emerging evidence that the alpha/beta for breast tumours is about 4 Gy, which implies that local control may improve with a higher dose per fraction [31]. In addition, local radiotherapy could be completed before systemic therapy without significant delay of either treatment.

To date, there is a paucity of data relating to the normal tissue consequences of partial breast irradiation. Over a decade ago, Emami et al. [32] stated in his seminal paper that: ‘there is a critical need for more accurate information about the tolerance of normal tissue to radiation. This is not only related to the time-dose parameters, but specifically to the partial volumes of normal tissue receiving variable dose levels’. Unfortunately, this extensive literature review did not include any information specifically pertaining to the breast tissue, because whole-breast radiotherapy was (and still is) the standard treatment. Probably, the best evidence available is from the EORTC ‘boost versus no boost’ randomised trial, which investigated the effect of a boost to the tumour bed in addition to whole-breast radiotherapy. This showed that a boost volume of over 200 cm3 decreased the probability of an excellent or good global cosmetic result in the univariate analysis, but significance was not retained in the multivariate model [33].

A number of studies have investigated the effect of partial breast irradiation, and these can be divided into brachytherapy, intraoperative radiotherapy and external beam techniques. A discussion of these studies follows, with particular attention to the effect on normal tissue side-effects and local control, of irradiated breast volume, dose
and fractionation and patient selection (where this information is available).

Brachytherapy Techniques

A series of 27 patients at Guy’s Hospital in the UK were treated with a low-dose-rate (LDR) iodine implant to the tumour bed as sole radiation treatment [34]. The surgery consisted of tumourectomy with no attempt to achieve wide excision. A rigid implant was inserted at this time, with the aim of achieving a 2 cm margin of normal tissue around the tumour bed. The dose delivered was 55 Gy to the 85% isodose continuously over 5 days. After 6 years median follow-up, local recurrence was apparent in six patients (37%), which compared unfavourably with historical controls. None of the patients developed fibrosis, but one patient developed telangiectasia at the site of a superficially placed iodine wire. It was concluded that this was an ineffective method of radiotherapy treatment. However, 15 patients had positive margins and 12 patients were node positive, suggesting that inadequate surgery and unsuitable patient selection contributed to the outcome.

Perera et al. [35] originally reported a series of 39 patients who were treated with high-dose-rate (HDR) brachytherapy only after conservation surgery. The total dose was 37.2 Gy delivered in 10 fractions, twice daily over 5–7 days. The median volume encompassed by the 37.2 Gy isodose shell was 30.35 cm³ (range: 9.6–100.8 cm³). After a median follow-up of 20 months, one patient had recurred, and was salvaged with further surgery and external beam radiotherapy. Patient-rated satisfaction was high, but four cases of fat necrosis were noted. An update of the same series has recently been published at a median follow-up of 91 months [36]. They reported a total of six recurrences (16%), which is greater than expected for whole-breast radiotherapy after breast-conservation surgery. Four recurrences were outside the treated volume. An accompanying editorial has suggested that these results may be due to a sub-optimal technique and less than ideal set of patients, as three patients had an extensive intraductal component (EIC), six had positive lymph nodes, two had unknown nodal status, and 12 had less than 2 mm margins [30]. In addition, the dose was prescribed to encompass the tumour bed without a margin for sub-clinical spread, resulting in a small median implant volume with no allowance for CTV.

Other brachytherapy studies have reported more favourable results. Vicini et al. [37] at the William Beaumont Hospital in the USA, used LDR iodine-125 implant as sole radiotherapy treatment for 60 women [37]. A total of 50 Gy was delivered over 96 h to the surgical bed plus a 2 cm margin. All 19 patients followed up for a minimum of 24 months after treatment were noted to have good to excellent cosmetic results. It was reported that 51 patients had obtained their 6–12 month follow-up mammogram, and no local recurrences were noted at this early stage. The patient characteristics were different as EIC, infiltrating lobular features, young age and node positivity (from 1995) were all excluded from this treatment. In addition, the negative margins required were equal to or more than 2 mm. This institution has also reported its experience of HDR brachytherapy (32 Gy in 8 fractions twice daily over 4 days) in 37 patients; the patient selection criteria remained stringent [38]. There was one breast recurrence after a median follow-up of 31 months, and cosmetic outcome was reported as good or excellent in all patients. A more recent report of 190 patients receiving either LDR or HDR brachytherapy at William Beaumont showed a 5-year actuarial total recurrence rate of 1.2% at a median follow-up of 65 months [30].

King et al. [39] carried out a phase I/II trial of either LDR or HDR brachytherapy in a total of 50 patients (51 breasts). A dose of either 45 Gy continuously over 4 days or 32 Gy in 8 fractions, twice daily over 4 days, was given to the surgical bed (segmental mastectomy) with a 2–3 cm margin. Patient eligibility criteria included tumour 4 cm or less in diameter, negative inked surgical margins and no more than three positive axillary nodes. After a median of 75 months follow-up, there was one in-field recurrence, and grade II toxicities and cosmetic scores were similar to whole-breast radiotherapy case-controls.

Arthur et al. [40] treated a group of 44 patients with partial breast brachytherapy (13 LDR: 45 Gy with a dose rate of 0.5 Gy per h and 31 HDR: 34 Gy in 10 fractions over 5 days). The median implant volume for this institution has been reported to be 190 cm³ (range: 71–510 cm³) [30]. Patient selection criteria were similar to those reported by King et al. [39], but later node-positive patients were excluded. After a median follow-up of 42 months, all patients remained locally controlled. The overall rate of good/excellent cosmetic outcome was 80%, but both LDR brachytherapy and subsequent doxorubicin treatment were significant predictors of an unfavourable cosmetic result on univariate analysis.

Wazer et al. [41] reported an HDR brachytherapy technique as single radiotherapy modality in 32 women followed up for a median of 33 months [41]. Selection criteria were similar to those reported by King et al. [39], and dose and fractionation was the same as that by Arthur et al. [40]. The target volume was defined as the surgical cavity plus a 2 cm margin. There was a 33% incidence of grade 3–4 subcutaneous toxicity, which appeared to be related to the implant volume. One case of ipsilateral breast tumour recurrence was diagnosed 23 months after HDR brachytherapy. This failure seemed to be a new primary tumour, because it was histologically distinct from the initial tumour, and was located 9 cm from the initial tumour bed and 3 cm from the edge of the implant volume.

Polgar et al. [42] treated 45 patients with HDR brachytherapy within a phase I–II trial. Eligibility criteria were tumour size 2 cm or less in diameter, clear resection margins, N0 or pN0-1a, less than grade 3. Exclusion criteria were EIC and invasive lobular carcinoma. Seven fractions of either 4.33 Gy (n = 8) or 5.2 Gy (n = 37) were given over 4 days, treating the tumour bed with a 2 cm margin. After a median follow-up of 53 months, the local
Reduction of Radiotherapy-Induced Late Complications

Intra-operative Radiotherapy Techniques

The technique of intra-operative radiotherapy using a portable electron beam-driven device has the advantage of delivering partial-breast irradiation at the time of surgery and avoiding outpatient visits for external beam or HDR brachytherapy. It has the disadvantage, however, that the definitive histological resection margins are unknown at the time of irradiation [45]. Veronesi et al. [46] have considerable experience of using ELIOT (electron intra-operative therapy), which consists of a mobile linear accelerator with a robotic arm. A single fraction of radiotherapy is given with a perspex applicator using 3–9 MeV electrons. The chest wall is shielded with an aluminium–lead disc, and the skin is stretched out of the radiation field. The target volume consisted of the surgical bed plus a 1–3 cm margin. A series of 86 women have been treated with a single fraction of 17–21 Gy, and has been well accepted by the patients. With a reported mean follow-up of 8 months, it is not possible to comment on late normal tissue side-effects and local control. An ongoing trial in Milan has randomised either whole breast radiotherapy (60 Gy) or ELIOT (21 Gy) after quadrantectomy.

An alternative intraoperative radiotherapy device is the Intra-beam, a portable device that delivers 50 kV photons [45]. Pilot studies of intraoperative targeted radiotherapy (Targit) in the UK, USA, Europe and Australia have treated a total of 185 patients. In most of them, whole-breast radiotherapy was given, and Targit replaced the boost to the tumour bed. At a median follow-up of 22 months, there have been two recurrences and satisfactory cosmetic results. A multicentre, randomised trial is currently underway, which randomises breast conservation patients to whole-breast radiotherapy or Targit (20 Gy to the surface of the applicator, which falls to 5 Gy at 1 cm) [47]. Individual centres can add external beam radiotherapy to those patients deemed as ‘high risk’.

External Beam Radiotherapy Techniques

An early trial randomised 708 breast-conservation patients to limited-field radiotherapy (LF) to the tumour bed or to wide-field radiotherapy (WF) to the whole breast and regional nodes [48]. LF technique consisted of 40–42.5 Gy in 8 fractions over 10 days using 3–14 MeV electrons to an average field size of 8 cm by 6 cm. WF consisted of 40 Gy in 15 fractions over 21 days. Marked fibrosis was seen in 14% of patients receiving LF compared with 5% of patients receiving WF. The overall survival was 72.7% and 71.2% for the LF and WF groups, respectively. The actuarial breast recurrence rate (first event) was 15% (LF) compared with 11% (WF) for infiltrating ductal carcinoma, whereas, for infiltrating lobular carcinoma, the recurrence rate was 34% (LF) compared with 8% (WF). A high actual recurrence rate of 21% (LF) and 14% (WF) was also found for EIC. Even when the lobular carcinoma and EIC were excluded from the analysis, there was still a worse recurrence rate in the LF group. This may have been due to a geographical tumour miss in the LF treatment arm, as radiotherapy planning was based on clinical assessment rather than using specific imaging techniques. This indicates an important potential problem with partial-breast irradiation. In addition, other patient characteristics, such as node positivity (nodal status was unknown in all) and positive margins (present in 56%) may have contributed to the higher recurrence rate in the LF group.

More recently, the William Beaumont Hospital, USA, have used a CT planned three-dimensional conformal...
(3D-CRT) technique for partial-breast irradiation [49]. The same stringent patient selection criteria were used as per their brachytherapy studies. The prescribed dose was 34 Gy in six patients and 38.5 Gy in 25 patients, delivered in 10 fractions twice daily over 5 consecutive days. The median volume for CTV and PTV were 112 cm$^3$ and 240 cm$^3$, respectively [50]. Cosmetic results were rated as good/excellent in all patients at a median follow-up of 10 months. Potential advantages of this approach over brachytherapy are elimination of a second surgical procedure and improved dose homogeneity within the target, which may improve cosmesis and decrease the risk of fat necrosis. Possible disadvantages of 3D-CRT are that additional margins must be added to the target to account for patient movement and organ motion. This may result in a larger breast volume irradiated than with brachytherapy, which could affect the cosmetic result.

The Radiotherapy Oncology Group of the American College of Radiology has recently completed accrual for a phase I/II study (RTOG 0319) testing the feasibility and efficacy of 3-DCRT confined to the lumpectomy cavity in women with low-risk early breast cancer. This study was developed by the William Beaumont Group and consisted of 10 fractions of 3.85 Gy over 5 days to the tumour bed plus identical margins, as previously discussed. The protocol states that, ideally, less than 25% of the whole breast should receive the prescribed dose. A proposed NSABP/RTOG randomised phase III trial using 10 fractions of whole-breast radiotherapy as the control arm, with the same phase II dose and fractionation schedule as RTOG 0319, is due to open in the near future. Participating centres will be able to choose between interstitial brachytherapy, MammoSite brachytherapy and three-dimensional conformal external beam radiotherapy for partial breast irradiation. A proposed RCT testing IMRT and partial-breast radiotherapy after breast-conservation surgery for early breast cancer (IMPORT) is currently being developed for external beam irradiation techniques. Some trials are needed to give more information regarding local recurrence rates. Clearly, mature data from randomised trials are needed to give more information regarding local recurrence and late normal tissue morbidity. Ultimately, we need answers to the following questions: first, which patient groups will benefit? Second, what is the optimal treatment volume in terms of local control and cosmetic result? Third, what is the optimal dose/fractionation regimen? It is likely that many institutions will opt for an external beam technique for delivering partial breast irradiation because of availability and familiarity of the equipment. In addition, it has been shown in a modelling exercise, that brachytherapy seems to be significantly more expensive than teletherapy [51]. Accurate localisation of the tumour cavity, and assessment of radiotherapy margins for external beam irradiation techniques are therefore essential for this approach. These will now be discussed in more detail.

**Localisation of the Post-operative Breast Tumour Cavity**

Planning of the radiotherapy boost CTV to the tumour bed requires an assessment of the location of the postoperative tumour cavity. In general, this is done using a combination of information: preoperative radiological imaging, surgical annotation, clinical palpation of the surgical defect and position of the breast scar, and patients' recollection of the site of the mass. In the past, the position of the scar has been relied on heavily to assist with locating the tumour bed. However, breast surgical technique has changed, with the scar frequently being placed some distance from the site of the tumour in order to achieve a better cosmetic result. This has prompted some institutes to compare traditional 'clinical' methods of boost planning with various imaging techniques.

**Surgical Clips for Localisation of the Tumour Cavity**

Several studies have reported the superiority of using surgical clips to locate the tumour bed compared with clinical methods [52–58]. All studies showed that the tumour cavity would have been under-dosed using traditional planning techniques. The clinical method could also result in a substantial volume of normal tissue being irradiated unnecessarily [58]. In addition, it was reported that medi ally and laterally located tumour cavity could also be missed by the tangential fields [54,57]. Detailed descriptions of the planning techniques using surgical clips have been reported using CT scanning and simulator films [59,60]. A consistent policy of clip placement at the time of surgery is necessary. An example of this is to place a clip at the medial, lateral, superior and inferior extent of the tumour bed, and a fifth clip at the deepest extent of the tumour bed in the direction of the surgical excision [59]. There is the potential risk of surgical clips becoming dislodged and tracking away from the tumour bed. There have been no specific studies investigating this issue; anecdotally it seems to be a relatively rare occurrence [52].

**Ultrasound for Localisation of the Tumour Cavity**

Breast ultrasonography has also been exploited as a method of localising the tumour bed for radiotherapy planning. One study compared clinical methods with ultrasound localisation, and found that the full extent of the tumour cavity was underestimated in 87% of women, and the chest wall depth was incorrectly estimated in 90% using traditional methods [61]. Another study reached similar conclusions: conventional electron boost planning resulted in 55% of patients having areas of undertreatment and 20% of patients received significant overtreatment [62].

The location and appearance of the tumour cavity has been found to be highly reproducible on repeated scans, with a mean depth difference between scans of 2 mm [63].
There is some discrepancy whether the ability to localise the tumour cavity is more difficult with increasing time from surgery. This is important to consider with many women receiving up to 6 months of adjuvant chemotherapy before irradiation and, in those who do not, there is the current UK problem of long waiting times for radiotherapy treatment. One study reported that it was difficult to visualise the cavity after 8 weeks from surgery [61]. This view was reflected by another study, which found that the optimal time for radiotherapy planning was within 60 days after surgery [64]. Other reports contradict this view, stating that the tumour cavity can be seen many months after surgery [63] (personal communication, Dr R. Sinnatamby, Consultant Radiologist).

All published studies have used two-dimensional ultrasound scanning techniques. This is perfectly adequate for placement of a direct anterior electron boost field, as the dimensions of the cavity with a suitable margin can be marked on the patient’s skin, and the electron energy can be selected from measurement of the cavity depth. However, other radiotherapy techniques, such as a brachytherapy interstitial implant or a concomitant boost to the tumour bed using IMRT, require more detailed three-dimensional information. This can be achieved by using a combination of ultrasound examination, and placement of radio-opaque skin markers and measurement of cavity depth, followed by CT scanning in the same position [65]. Another new method is to use a three-dimensional ultrasound scanning technique (currently under investigation at Addenbrooke’s Hospital, Cambridge). This requires spatial registration of the ultrasound scan with fixed points around the breast using a camera system. A three-dimensional volume of the tumour cavity can be produced, which is then imported into the radiotherapy planning system (Fig. 3).

Magnetic Resonance Imaging for Localisation of the Tumour Cavity
Magnetic resonance provides excellent definition of the breast and surrounding tissues. Its use in breast radiotherapy planning, however, has been limited. This has largely been due to a combination of limited magnetic resonance resources and the difficulty of scanning the patient in the treatment position. The Bristol Haematology and Oncology Centre Hospital have experience in the use of a low-field open magnetic resonance scanner for breast radiotherapy planning, which allows imaging in the treatment position (Fig. 4) [66]. This group has shown that, with magnetic resonance imaging, the conventional breast radiotherapy planning of the boost, and sometimes the tangential fields, can result in under-treatment of the target. In addition, greater sparing of surrounding OAR can be achieved with magnetic resonance-assisted planning. Potential problems with magnetic resonance radiotherapy planning include image distortion and co-registration with radiotherapy planning systems.

Computed Tomography for Localisation of the Tumour Bed
Despite the improvement with computed-tomography (CT) scanning for breast-radiotherapy planning, it is still often difficult to distinguish glandular breast tissue from the surrounding anatomy, without the additional guidance of

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Fig. 3 – A three-dimensional ultrasound technique to define the breast tumour bed. It uses a freehand system with an optical sensor to continuously track the position of the hand-held probe. The image on the left shows one of many two-dimensional B-scans obtained by sweeping the probe over the tumour bed. Manual segmentation of representative B-scans is carried out, and the image is reconstructed in three-dimension (centre image). The ultrasound three-dimensional data set is co-registered to the planning computed tomography and imported into the radiotherapy planning system (right image). The red outlines show the tumour bed, the orange outlines represent the contour of the breast and the green rectangle is the radiotherapy field. Printed with kind permission from Dr Charlotte Cash and Dr Graham Treece.
surgical clips. Clinically palpating then marking the breast tissue with radio-opaque wire before CT scanning has been shown to be helpful [67]. However, CT alone is inadequate for accurate localisation of the tumour bed, as it is difficult to visualise and varies according to the CT window setting.

### Patient Set-up Errors and Organ Motion: Planning Target Volume

A margin should be added to the breast or tumour bed CTV, which takes into account set-up error and patient movement (including breast swelling and breathing) if external beam irradiation techniques are used [68–70]. This is the planning target volume (PTV). Several studies have used electronic portal imaging devices to quantify the extent of positional errors and patient movement for breast radiotherapy [71–74]. Lirette et al. [72], Fein et al. [73] and Hector et al. [74] calculated a weighted standard deviation of the central breast distance (reflecting movement in the anterior–posterior direction) of 4.5 mm, 4.6 mm and 2.2 mm, respectively, for the systematic component of set-up error. Lirette et al. [72], Fein et al. [73], and van Tienhoven et al. [71] calculated a weighted average standard deviation of 3.9 mm, 6.1 mm and 4.7 mm, respectively, for systematic variation in set-up error for the crano-caudal distance (reflecting movement in the superior–inferior direction). Another study found that a vac-fix immobilisation device was superior to a breast board, as it improved transfer of the planned set-up from the simulator to the treatment unit [75]. It was felt that implementation of the vac-fix device was not justified for standard tangential breast radiotherapy, but may be important for more complex techniques such as IMRT.

It is difficult to determine from the portal imaging studies exactly which part of the displacement was due to set-up error and which was due to patient movement. Hector et al. [74] showed that the average increase in breast volume during treatment was 5%, and this peaked between fractions 5 and 8 and then decreased back below the initial volume. It has been stated that the effects of breathing motion are in general about half the size of the effects of set-up error [76]. Breathing motion may be particularly important in dynamic-MLC IMRT techniques, and a study has shown that dosimetric errors are dependent on the speed of the travelling leaves relative to the speed of the target motion [77]. Certain centres have implemented methods to limit breathing motion, such as gated radiotherapy and breath-holding techniques [78].

One institution, developing 3D-CRT for partial breast irradiation, measured the effect of patient set-up error and breathing motion to establish CTV to PTV margins [49]. This was then tested clinically for adequate coverage of treatment. The CTV-PTV margin for ‘breathing only’ was calculated by measuring the displacement of surgical clips during three types of CT scan: free breathing, breath holding at the end of normal inhalation, and at the end of normal expiration using an active breathing control device. A margin of 5 mm in all directions was subsequently selected to completely account for breast motion during quiet breathing. The combined uncertainty of random patient set-up error and respiratory motion, and the distribution of systematic error across all fields and all patients were measured. This was achieved by measuring the movement of the chest wall/ribs with portal imaging, as a surrogate for the tumour bed. A margin for set-up uncertainties of 5 mm was proposed from these data, producing a total CTV-PTV margin of 10 mm, which was tested in nine patients. Ninety-eight to 100% of the CTV was covered by the 95% isodose surface at the extremes of normal inhalation and exhalation using the ‘breathing only’ margin of 5 mm. The total CTV-PTV margin of 10 mm also seemed to provide coverage for most patients. The authors state that there is still uncertainty regarding the stability of the tumour cavity relative to the chest wall, and that this may vary more in patients with larger breasts. Therefore, slightly larger CTV-PTV margins may be needed in this group of patients.

A slightly different approach has been taken in the recent British Institute of Radiology publication *Geometric uncertainties in radiotherapy treatment planning* [70]. It suggests dividing the CTV-PTV margin into two volumes. The volume enclosing the mean position of the CTV in 90% of cases is called the systematic target volume (STV). The systematic errors (also considered treatment preparation errors) contributing to the CTV-STV volume include clinician’s delineation, phantom transfer (error accumulated by transferring image data from the CT scanner, through the treatment planning system to the linear accelerator), systematic set-up, breathing and treatment planning system beam algorithm. The second volume (STV-PTV) consists of random treatment execution errors that vary between
fractions. These include daily set-up error, organ position and shape, and unblurred beam penumbra width. Mathematical modelling has produced equations that estimate the volume of uncertainty with a given set of errors. A worked example, which assumes correction of systematic errors using portal imaging, suggests total CTV-PTV margins of 21 mm, 17 mm and 24 mm in the anterior–posterior, right–left and superior–inferior directions, respectively. It was noticed that the clinician's delineation error was likely to be the largest single contributor to the required margins.

In summary, the concept of CTV and PTV is widely used for radiotherapy planning in many tumour types. However, it is less commonly used for breast radiotherapy, in which the whole breast is treated and planned clinically using anatomical landmarks. Partial breast radiotherapy using more complex three-dimensional radiotherapy techniques, however, does require the use of this concept to ensure accurate target coverage. The margins for PTV may vary between institutions depending on accuracy of localisation and set-up errors, and may be larger than initially supposed. Further work is required to determine the intra- and inter-clinician variability in target delineation.

**Conclusions**

Despite recent advances in radiation technology, most centres worldwide use basic radiotherapy techniques based on two-dimensional breast data. Incorporating new approaches to breast radiotherapy, such as IMRT and partial breast irradiation, may result in a reduction in morbidity.

These more complex radiotherapy methods will require precise localisation of the tumour bed and application of appropriate margins. On-going and proposed randomised trials will test these concepts, and will need to demonstrate the safety and efficacy of these techniques, and also the cost-effectiveness compared with conventional methods.

**Acknowledgements.** We would like to thank Professor John Yarnold and the IMPORT Trial Management Group for the material pertaining to the proposed IMPORT trial. We would also like to thank Dr Charlotte Cash, Dr Graham Treece and Dr Elisabeth Whipp for the information and figures regarding three-dimensional ultrasound and magnetic resonance imaging techniques, respectively. In addition, we wish to thank Dr Jonathan Coles for his assistance in preparing the figures.
## Appendix 2 – Summary for proposed IMPORT HIGH trial

### Title
Randomised trial testing dose escalation delivered by intensity-modulated radiotherapy in women with higher than average local tumour recurrence risk after breast conservation surgery and appropriate systemic therapy for early breast cancer.

### Aim
To test dose escalation delivered by intensity-modulated radiotherapy after conservation surgery for early breast cancer in women with higher than average local recurrence risk.

### Eligibility criteria

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<th>Inclusion criteria</th>
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<tr>
<td>(i) Age 18 years or older</td>
<td>(i) Mastectomy</td>
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<tr>
<td>(ii) Operable unilateral breast cancer</td>
<td>(ii) Concomitant chemotherapy (sequential therapy allowed).</td>
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<td>(iii) Breast-conserving surgery</td>
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<td>(iv) Histological confirmation of invasive carcinoma</td>
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<td>(v) Complete microscopic resection</td>
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<td>(vi) Requires whole-breast radiotherapy plus boost dose</td>
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<td>(vii) Written informed consent and availability for follow-up.</td>
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### End points
The primary end point is palpable induration in the ipsilateral breast. Secondary end points include other late adverse effects in normal tissues, local tumour control, location of tumour relapse in breast, contralateral primary tumours, regional and distant metastases.

### Sample size
Eight hundred and forty patients will provide 80% power to detect a difference of 7% in palpable induration at 3 years (assuming 20% rate of induration in the control arm, and allowing for 5% rate to loss to follow-up by 3 years).

### Study design
Prospective randomised-controlled clinical trial.

### Radiotherapy

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
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<td>The control arm delivers 23 fractions:</td>
<td>40 Gy in 15 fractions to whole breast volume.</td>
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<td>16 Gy in 8 fractions sequential photon boost to the tumour bed.</td>
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<td>The two test arms deliver 15 fractions:</td>
<td>36 Gy in 15 fractions to low-dose breast volume.</td>
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<td>40 Gy in 15 fractions to standard dose breast volume.</td>
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<td>48 Gy (Test Arm 1) or 53 Gy (Test Arm 2) in 15 fractions concomitant photon boost to the tumour bed.</td>
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### References

REDUCTION OF RADIOTHERAPY-INDUCED LATE COMPLICATIONS


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CLINICAL ONCOLOGY


Quantitative assessment of inter-clinician variability of target volume delineation for medulloblastoma: quality assurance for the SIOP PNET 4 trial protocol

Charlotte E. Coles, Andrew C.F. Hoole, Susan V Harden, Neil G. Burnet, Nicola Twyman, Roger E. Taylor, Rolf D. Kortmann, Michael V. Williams

1. Introduction

The ultimate goal of radical radiotherapy is to improve local control and survival without the legacy of normal tissue complications. Oncologists, therefore, aim to deliver a tumouricidal radiation dose to the target whilst ensuring that surrounding normal tissues receive minimal irradiation. This ethos is of paramount importance in the treatment of children with cancer, as many paediatric tumours are curable, but the immature normal tissues are more susceptible to late radiotherapy complications. Moreover, 'no advantage to any patients for any irradiation of any normal tissue exists' [11].

Modern conformal radiotherapy treatment techniques, which incorporate the use of computed tomography (CT) images for planning, have assisted greatly in the optimisation of the therapeutic ratio. In principle, their application can facilitate reduction in normal tissue toxicity for the same dose, or dose escalation without increasing normal tissue toxicity.

It is essential that the clinical target volume (CTV) is precisely defined to prevent a geographical miss of the tumour. This problem has become more important with conformal radiotherapy where margins may be reduced...
CT planning may present problems for clinicians compared to ‘standard’ radiotherapy. The introduction of previously planned radiotherapy using bony landmarks may be unfamiliar. This is of particular relevance when introducing new radiotherapy trial protocols. The difficulties encountered when learning a new radiotherapy technique are additional to inter-clinician variability in delineating the CTV. It is crucial that these factors are kept to a minimum to facilitate reliable multi-centre trials.

Previous studies have shown that education and training can decrease protocol violation [10,14]. We use the introduction of a new clinical European trial for medulloblastoma, PNET 4, as an example of this process.

The proposed randomised SIOP (International Society of Paediatric Oncology) trial protocol for treatment of medulloblastoma in Europe, PNET 4, recommends conformal planning to the posterior fossa and tumour bed boost, which is a change from the previous PNET 3 study. For further details of the proposed PNET 4 study, see Appendix A. Many UK centres had previously planned the posterior fossa treatment fields using bony landmarks from orthogonal radiographs. Given this change in the process of target definition, it was felt that measures should be taken to ensure the uniform implementation of the new radiotherapy protocol across the country.

This study’s unique achievement was to compare delineation of CTs for a single medulloblastoma case between the majority of specialised consultant paediatric radiation oncologists practising in the UK. There has been a similar medulloblastoma study involving 10 French paediatric radiation oncologists, which demonstrated significant inter-physician variability in producing CTVs [8]. Other studies have investigated inter-observer variability for planning conformal radiotherapy to the prostate [2,3,10], brain [7,15], oesophagus [12,13], head and neck [6,14] and breast [5,9]. In several studies, individual variation in CTV delineation affected tumour control probability and normal tissue complication probability [4,10,15]. This is of particular importance in multi-centre trials where inter-physician variation could be a confounding factor during outcome analysis. Indeed, quality assurance is vital at the start of such trials to minimise this [10,14].

2. Methods

A UK Children’s Cancer Study Group (UKCCSG) meeting was held in Cambridge in September 2001. This was a multi-disciplinary meeting for all those involved in UK paediatric radiotherapy, and invitations were sent to each of the 22 UKCCSG centres, of which 17 sent representatives. All participating radiotherapists received a clinical case summary about a child with medulloblastoma. The information included the history, examination findings, surgical annotation, histology report, reports of the pre- and post-operative magnetic resonance imaging (MRI) scans (axial and sagittal T1 weighted post-gadolinium contrast) of the head and spine, and the proposed PNET 4 trial protocol. The pre-operative appearances are shown in Fig. 1. In addition, the MRI scans and the CT planning scan were enclosed in electronic form.

At the meeting, participants received three lectures covering the treatment of posterior fossa tumours, a review of the medulloblastoma trials and a tutorial on planning posterior fossa volumes. Planning computers were then made available so that all participants were able to outline CTVs, using 5 mm CT slice spacing, for the posterior fossa and the tumour bed boost on their own workstation. Clearly, there are several important aspects of radiotherapy planning for medulloblastoma tumours, such as cribiform plate inclusion, but the emphasis of this study was delineation of the posterior fossa and tumour bed boost. The clinicians performed the delineations alone and there was no facility to review the radiology with a neuro-radiologist during the planning exercise. The variation between the individual CTVs was analysed in order to identify any regions of discrepancy. Quantitative analysis of each CTV for both the posterior fossa and the tumour bed boost was carried out. Volumes were calculated by importing the planning data into a commercial software package, Metris Base 5.0 (Metris NV, Belgium), which allowed interpolation between the outlines by creating a smooth surface over the outlines, thus producing more accurate volumes. Lengths of the CTVs were obtained by measuring the distance between the CT slices on which the most superior and inferior outlines were drawn and account was made for the CT tilt. Variation in the axial plane was analysed by measuring the distance from an arbitrary fixed central point to the edge of the CTV in eight radial directions at 45° intervals (see Fig. 2). This was carried out at representative lower, middle and upper CT slices for the larger posterior fossa volumes and using a single central CT slice for the smaller tumour bed volumes. Metris Base 5.0 software was also used to produce measurements for the centre of gravity.

Fig. 1. Pre-operative MRI scans showing tumour infiltration towards the left internal auditory meatus. The right-sided enhancement shown on the first scan represents CSF, not tumour.
for each CTV. This is described by X, Y and Z co-ordinates which represent where each CTV was positioned in space. The results were analysed using basic quantitative statistics i.e. the mean, range and standard deviation.

3. Results

All 17 clinicians outlined the posterior fossa, but due to time constraints, only 12 clinicians outlined the tumour bed boost. The mean volumes of the CTVs were 198 ml (1 SD of 21 ml) and 12 ml (1 SD of 6 ml), for the posterior fossa and tumour bed boost CTVs, respectively. The mean length for the posterior fossa CTVs was 74 mm (1 SD of 13 mm), and 30 mm (1 SD of 3 mm) for the tumour boost CTV (see Table 1).

The variation of the centre of gravity co-ordinates for the both the posterior fossa and tumour bed boost were demonstrated by comparing each individual’s measurements with the mean centre of gravity co-ordinates (see Figs. 3 and 4). There was more variation in the Y- (medial-lateral) and Z-axes (superior-inferior) than the X- (anterior-posterior) axis.

For the posterior fossa CTVs, the radial measurements showed little variation in the middle CT slice, where the boundaries were well defined by bony landmarks (see Table 2. and Fig. 5). There was much more variation in the upper CT slice, demonstrating the difficulty of defining the superior aspect of the tentorium (see Table 3. and Fig. 5). In addition, there was particular variation in the lower CT slice, which was due to the individual clinicians choosing to either include or omit the post-surgical meningocoele (see Table 4 and Fig. 5). The radial measurements for the tumour bed boost also showed a lack of concordance between clinicians (see Table 5 and Fig. 5).

4. Discussion

This study highlights that even between experts in the field, there is variation between individuals and emphasises the need for highly specific protocol definitions and training to improve uniformity. It is possible that some of the variation was due to clinicians carrying out planning with a strict time limit on an unfamiliar system without their usual support structure.

The major qualitative discrepancy between physicians was the decision whether or not to include the post-surgical meningocoele in the CTV. This should be included to ensure disease control and had been discussed in the preceding lectures but was not explicitly stated in the draft PNET 4 protocol. This instruction was therefore specifically added to the protocol as a result of this study.

In addition to the meningocoele, variation was seen in defining the superior borders of the posterior fossa, where there was a lack of bony landmarks to easily define the volume. A CT planning scan with contrast medium, as used

Table 1

<table>
<thead>
<tr>
<th>Planning target</th>
<th>Mean</th>
<th>Range</th>
<th>One SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior fossa*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTV length (mm)</td>
<td>74</td>
<td>54–109</td>
<td>13</td>
</tr>
<tr>
<td>CTV volume (ml)</td>
<td>198</td>
<td>164–232</td>
<td>21</td>
</tr>
<tr>
<td>Tumour bedb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTV length (mm)</td>
<td>30</td>
<td>25–35</td>
<td>3</td>
</tr>
<tr>
<td>CTV volume (ml)</td>
<td>12</td>
<td>6–24</td>
<td>6</td>
</tr>
</tbody>
</table>

* n = 15 outlining clinicians.

b n = 12 outlining clinicians.
Table 2
Radial measurements from a central point to the edge of the posterior fossa CTV for the middle CT slice

<table>
<thead>
<tr>
<th>Angle</th>
<th>Mean (mm)</th>
<th>Range (mm)</th>
<th>One SD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36</td>
<td>29–44</td>
<td>5</td>
</tr>
<tr>
<td>45</td>
<td>44</td>
<td>41–47</td>
<td>2</td>
</tr>
<tr>
<td>90</td>
<td>52</td>
<td>49–55</td>
<td>2</td>
</tr>
<tr>
<td>135</td>
<td>37</td>
<td>35–38</td>
<td>2</td>
</tr>
<tr>
<td>180</td>
<td>35</td>
<td>32–37</td>
<td>1</td>
</tr>
<tr>
<td>225</td>
<td>35</td>
<td>32–37</td>
<td>1</td>
</tr>
<tr>
<td>270</td>
<td>49</td>
<td>47–52</td>
<td>1</td>
</tr>
<tr>
<td>315</td>
<td>43</td>
<td>40–45</td>
<td>1</td>
</tr>
</tbody>
</table>

In this study, can improve the definition of the tentorium, but this alone does not eliminate the variation between clinicians. In delineating the non-bony borders of the posterior fossa, some experience is helpful. Thus, oncologists who normally plan from orthogonal films may not find identification of the tentorium immediately straightforward. There is no completely robust definition of the apex of the posterior fossa. At the apex, the edge of the tentorium cerebelli forms a wishbone shape, which is visible on axial CT. However, there may be several CT slices on which this wishbone is visible but contains only CSF. Whether this area needs to be included was not explicit in the protocol.

It was also noted that there was considerable variation in the posterior fossa CTV depending on which CT settings were used. Usually ‘brain CT settings’ were used for outlining, as this provided maximum definition between the posterior fossa and the rest of the cerebral cortex. However, if brain settings are used to plan the entire CTV, then the bone encasing the posterior fossa appears thicker as the result of a partial volume effect. This resulted in the volume being underestimated (see Fig. 6). Therefore, a combination of both brain and bone CT settings should be used to plan the posterior fossa optimally.

For planning the tumour boost, none of the clinicians had correctly taken into account the pre-operative extent of the tumour around the brain stem and the left internal auditory meatus (see Fig. 1). This was partly due to ambiguous wording of the draft protocol, which stated that the tumour bed boost should include ‘the tissues which previously surrounded the tumour prior to resection, with a 0.5 cm margin’. Therefore, the tumour bed boost will generally consist of the surgical defect with a 0.5 cm margin. An exception is illustrated by this case, where the tumour had extended to the periphery of the posterior fossa and had been in contact with other tissues. A 0.5 cm margin should be added to this pre-operative extension, but this can be reduced if limited by the bony margins of the posterior fossa. A second reason for all the clinicians underestimating the true extent of the tumour bed boost was the unfamiliar setting in which the planning exercise was carried out. Many of the clinicians stated that they would have reviewed the radiology with a neuro-radiologist prior to outlining and this

Fig. 5. Top left picture shows posterior fossa CTVs for the middle CT slice, top right picture shows posterior fossa CTVs for the upper CT slice, bottom left picture shows posterior fossa CTVs for the lower CT slice, and bottom right picture shows tumour bed CTV for middle the CT slice.
Table 3
Radial measurements from a central point to the edge of the posterior fossa CTV for the upper CT slice

<table>
<thead>
<tr>
<th>Angle</th>
<th>Mean (mm)</th>
<th>Range (mm)</th>
<th>One SD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>25</td>
<td>23–31</td>
<td>2</td>
</tr>
<tr>
<td>45</td>
<td>17</td>
<td>15–22</td>
<td>2</td>
</tr>
<tr>
<td>90</td>
<td>15</td>
<td>13–19</td>
<td>2</td>
</tr>
<tr>
<td>135</td>
<td>21</td>
<td>3–29</td>
<td>3</td>
</tr>
<tr>
<td>180</td>
<td>26</td>
<td>1–37</td>
<td>13</td>
</tr>
<tr>
<td>225</td>
<td>18</td>
<td>1–29</td>
<td>6</td>
</tr>
<tr>
<td>270</td>
<td>13</td>
<td>4–19</td>
<td>4</td>
</tr>
<tr>
<td>315</td>
<td>15</td>
<td>10–19</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 4
Radial measurements from a central point to the edge of the posterior fossa CTV for the lower CT slice

<table>
<thead>
<tr>
<th>Angle</th>
<th>Mean (mm)</th>
<th>Range (mm)</th>
<th>One SD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>29</td>
<td>11–36</td>
<td>7</td>
</tr>
<tr>
<td>45</td>
<td>27</td>
<td>15–37</td>
<td>5</td>
</tr>
<tr>
<td>90</td>
<td>38</td>
<td>35–40</td>
<td>1</td>
</tr>
<tr>
<td>135</td>
<td>20</td>
<td>17–26</td>
<td>2</td>
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<tr>
<td>180</td>
<td>31</td>
<td>28–36</td>
<td>3</td>
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<tr>
<td>225</td>
<td>21</td>
<td>13–28</td>
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<td>270</td>
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<tr>
<td>315</td>
<td>26</td>
<td>13–31</td>
<td>5</td>
</tr>
</tbody>
</table>

The process of ensuring minimal variation in target definition consists of several components. First, this study shows that even after a thorough review of the draft protocol, involving experienced clinicians to plan an actual case resulted in revision and improvement of the protocol. It is important to ensure unambiguous protocols for the planning process, particularly where variation in CTV delineation might be most marked. This is at sites where the anatomical boundaries are less well defined (such as the tentorium) on axial slices, or where opinion about whether or not a region should be included in the boost volume may differ (e.g. the meningocoele). In addition, the treatment of Organs at Risk (OARs) needs to be defined. Due to insufficient time, it was not possible to outline the OARs (eyes, pituitary, inner ear and optic chiasm) as stated in the proposed protocol. However, it is clear that variation in delineation of the posterior fossa can greatly affect the dose to the OARs, in particular the pituitary and inner ear. It is unclear whether the entire internal auditory meatus should be included within the posterior fossa volume, but its inclusion would significantly increase the dose to the cochlea.

Secondly, education and training are essential prior to the introduction of any new radiotherapy treatment technique. This should address both the use of new technology, such as computer planning equipment, and a revision of the relevant anatomy. This would highlight specific potential problems such as the correct selection of CT settings to ensure optimal target delineation.

Thirdly, peer review has an important role in ensuring quality assurance. Peer review of treatment volumes has usually been conducted after the closure of a trial [1]. It is now possible to conduct review of treatment plans early during the course of treatment by electronic image transfer (Taylor and Williams, personal communication, 2002). It should be feasible to develop systems to allow peer review before treatment is actually commenced so as to allow the highest standard of prospective quality assurance.

Fig. 6. Top picture shows the posterior fossa CTV outlined using bone settings. Bottom picture shows the same CTV displayed using brain settings.
5. Conclusion

This study clearly highlighted ambiguities in the draft PNET 4 protocol. As a result, the protocol was amended and improved to take into account the problems demonstrated. The UKCCSG has since officially approved activation of the protocol. We recommend that such dry run planning exercises, in conjunction with education and training, should be implemented before the start of any new radiotherapy trial. Thus, these findings have general applicability for future radiotherapy protocol development.

Acknowledgements


Appendix A. Summary of the SIOP PNET 4 protocol

The randomised trial protocol for treatment of medulloblastoma in Europe, PNET 4, defines the control arm for standard risk medulloblastoma as 23.4 Gy craniospinal radiotherapy with a boost to the posterior fossa to 55.8 Gy using 1.8 Gy daily fractions, plus eight courses of CCNU, cisplatin and vincristine. The experimental arm is a hyperfractionated radiotherapy schedule consisting of 36 Gy to the craniospinal axis, 60 Gy to the posterior fossa and 68 Gy to the tumour bed given in twice daily 1 Gy fractions, followed by the same chemotherapy. The hyperfractionation aims to increase the therapeutic index of the radiotherapy, by delivering a higher biologically effective dose to the tumour whilst maintaining a dose equivalent to standard fractionation for late normal brain tissue effects. This difference depends on assuming that the α/β ratios for tumour and normal tissues are 10 and 2, respectively. The protocol recommends conformal planning to the posterior fossa and tumour bed boost, which is a change from the previous PNET 3 study.