THREE-DIMENSIONAL CONFORMAL VERSUS INTENSITY-MODULATED RADIATION THERAPY PLANNING FOR LEFT BREAST, CHEST WALL AND SUPRACLAVICULAR FOSSA OF CANCER PATIENTS

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by

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DECLARATION OF INDEPENDENT WORK

I, STEPHAN LOOTS, do hereby declare that this project submitted for the degree MASTER of RADIOGRAPHY at the faculty of Health and Environmental Sciences, department of Clinical sciences at the Central University Of Technology, Free State Bloemfontein, is my own independent work that has not been submitted before, to any institution by me or anyone else as part of any qualification.

19/01/2021

Signature of student

Date

Dedicated to my parents:

Rasmus Pieter Loots

and

Loraine Loots

My son keep your father's commandment, and

forsake not your mother's teaching.

Proverbs 6:20

To my wife, Yolandie

And our children Carolie and Stephan –

Thank you.

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Three-dimensional conformal versus intensity-modulated radiation therapy planning for left breast, chest wall and supraclavicular fossa of cancer patients

ABSTRACT

Introduction: The use of radiation therapy has led to the instance where breast cancer now has a favourable prognosis post-surgery. For later stage breast cancer, radiation therapy is performed post-mastectomy. In the Oncology Department, University of the Free State, the use of radiation therapy post-mastectomy is a standard treatment technique and it includes the axillary nodes as well as the supraclavicular nodes, where indicated. The planning technique for radiation therapy has changed with the introduction of Intensity Modulated Radiotherapy (IMRT) for many cancer treatments. In this study, the use of IMRT for breast cancer was compared to 3-dimensional conformal radiation therapy (3D-CRT) for post-mastectomy breast cancer patients that include the supraclavicular fossa on the left-side. The left-side was selected to indicate the dose to the heart specifically. The study questioned how 3D-CRT planning compare with IMRT planning for post mastectomy patients receiving radiation therapy to the left chest wall and supraclavicular fossa.

Aim: The aim of the research study was to compare 3D-CRT- with IMRT treatment planning techniques for the treatment delivery of post-mastectomy, left breast, chest wall and supraclavicular fossa for cancer patients. The objectives were to compare (i) the dose coverage for the planned target volumes (PTV), (ii) clinical target volumes (CTV), (iii) the dose received by organs at risk (OAR) and (vi) the dose volume histograms (DVH) created for each patient's plans.

Methodology: The retrospective study was conducted between January 2019 and June 2020 in the Oncology Department, University of the Free State, after having obtained ethical approval. The study was conducted in four stages: 1) contouring and delineation of structures, 2) generating 3D-CRT plans for 30 patients, 3) generating 30 IMRT plans and 4) comparing the data from the DVH's. A pilot study was conducted in order to confirm the reliability and validity of methods and materials utilised. The patients' scans were utilised to draw in the PTV, CTV and the OAR by an oncologist. The 3D-CRT plans were generated by the researcher on the XiO treatment planning system© (TPS) (Version 4.33.02) and the computed medical system (CMS) Elekta Software. The IMRT plans were derived from the Monaco© treatment planning system (V5.11.02). Both the 3D-CRT plans as well as the IMRT plans were compared on the Monaco planning system. The plans were compared for PTV and CTV dose coverage and dose delivered to the OAR. The plans were approved by an oncologist for reliability. The data was captured on a Microsoft Excel spreadsheet and analysed by a statistician.

Results: Twenty-six of the thirty patients' scans conformed to the inclusion criteria and were used to create the IMRT plans for comparison with the existing 3D-CRT plans. Four of the IMRT plans were excluded due to unacceptable dose coverage for either the PTV coverage or OAR. The PTV coverage for the 105% dose was higher for the IMRT plans with 1.1% versus 0.2% for the 3D-CRT plans. The 95% dose to the PTV was superior for the IMRT plans with 7.7% for IMRT versus 32.9% for 3D-CRT plans. The CTV coverage for the 3D-CRT plans and the IMRT plans had mean values of 0.3% and 1.1% for the 105%, respectively. The 3D-CRT plans had a mean difference of -0.8% and fewer areas of 105% to the PTV compared to the IMRT plans. The 3D-CRT plans produced areas of less than 95% dose with a mean of 14.5%, whereas the IMRT plans had a mean dose of 0.9%. The V_{22} for the 3D-CRT to the heart was higher compared to IMRT with 7.7% versus 2.1%. The mean heart dose was less for 3D-CRT with 4.9Gy versus 5.4Gy for IMRT. The mean dose to the oesophagus was less for the 3D-CRT with 5.1Gy versus 9.3Gy for IMRT. The maximum dose was less for the 3D-CRT with 34.6Gy versus 39.4Gy for IMRT. The percentage of both lungs receiving 18.87Gy was less for IMRT plans with 13.7% versus 16.1% for 3D-CRT plans. The percentage of left lung receiving 18.87Gy was less for the IMRT plans with 28.1% versus 33.5% for 3D-CRT plans. The maximum dose to the left humeral head was less for IMRT with 34.6Gy versus 37.4Gy for 3D-CRT. The percentage of 5Gy to the right breast was less for 3D-CRT versus IMRT with 3.5% versus 11.4%, respectively. The dose to the spinal cord was less for IMRT with 13.3Gy versus 22.6Gy for the 3D-CRT. The percentage of the dose delivered to the normal tissue that received 5Gy was less for 3D-CRT plans with 12.9% versus 24.9% for IMRT plans.

Conclusion: This comparative study demonstrated that the IMRT planning technique for post mastectomy, left breast cancer patients had superior PTV coverage and OAR sparing compared to the 3D-CRT planning technique. The IMRT planning technique did however have larger areas of normal tissue and contralateral breast tissue with low dose radiation. It should be noted though that this low dose radiation is a concern for secondary malignancies. The study limitations include the use of a single isocenter for the 3D-CRT plans, which limited the field size when the mastectomy scar extended beyond the mid-axillary line, in turn limiting the dose to the PTV dose coverage for both 3D-CRT and IMRT plans, respectively. The 7-field IMRT planning technique was utilised in this study. However there are 9- and 11- field IMRT planning techniques that could contribute more to this study. The use of 9- to 11-field IMRT plans could benefit and expand this study for a more in-depth comparison of different 3D-CRT and IMRT approaches. In future, the use of breathing techniques, such as deep inspiration breath hold or inspiration gating, should be considered when using IMRT planning techniques for breast cancer treatment.

Key words: 3D-CRT, IMRT, Left breast, Heart dose, Lung dose, Supraclavicular fossa

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LIST OF ABBREVIATIONS

3D	Three-dimensional
BCS	Breast conserving surgery
CI	Conformity index
CMS	Computed medical system
CRT	Conformal radiation therapy
CT	Computed tomography
CTV	Clinical target volume
DVH	Dose volume histogram
Gy	Gray
HI	Heterogeneity index
IMRT	Intensity modulated radiation therapy
MLC	Multileaf collimator
OAR	Organ at risk
PD	Prescribed dose
PTV	Planning target volume
QoL	Quality of life
ROR	Radiation oncology radiographer
RP	Radiation pneumonitis
RT	Radiotherapy
SRP	Symptomatic radiation pneumonitis
TAN	Tangential

TPS	Treatment planning system
UHA	Universitas Hospital Annex
VMAT	Volumetric modulated arc therapy

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DEFINITIONS

3D-CRT – The use of external radiation beams is used to conform the dose to the target or structure by using the computed tomography scan of the patient. (Halperin, Wazer, Perez, 2013)

CTV – The Clinical target Volume is defined as “a volume to account for uncertainties in microscopic tumour spread” (Halperin, Wazer, Perez, 2013)

DVH - A dose-volume histogram (DVH) is a summary in a graph that provides the simulated dose distribution in a volume of interest from a radiation therapy plan (Drzymala, *et al.*, 1991).

IMRT – Is an planning technique that makes use of small segments of the radiation beam, also referred to as “beamlets”, with different intensities to deliver a homogeneous dose to the target and spare the OAR. This dose control may lead to improved tumour control and lower dose toxicities to the OAR (Halperin *et al*., 2013).

OAR – “These are critical normal tissues whose radiation sensitivity may significantly influence treatment planning and/ or prescribed dose.” (Barrett, *et al.*, 2009).

PTV – “Margins must be added around the CTV. The planning target volume (PTV) is used in treatment planning to select appropriate beams to ensure that the prescribed dose is actually delivered to the CTV.” (Barrett, *et al.*, 2009).

Therapeutic ratio - “Cure is always achieved at some cost in terms of normal tissue damage. There must be a balance between the attempt to ensure that all tumour cells receive a lethal dose of radiation and that acute and late effects are tolerable” (Barrett, *et al.*, 2009).

V_{22} - The volume of a structure (e.g. the heart) that receives 22Gy of dose. The percentage of tissue volume that received doses exceeding 5, 10, 20, 30, and 40 Gy (V5, V10, V20, V30, and V40, respectively) (Wen, *et al*., 2017).

CHAPTER 1

STUDY OUTLINE

"Nothing in life is to be feared, it is only to be understood. Now this is the time to understand more, so that we may fear less". Marie Curie.

1.1 INTRODUCTION

Breast cancer is a malignancy that develops in breast cells. Typically, the cancer forms in either the lobules or the ducts of the breast. The uncontrolled cancer cells often invade other healthy breast tissue and can spread to the lymph nodes. The lymph nodes are a primary pathway that enables the cancer cells to move to other parts of the body (Herndon, 2019). The axillary lymph nodes continue underneath the clavicle to become the supraclavicular lymph nodes, which can be involved in locally advanced breast cancer (Goyal *et al*., 2013). Of all prognostic factors, nodal status continues to be the strongest predictor that governs breast cancer staging (Refer Appendix H).
Breast cancer radiation therapy aims to treat the cancer cells, but in the process the normal tissue receives radiation as well. The planning of the treatment delivery involves the balance between irradiating the cancer cells and delivering as little radiation dose as possible to the normal tissue and organs at risk in the area. The organs at risk with breast cancer patients are the organs in proximity to the treatment field, namely the heart and lungs.

Radiation oncology is the discipline of human medicine concerned with the generation, conservation and dissemination of knowledge concerning the causes, prevention and treatment of cancer and other diseases involving special expertise in the therapeutic applications of ionizing radiation (Halperin, Wazer, Perez, 2013). Radiation therapy is a clinical modality dealing with the use of ionising radiation in the treatment of patients with malignant neoplasias, such as breast cancer. It performs an essential and critical role in the management of breast cancer (Goyal, Buscholtz, Haffty, 2013). The aim of radiation therapy is to deliver a precisely measured dose of irradiation to a defined

tumour volume with the least possible damage to the surrounding healthy tissue, resulting in eradication of the tumour (Halperin, Wazer and Perez, 2013).
Depending on the stage of diagnosis and resources available, surgery may vary from breast conserving surgery (BCS) to mastectomy with sentinel node or axillary node dissection (Halperin, Wazer and Perez, 2013). The use of breast conserving surgery for early breast cancer is widely accepted (Ma, *et al.*, 2013).

Radiation therapy reduces the risk of recurrence after mastectomy and offers an incremental improvement in overall survival. Traditionally, post-mastectomy radiation therapy included treatment to the chest wall and draining lymphatics in the un-dissected axillary apex/supraclavicular fossa. It is clear from the pattern-of-failure studies from patients treated with mastectomy without radiation that the chest wall is the most common site of recurrent disease, accounting for two-thirds to three-fourths of all local-regional recurrence (Goyal, *et al.,* 2013). Radiation therapy seems to offer the greatest benefit when utilising modern treatment techniques that minimise the risk of normal-tissue injury and maximise the probability of tumour control (Goyal *et al.,* 2013).

The treatment techniques vary throughout the world with different approaches for different stages of cancer. 3D-CRT is the conventional treatment modality. For certain early stage breast cancer patients, breast conserving surgery is done, and these patients receive tangential fields only. The tangential fields can be delivered via 3D-CRT or IMRT planning. For later stage breast cancer patients, the inclusion of regional nodes in the planning technique is necessary. Some of these patients also underwent a full mastectomy. In these cases, the treatment of the chest wall with nodal treatment is delivered via 3D-CRT or IMRT. The approach to treatment planning can impact the treatment outcome for the patient.

1.2 INCIDENCE OF BREAST CANCER

Worldwide, there is an estimated 18.1 million new cases of cancer and 9.6 million cancer deaths reported in 2018 (Bray *et al*., 2018). The second largest cause of cancer deaths was breast cancer. Breast cancer is estimated at 2.08 million new cases and 626, 679 deaths, respectively.

In the United States, breast cancer was the most frequently diagnosed cancer and second largest cause of cancer deaths in women during 2012 (Halperin, *et al.*, 2013). From 1990 through 2015, death rates resulting from breast cancer in the United States decreased by 39%. The decrease occurred in both younger and older women and was due to early detection and improved treatment modalities (Chalasani, 2020). In Africa, breast cancer was diagnosed second to cervical cancer in 2004, but the mortality rate has increased noticeably (Bray, McCarron and Parkin, 2004). One in twenty-nine South African women will develop breast cancer during their lifetime (ICON SA, 2020).

According to statistics from the National Cancer Registry (NCR) 2016, breast cancer lists in the top five. Breast cancer has been identified as a national priority with increasing incidences occurring. Approximately 19.4 million women aged 15 years and older live at-risk of being diagnosed with breast cancer. In 2013, deaths from breast cancer and cancers of the female genital tract accounted for 0.7% and 1% of all deaths in South Africa respectively. (CANSA, 2020).

In the Oncology Department, University of the Free State, the statistics have indicated that from 2013 to 2017, 729 new patients with breast cancer received radiation therapy. Of the 729 patients treated for breast cancer, 355 patients received radiation therapy for left breast cancer, of which only 49 patients were treated with tangential fields only (Figure 1.1).

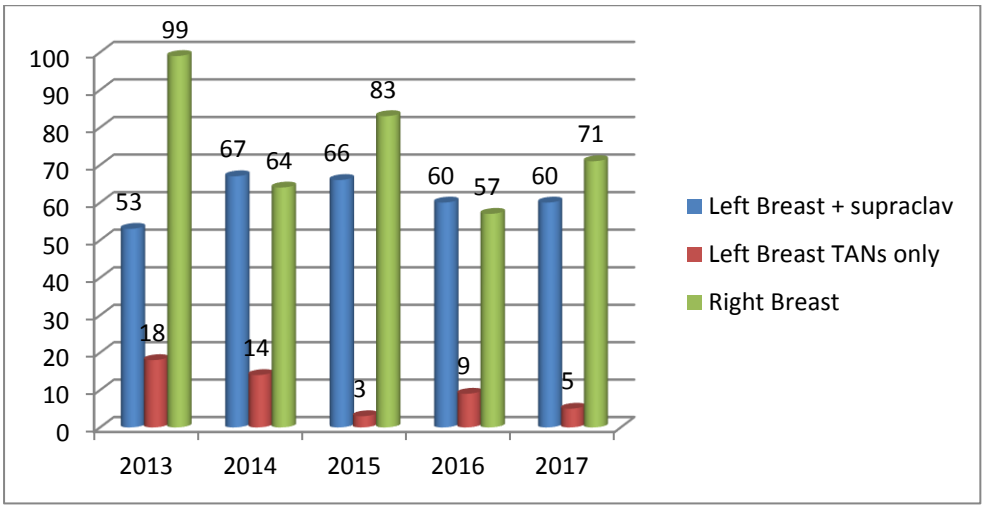

Figure 1.1 Breast cancer treatment statistics, (statistical data, Oncology Department, University of the Free State, 2018).

1.3 DEPARTMENTAL APPROACH FOR BREAST RADIOTHERAPY

At the Oncology Department, University of the Free State, the use of three-dimensional conformal radiotherapy (3D-CRT) for breast cancer patients is a standard treatment technique (refer Appendix A). The department utilises a hypo-fractionation protocol of 40.05Gy in fifteen daily fractions. The UK Standardisation of Breast Radiotherapy (START B protocol) is used instead of the conventional fractionation of 50Gy in 25 fractions (Agrawal *et al.*, 2008) (refer Appendix I). Agrawal *et al.* (2008) reported that the hypo-fractionated protocol does have similar outcomes for tumour control and better normal tissue response, rendering it a useful protocol. Besides, the hypofractionated protocol reduces the total treatment time from six weeks to four weeks for patients on the linear accelerators.

New technological advancements in the Oncology Department, University of the Free State have made the implementation of intensity modulated radiation therapy (IMRT) possible and provided a viable treatment technique for different cancer sites. Since the installation of the Elekta©, Synergy Linear accelerator in 2011, the use of IMRT as a treatment technique was incorporated to treat certain cancers, such as prostate cancer as well as a few head, neck, and brain tumours, but it was not a treatment technique for breast cancer. In 2014 an agility head was installed to the Synergy and the use of volumetric modulated arc therapy (VMAT) and stereotactic radiotherapy became possible.

In 2017 a secondary Monaco planning station (V5.11.02) was installed at the planning unit, thereby reducing the workload on the single planning workstation. The additional planning workstation made it possible for planning radiation oncology radiographers (ROR) to explore different treatment methods/techniques. The implementation of IMRT for breast cancer patients in the department was discussed with the radiation oncologists, but the notion did not pass as there were only a few studies which indicated an advantage of IMRT over 3D-CRT for post-mastectomy breast cancer patients. Literature indicate that limited published studies have been conducted to illustrate the effect of IMRT on breast cancer patients where supraclavicular radiation was indicated. These studies only concentrated on single aspects of the treatment such as the skin sparing effect, tumour control and organs at risk, respectively (Selvaraj *et al*., 2007, Saibishkumar *et al.*, 2008 and Ayata *et al.*, 2011).

During the course of this research several databases, the likes of Elsevier and Science Direct specifically, but not exclusively, were mined without any success for articles or studies published between 2000 and 2020 concerning the dose to the heart of left-breast cancer patients receiving radiotherapy that includes the supraclavicular fossa for post-mastectomy patients. Some studies did however compare three-dimensional conformal radiation therapy (3D-CRT) with IMRT, but for either breast conserving surgery or for tangential fields only. The obvious lack in and absence of relevant literature led to a comparison being made in this specific study between the two treatment modalities, being 3D-CRT and IMRT for post-mastectomy left-breast cancer patients. This study will indicate whether the radiation therapy plans for patients who received post-mastectomy radiation therapy on the left side could benefit from the newly created IMRT plans. It will also indicate whether the dose coverage of the planned target volume (PTV) and the dose administered to the organs at risk (OAR) for the patients treated at the Oncology Department, University of the Free State are superior for IMRT or 3D-CRT.

1.4 PROBLEM STATEMENT

The literature suggests (refer Chapter 2.3) that IMRT as treatment modality provides an improved PTV coverage and lower dose to the OAR when compared to other treatment modalities. It has also indicated that some IMRT treatment planning techniques increase the volume of normal tissue that receives low doses. The research question of this specific study arose directly as a result of this situation:

How does 3D-CRT planning compare with IMRT planning for post-mastectomy patients receiving radiation therapy to the left chest wall and supraclavicular fossa?

1.5 THE OBJECTIVES OF THE CURRENT STUDY

In order to be able to compare the 3-CRT planning technique with the IMRT planning technique for left-sided breast cancer, including the supraclavicular fossa, the following objectives were determined:

(a) To generate an IMRT plan from archived images of patients who already had a 3D-CRT plan in order to draw a comparison with the newly generated 3D-CRT plan;

(b) To compare the dosimetric dose distributions administered to the PTV, by comparing the hot spots (areas receiving ≥ 107% of the prescribed dose) and cold spots (areas receiving ≤ 95% of the prescribed dose);
(c) To compare dosimetric dose distributions given to the OAR, such as the heart, lungs, spinal cord, oesophagus and contralateral breast; and
(d) To compare the DVH of both treatment modalities.

1.6 THE MOTIVATION AND SIGNIFICANCE OF THE STUDY

This research study aims to compare the dosimetric dose distributions of the PTV and the OAR of 3D-CRT plans with that of IMRT plans created. The dose to the OAR was of concern as the dose received could lead to acute and late toxicities. In addition, the dose received by the heart, especially for left sided breast cancer radiation therapy, and the dose to the ipsilateral lung for both 3D-CRT and IMRT created plans needed to be determined to evaluate the departmental protocol for breast cancer patients. The low dose to the contralateral breast and the normal tissue was a concern, especially for the IMRT planning technique. If either the 3D-CRT or IMRT plans indicate an advantage over the other in the sparing of OAR, it may lead to improved quality of life for the patients and limit the late toxicities to the OAR, such as the heart and lungs of the patients.

1.7 ETHICAL CONSIDERATION

Ethical consideration was obtained for this retrospective study (See Chapter 3.5).

1.8 ARRANGEMENT OF THE DISSERTATION

CHAPTER 1: Study outline

This chapter contains an introduction to the relevance of the study, the incidence of breast cancer, departmental approach, problem statement, objectives of the study, motivation and significance and the desired outcome of the study.

CHAPTER 2: Literature perspectives

The literature review reports on the studies published to compare 3D-CRT with IMRT planning for breast cancer patients. The complications and recommendations for improved treatment planning techniques for breast cancer are expounded in detail.

CHAPTER 3: Methodology

This chapter of the study discusses the methods and materials used for patient selection, 3D-CRT planning, IMRT planning as well as the comparison drawn from the PTV, CTV and OAR of both treatment techniques for left breast cancer patients.

CHAPTER 4: Results

The results of this study are elucidated in this chapter. The results for PTV and CTV coverage and dose to the OAR, such as the heart, lungs and unspecified tissue, are illustrated in this chapter with the aid of the DVH's.

CHAPTER 5: Discussion

This chapter discusses the results from this study, with specific reference to the dose to the PTV and the OAR. The dose to the heart as one focus OAR is discussed. It also contains the comparisons drawn between both techniques and the literature.

CHAPTER 6: Conclusion

In this final chapter the study results and findings are concluded, and the research question answered. In addition, recommendations for possible future studies are put forward. A discussion regarding the limitations of this study concludes this chapter.

1.9 CONCLUSION

IMRT planning and treating of cancer is used for various cancers. The use of IMRT for breast cancer is still a debated topic. Post-mastectomy radiation therapy is exercised in the Oncology Department, University of the Free State, Bloemfontein. In Chapter 2 the literature perspective focusses on 3D-CRT versus IMRT planning for radiation therapy of breast cancer after breast conserving surgery.

CHAPTER 2

LITERATURE PERSPECTIVES

2.1 INTRODUCTION

The aim of the study is to create and compare 3D-CRT and IMRT plans from archived scans of patients who received radiotherapy for left-sided breast cancer, including the supraclavicular fossa, post-mastectomy. Special reference was made in terms of the dose coverage to the CTV and PTV as well as the dose received by the OAR.

Some academic studies suggest that IMRT is a viable treatment modality for breast cancer patients and that there are institutions that use this modality as a treatment regime (Ma, *et al*., 2013). There are also a few studies that include the supraclavicular fossa in the treatment volume, as most studies included patients receiving radiation to the chest wall only (Ma, *et al*., 2013). There are also studies that compare 3D-CRT to IMRT, but these studies concentrate on patients who had breast conserving surgery and not a mastectomy, they also suggest that IMRT is a viable treatment modality (Schubert, *et al*., 2011, Beckham, *et al*., 2007 and Mayo, *et al*., 2005).

The studies furthermore compare different treatment options for radiation therapy to the breast, mainly 3D-CRT compared with IMRT, but in most cases the chest wall alone is the treatment area. Few studies compare the treatment of breast cancer that includes the supraclavicular fossa. The studies have different focus areas, as some only look to include PTV coverage and others only compare skin dose. Some studies only compare different approaches for IMRT planning to improve the plans and to save time on the planning of the treatment.

This chapter will provide the theoretical framework for this specific study by examining the literature on 3D-CRT and IMRT planning. In addition, a comparison between 3D-CRT and IMRT planning for breast cancer, a comparison between 3D-CRT and IMRT for PTV dose coverage and the dose to the organs at risk with their dose tolerances will be provided. The DVH and the role in treatment planning will be stated and finally, the risk of secondary malignancies will be indicated.

2.2 RADIATION THERAPY PLANNING TECHNIQUES

This study compared two planning techniques for left-sided breast cancer patients that include the supraclavicular fossa. The planning techniques include the 3D-CRT single isocenter and IMRT single isocenter techniques with seven fields, respectively.

2.2.1. Three-dimensional conformal radiotherapy planning

Three-dimensional conformal radiotherapy planning applies a single isocenter approach that covers the chest wall as well as the supraclavicular nodal area of the patient. The single isocenter plan consists of tangential fields covering the chest wall and closed-end fields or offset fields are used to make the junction between the tangential and supraclavicular fields flush without any cold or hot areas. Barrett, *et al.* (2009) described this technique. The authors reported that the use of a posterior axillary field contributes dose to the axillary nodes and the supraclavicular nodes. This technique does however have its limitations due to the fact that the offset fields, that is the size of the TAN fields, are limited to a 20-centimetre field size (Barrett, *et al.*, 2009).

A study conducted by Haciislamoglu, *et al.* (2015) compared 3D-CRT with IMRT planning techniques for whole breast radiation. The 3D-CRT technique utilised was a conventional planning technique and the beam arrangement consisted of two parallel opposing tangential beams. This ensured the best possible dose coverage of the breast tissue and minimised the dose to the adjacent critical structures. The “isocenter” of the treatment machine was positioned at the centre point of the midline that joins two parallel opposing fields (Haciislamoglu, *et al*., 2015).

In the study of Schubert, *et al.* (2011) they compared 3D-CRT with IMRT planning techniques for left sided whole breast irradiation. The 3D-CRT plans were created using a PTV. The 3D-CRT plans consisted of two opposed tangential beams of 6 or 10 MV energies. Multileaf collimators (MLC) were used to shield the heart and lung as necessary. Thirty- and forty-five-degrees physical wedges and dynamic wedges were used when indicated (Schubert, *et al*., 2011). The purpose of the wedges was to compensate for the patient’s body shape, as the use of wedges allows for a more hemogenic dose distribution of the treatment plan. The wedge and wedge effect is a planning tool that the thin side allows more radiation, typically where there is more tissue and allows more radiation through where there is less tissue in order to

compensate for the different tissue thickness and areas of bone and air. The orientation of the wedge is changed by changing the collimator angle.

2.2.2. Intensity-modulated radiotherapy planning

IMRT is based on the principles of inverse planning, where the desired outcomes (target dose and OAR tolerances) are entered and the computer applies algorithms to plan the desired dose. IMRT makes use of small segments of the radiation beam, also referred to as “beamlets”, with different intensities to deliver a homogeneous dose to the target and spare the OAR. This dose control may lead to improved tumour control and lower dose toxicities to the OAR (Halperin *et al*., 2013).

IMRT has been applied to different sites of cancer, including prostate, lung, head and neck primary tumours. In the treatment of head and neck tumours, the improved sparing of the OAR has been illustrated. The same accounts for prostate cancers, as the reduction in dose to the rectum made it possible to escalate the dose to the prostate and PTV (Selvaraj, *et al.*, 2007).

The use of IMRT in breast cancer radiotherapy offers the potential advantages of improved dose homogeneity and reduced dose to the ipsilateral lung (mean dose 9.9% and V20 = 2.2%) and heart (mean dose 6.8% and V30 = 7.9%), compared to 3D-CRT (Selvaraj *et al*., 2007). These dosimetric improvements from Selvaraj *et al*. (2007) may lead to improved results in lowered cardiac and pulmonary complications. The results from the Selvaraj *et al*. (2007) study suggest improved dose homogeneity and may translate into reduced skin toxicity and cosmetic outcome in comparison to conventional 3D-CRT.

Ayata, *et al.* (2011) state that the IMRT technique for breast cancer treatment has been widely used for many treatment sites, allowing both improved sparing of normal tissues and more conformal dose distributions. IMRT is used to improve conformity and homogeneity and used to reduce OAR doses. IMRT plans have significantly improved the CI and HI compared to the conventional tangential techniques (CTT). IMRT plans have also decreased the volume of ipsilateral lung receiving more than 20Gy and volume of heart receiving more than 30Gy, compared to CTT. But IMRT has also increased the volume of OAR receiving radiotherapy, contralateral lung receiving 5Gy and 10Gy respectively (Ayata, *et al.*, 2011).

In a review article Dracham, *et al*. (2018) raised a concern to radiation-induced second malignancies. They report that the increased use of IMRT may be associated with a greater risk for secondary malignancies.

2.3. COMPARISON BETWEEN 3D-CRT AND IMRT TREATMENT PLANNING

This study compared the two planning techniques (3D CRT and IMRT) by comparing the dose coverage to the PTV and CTV. The doses delivered to the OAR, such as the heart, lungs, humeral head, oesophagus, contra-lateral breast and spine were also compared. The data from the DVH's were used to compare the PTV and CTV coverage as well as the dose to the OAR. Throughout treatment planning the therapeutic ratio is implemented; there is always the balance between dose to the tumour and dose to the OAR.

According to a study conducted by Saibishkumar, *et al*. (2008), the standard radiotherapy technique known as 3D-CRT, substantially improves local tumour control, with a 15-year survival rate. It does however also result in some severe acute and late side effects, which include skin desquamation and fibrosis. Their study included patients with stages T1 to T2 N0.

The following studies have presented dosimetric advantages of IMRT over the conventional methods with better dose homogeneity and sparing of the OAR (heart, lung, and contralateral breast) (Saibishkumar, *et al*., 2008). This improvement in dosimetric advantages with IMRT vs. 3D-CRT with TAN fields alone, has been proven in several studies that compared conventional tangential techniques with IMRT for left side breast cancer treatment to determine the dose to ipsilateral lung, heart, contralateral lung and contralateral breast (Ayata, *et al*., 2011). In addition, Beckham, *et al*. (2007) investigated the dose received by the heart when the internal mammary nodes are included in the PTV and whether IMRT can avoid the heart dose. Caudrelier, *et al*. (2009) and Storm (2002) compared different IMRT techniques to indicate the dose to the heart, lungs and contralateral breast. This information however does not provide any evidence of an advantage in the treatment of the supraclavicular fossa, as the studies did not include the treatment of the supraclavicular fossa.

2.3.1 Planned target volume and clinical target volume

The CTV may move between fractions or during the treatment. Therefore, in order to ensure a homogeneous dose to the CTV, margins must be added. These margins allow for physiological movement and positioning variations. The PTV allows for the prescribed dose to be delivered to the CTV (Barrett, *et al.*, 2009).

A study conducted by Ayata *et al*. (2011) on 30 patients that underwent breast-conserving surgery, demonstrated that IMRT delivered superior homogeneity in the PTV compared to conventional treatment planning. In addition, larger areas of low doses in the contralateral breast and heart were found (Ayata, *et al*., 2011). However, the authors did find higher doses in the contralateral lung, receiving a dose of 5Gy and 10Gy. Another study conducted by Rudat *et al*. (2016) evaluated the impact of hypofractionation with IMRT and 3D-CRT on the PTV, employing a hypofractionated approach of 267cGy in 15 fractions. The results demonstrated that hypofractionation exhibits improved acute skin reactions of dermatitis grade 2, that is 2% versus 19% compared to the conventional fractionation of 50Gy in 25 fractions (Rudat, *et al.*, 2016). Two other studies by Shaitelman *et al*. (2015) and Kraus-Tiefenbacher *et al*. (2012) have revealed similar results when utilising the fractionation schedule of 267 cGy with dermatitis grade 2, that is 36 % versus 69 % for conventional fractionation (Shaitelman, *et al.*, 2015 and Kraus-Tiefenbacher, *et al.,* 2012).

A study conducted by Sethi *et al*. (2012), which compared patients in the supine versus prone position, demonstrated that IMRT delivers good dose coverage to the nodal areas in patients in a prone position. However, the authors stated that IMRT does contribute to a higher percentage of low doses to the ipsilateral lung (V20 = 23% for 3D-CRT supine, versus 27% for IMRT supine and 8% for 3D-CRT prone versus 12% for IMRT prone) (Sethi, *et al.*, 2012).

A study conducted by Schubert, *et al.* (2011) compared four different planning techniques to 3D-CRT. The techniques the authors compared were: (a) 3D-CRT with (b) forward-planned IMRT, (c) inverse-planned IMRT, (d) helical tomotherapy and (e) topotherapy.

The results indicated that the target coverage was similar for all the planning techniques. However, the IMRT plans did have superior homogeneity compared to the 3D-CRT plans. The heart dose for 3D-CRT was higher than the other techniques:

Helical tomotherapy displayed the lowest heart dose and the dose to the ipsilateral lung was higher for the forward planned IMRT planning technique, helical tomotherapy had the highest mean dose and the largest low dose volume. The contralateral lung for 3D-CRT had the lowest mean dose, helical tomotherapy had the highest mean dose. The contralateral breast had the lowest mean dose for the 3D-CRT plans with tomotherapy the highest mean dose. The study was conducted on whole breast irradiation of ten consecutive patients (Schubert *et al*. 2011).

A comparative study conducted by Selvaraj *et al*. (2007) using only two TAN fields in both 3D-CRT and IMRT, revealed a significant decrease in OAR dose for IMRT, while improving the PTV coverage. The study was conducted on patients who underwent BCS and did not receive treatment to the supraclavicular fossa (Selvaraj, *et al.*, 2007).

2.3.2 Organs at risk

The OAR commonly described in published studies were the heart, ipsilateral lung, contralateral lung and the contralateral breast. Some studies include the normal tissue dose as well. This normal tissue is a tissue that is not specifically contoured but that is within the patient contour.

A comparative study done by Caudrelier *et al*. (2009) compared a four-field forward planning technique to an IMRT-HT (helical tomography) plan, similar to VMAT (Caudrelier, *et al.*, 2009). The authors reported that the supraclavicular nodal region was included, but only on patients who underwent breast conserving surgery (BCS). The results for the PTV were similar for the different modalities, except for the hotspot areas. The forward planning of the four-field planning technique had 115% higher hotspots than that of IMRT-HT and VMAT plans. The percentage of dose to the heart receiving 30Gy was lower for the IMRT-HT than for the four-fields forward planned IMRT. The mean lung doses to the lungs were lower for IMRT-HT as well as the volume of lung receiving 20Gy. The volume of contralateral breast receiving 5Gy was larger for the IMRT-HT. The mean dose to the contralateral lung was lower for the forward planning technique. The IMRT-HT did improve the dose to the heart and the dose to the ipsilateral lung but it also increased the volume of tissue receiving low doses, when compared to standard treatment planning where the internal mammary nodes are included.

2.3.2.1 Heart dose

Darby, *et al.* (2010) indicate that radiation to the heart can lead to pericarditis, pericardial fibrosis, diffuse myocardial fibrosis, and coronary artery disease. With maximum doses over 20Gy, the evidence has revealed that radiation-related heart disease can occur.

A study by Rudat, *et al.* (2011) demonstrated that IMRT plans of post-mastectomy patients had a dose reduction of 43% on average to the heart dose of V70 ≥ 35Gy. They also stated that the mean heart dose was reduced by an average of 20%.

The study by Schubert, *et al*. (2011) indicated that the helical tomotherapy had the lowest high dose to the heart compared to IMRT and 3D-CRT, but had higher mean doses. Helical tomotherapy (HT) had reduced V20 dose to the heart, but had higher V5 compared to IMRT and 3D-CRT. A study by Caudrelier, *et al.* (2009) compared HT to IMRT for left-sided breast cancer. In this study they found that the heart dose of V30 was lower for the IMRT plans. The study of Ayata, *et al*. (2011) compared IMRT with 3D-CRT. It revealed that the V30 to the heart was higher for 3D-CRT than for the nine-field and 11-field IMRT plans, but not statistically different for the seven-field IMRT plans.

2.3.2.2 Contralateral breast dose

The study conducted by Caudrelier, *et al*. (2009) indicated that the contralateral breast did receive a greater volume of 5Gy with the IMRT than with the HT. The HT did however decrease the volume of contralateral breast that received dose above 50Gy.

According to Ayata, *et al*. (2011) in their study, with reference to the contralateral breast the V10 was lower for the 3D-CRT plans compared to the percentages for the IMRT plans. The different IMRT plans indicated no significant difference in percentages for the V10 of the contralateral breast.

2.3.2.3 Unspecified tissue dose

Beckham *et al*. (2007) utilised an eleven-field IMRT plan on patients who underwent BCS. The authors indicated that a larger volume of unspecified soft tissue receiving lower doses does raise a concern, as this lower dose will increase the chances for secondary malignancies (Beckham, *et al.*, 2007).

2.3.2.4 Lung dose

Wen, *et al*. (2017) performed a study on symptomatic radiation pneumonitis (SRP) after radiation. In this study they found that in follow-up the patients exhibited distinct injuries: Acute pneumonitis and chronic fibrosis, which usually occurs three months after radiation therapy. They indicated that the supraclavicular field does contribute to SRP as the majority of SRP were found in the apex of the lung. They suggest that IMRT should be investigated to limit the incidence of SRP.

According to Lee, *et al.* (2015), the lungs, which are located beneath the breasts, are among the most critical organs in radiation therapy in the treatment planning for breast cancer. Being the essential organ for respiration, a reduction in lung damage during breast cancer radiotherapy is important. Radiation pneumonitis (RP), which decreases the quality of life (QoL), is the most common pulmonary complication in patients receiving breast irradiation (Lee*, et al*., 2015).

The study results of Ayata, *et al*. (2011) indicated that the 3D-CRT had higher percentages of the ipsilateral lung that received 20Gy compared to IMRT. The nine-field IMRT plans had the lowest percentage of the ipsilateral lung that received 20Gy. 3D-CRT had 14.62 % versus the seven-field IMRT with 9.08 %, the nine-field IMRT had 8.12 % and the eleven-field IMRT had 8.57 % of V20 to the ipsilateral lung.

2.3.3 DOSE VOLUME HISTOGRAM

A dose-volume histogram (DVH) is a summary in a graph that provides the simulated dose distribution in a volume of interest from a radiation therapy plan (Drzymala, *et al.*, 1991).

A DVH provides a complete summary of the entire 3D dose matrix, showing the amount of target volume or critical structure receiving more than a specified dose level. Due to the fact that a DVH does not provide spatial dose information, it cannot replace the other methods of dose display; it can only compliment them (Halperin, *et al.*, 2013). The authors also stated that the most useful data reduction tool for conformal therapy planning is DVH. From the DVH, dose statistics are deducted. These include maximum point dose, minimum point dose, mean dose percentage volume receiving greater than or equal to the prescription dose for target volumes and maximum point dose, mean dose, and percentage volume receiving greater than or equal to an established tolerance dose for organs at risk.

Thus, a DVH provides the summary of the simulated dose from a radiation therapy plan on a graph. This graph can then be analysed to indicate the dose given to a structure. On the DVH not only can the maximum dose be evaluated, but also the minimum and mean dose to a specific structure. On the graph, specific doses can be selected to provide the volume of the structure receiving that amount of dose. The structures in the DVH can be selected, of which those can include the PTV for dose coverage and hot and cold spots. Structures, such as the OAR, can be selected to indicate if the dose to the OAR is acceptable. The evaluation of the DVH will influence the oncologist's decision to approve the plan, as the DVH will indicate the PTV coverage and the OAR doses. The DVH for both 3D-CRT and IMRT are depicted in Figure 2.1.

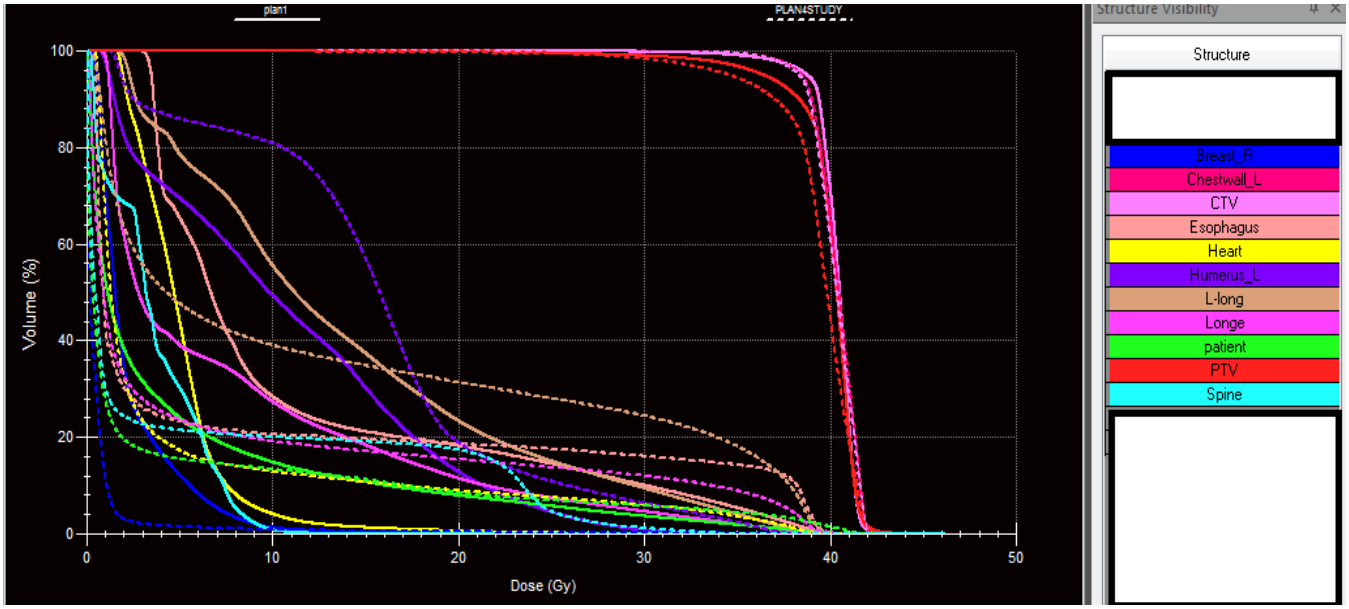

Figure 2.1 Dose Volume Histogram (Monaco© V5.11.02).

2.4 SECONDARY CANCER RISKS

The study conducted by Fogliata, *et al.* (2017), compared the volumetric arc with 3D-conformal in order to indicate the risk of secondary radiation-induced cancer. In the study, the authors applied a total dose of 40.05Gy in 15 fractions and indicated that the dose to the heart should not exceed 52.4Gy in order to prevent death and 49.2Gy to prevent pericarditis. In addition, the authors indicated the dose to the lung for pneumonitis is 34Gy, for symptomatic or radiographic fibrosis it is 28.8Gy and skin ulceration or necrosis it is 70Gy.

Zhang *et al.* (2020) conducted a study during which they compared the 3D-CRT with IMRT and VMAT in order to evaluate the secondary cancer risk between different techniques. They found that the IMRT and VMAT did reduce the mean dose to the OAR, compared to the 3D-CRT plans. They also indicated that the PTV had equivalent doses for the IMRT and VMAT, compared to the 3D-CRT plans. The areas of high doses were reduced by the IMRT and VMAT plans. The IMRT and VMAT indicated more low dose areas to the OAR than the 3D-CRT plans. The organs proximal to the fields, such as the contralateral breast, contralateral lung and ipsilateral lung had conceivably higher low dose volumes for IMRT and VMAT than for the 3D-CRT, which are associated with radiation-induced risk of secondary cancer. They stated that approximately 80% of secondary cancers are located either within the treatment field or in the beam bordering regions.

Furthermore, a study conducted by Abo-Madyam, *et al.* (2014) indicated that the absorbed dose to the OAR was lower for the 3D-CRT plans than for the IMRT and VMAT plans. The authors concluded that the secondary cancer risk for 3D-CRT is lower than for IMRT and VMAT by approximately 34% for the linear model and 50% for the linear-exponential and plateau models, respectively.

2.5 CONCLUSION

The literature perspective indicates that there is a gap with regard to the information that is currently available on post-mastectomy, breast cancer patients receiving radiotherapy to the chest wall and the supraclavicular fossa when comparing the two different planning techniques. A study conducted by Rudat, *et al.* (2011) revealed that data on the effect of IMRT of the chest wall in post-mastectomy breast cancer patients are scarce in the literature. They compared tangential IMRT plans with tangential 3D-CRT plans for post-mastectomy patients and further concluded that data on the impact of IMRT on the adjuvant radiotherapy of the chest in post-mastectomy patients are also scarce (Rudat, *et al*., 2011). This seems to be still the case, even in the literature that is available in 2020.

Several studies compare 3D-CRT with IMRT for breast cancer radiation therapy, each with their own particular aim and purpose. However, it must be noted that the literature

relevant to this specific study is sparse. The following chapter will elaborate on and describe the methods employed to conduct this study.

CHAPTER 3

METHODOLOGY

3.1 INTRODUCTION

In this chapter, the methods and methodology employed to collect the data for the study will be explained. The methods and materials for planning and evaluating the 3D-conformal and the IMRT plans for post-mastectomy, left sided breast radiation therapy will be described. The discussion of the findings is to be found in Chapter 5 after the comparison between the two different planning modalities and planning techniques.

3.2. THE RESEARCH DESIGN

This research study utilised a comparative research design. In order to compare the effectiveness of different treatment modalities, a comparative design was deemed to be the most appropriate. With a comparative design, as with most other designs, a study can be carried out either as an experiment or as a non-experiment (Kumar and Ranjit., 2011). For this research study, the comparison was done between the 3D-CRT and IMRT plans for left breast cancer patients receiving radiation therapy, which included the chest wall, supraclavicular fossa and axillary area.

This research followed a quantitative and retrospective approach of data collection for breast cancer patients that were treated in the Oncology Department, University of the Free State from January 2015 to December 2017. A quantitative research study is a formal, systemic and objective process where numerical data are used to obtain information. This method is used to describe variables, examine relationships between variables and to determine cause-and-effect interactions between variables (Burns and Grove, 2005). Kumar classified quantitative research as a structured approach because the objectives and measurements are predetermined (Kumar, 2011).

3.3. STUDY SAMPLE

Sampling is the process of selecting a few (a sample) subjects that meet the inclusion criteria from the targeted population (the sampling population) to become the basis for estimating or predicting the prevalence of an unknown piece of information, situation or outcome regarding the bigger group (Kumar, 2011). A sample is a subgroup of the population in which one has or shows specific interest (Kumar, 2011). This study utilised purposive sampling. The primary consideration in purposive sampling is one's judgement as to who can provide the best information in order to achieve the objectives of one's study (Kumar, 2011).

The sample for this research study included the archived 3D-CRT scans of breast cancer patients that were treated in the Oncology Department, University of the Free State from January 2015 to December 2017, when the hypofractionated protocol was introduced. At the Oncology Department, University of the Free State, the use of three-dimensional conformal radiotherapy (3D-CRT) for breast cancer patients is a standard treatment modality. The department utilises a hypo-fractionation protocol of 267 cGy in 15 daily fractions; the total dose being 40.05 Gy. The UK Standardisation of Breast Radiotherapy START B protocol is used rather than the conventional fractionation of 50Gy in 25 fractions (Agrawal, *et al.*, 2008).

A list of patients that have received 3D-CRT for breast cancer was obtained from the department's statistical records. All archived data of the 3D-CRT plans were retrieved according to the radiotherapy treatment (RT) number of the patient. Only the 3D-CRT scans of patients with left breast cancer were included in this research study in order to include the heart as an organ at risk, as the heart does receive more dose for left side breast treatment. The CT scans of thirty patients on the archive system who were treated between January 2015 and December 2017 and who adhered to the inclusion criteria were included in the study. The inclusion and exclusion criteria are illustrated in the following Table 3.1. The selected scans of the patients were then used to generate a new 3D-CRT and IMRT plan for the study.

Table 3.1 Inclusion and Exclusion Criteria

Inclusion criteria:	Exclusion criteria:
• CT scans of patients who received the hypofractionated protocol of 40.05Gy in 15 fractions. • CT scans of patients diagnosed with left breast cancer. • CT scans of patients treated with both tangential and supra-clavicular fields. • CT scans of patients treated with a 3D-conformal plan. • Inactive patients on the planning system who received breast cancer treatment. • 3D-CRT plans with PTV and OAR. • IMRT plans with PTV and OAR. • 3D-CRT plans that were approved by a radiation oncologist. • IMRT plans that were approved by a radiation oncologist.	• CT scans of patients who received palliative treatment for breast cancer. • CT scans of patients diagnosed with right breast cancer. • CT scans of patients who received only tangential fields. • CT scans of patients who underwent lumpectomies. • CT scans of male patients for breast cancer. • CT scans of bilateral breast cancer patients. • Active patients on the planning system for breast cancer treatment. • 3D-CRT plans without PTV & OAR. • IMRT plans without PTV & OAR.

3.4. VALIDITY AND RELIABILITY

The reliability of the study is deemed to be ensured by the skills and expertise of the oncologist responsible to delineate and approve the created IMRT plans. The appointed oncologist boasts ten years of clinical experience in radiation oncology, is currently the head of the Clinical Unit Oncology and is a senior lecturer at the University of the Free State, Bloemfontein. In addition, the same dose constraints will be applied to all plans, providing reliable and reproducible results. Studies have indicated that there are differences in the delineation of structures between professionals (Pitkänen, *et al.*, 2001). In lieu of this and specifically for this research study, one radiation oncologist in the department was appointed to delineate all the PTV's for both 3D-CRT and IMRT plans. The radiation oncologist delineated the following OAR that was not delineated by the radiographer: Heart, humeral head, oesophagus and the contralateral breast, as these structures require a more experienced person to

delineate them. These treatment plans also had to be approved by the appointed radiation oncologist for inclusion purposes.

The validity of the study largely depends on the consistency of collection of the data, research instruments/ tools being utilised. Kumar (2011) stated that: If the research tools are virtuous the findings will be valid and reliable. A pilot study was conducted after ethical approval had been obtained in order to discern whether the Excel spreadsheet /research tools would be appropriate for data collection. The researcher collected the data on the spreadsheet and controlled the data with the data from the DVH statistics.

A pilot study was conducted to verify the data collection and the process of the study. The pilot study was done to indicate whether the collected data were reliable and valid.

3.5. PILOT STUDY

A pilot study was conducted at the onset in order to test the research tool (refer Appendix B). The pilot study included archived scans of five patients, containing their 3D-CRT plans that adhered to the inclusion and exclusion criteria (refer Table 1.1). The appointed oncologist performed the delineation of the PTV's and OAR. The IMRT plans were generated and approved by the appointed oncologist. The 3D-CRT plans were then compared to the newly generated IMRT plans. The DVH's of the 3D-CRT and the IMRT plans were compared.

However, after having done the comparisons of the 3D-CRT and IMRT plans, it was realised that the archived 3D-CRT plans could not be compared to the IMRT plans, as the archived 3D-CRT plans did not include the PTV and the OAR, such as the heart, oesophagus, contralateral breast and humeral head delineated as OAR.

In consultation with the appointed radiation oncologist, it was decided to include a PTV and the OAR in the 3D-CRT plans, in order to compare the newly generated 3D-CRT plans with the IMRT plans. This resulted in having to create two plans instead of the initially planned one plan per patient.

3.6. RESEARCH TOOLS

In order to generate the 3D-CRT and IMRT plans and to compare the dosimetric dose given to the OAR, PTV's and DVHs, the following tools were utilised:

- XiO treatment planning system© (TPS) (Version 4.33.02) (Computed Medical System (CMS), Elekta Software for the archived 3D-CRT scans and plans.
- Monaco© treatment planning system for delineation of structures, IMRT planning and comparison of plans.
- Microsoft Excel 2007©for data collection. (Appendix B)

3.7. ETHICAL CONSIDERATIONS

Patient data was anonymised by renumbering the patient CT scans for the study. No patient CT scans were included in the study that received treatment at the time of the study and no changes were made to the archived patient treatment plans that may be used for future treatment purposes. The newly created 3D-CRT and IMRT plans of in-active patients will be used for the study purposes and not for treatment. The following approvals were obtained:

(a) Head of the Oncology Department, University of the Free State of Oncology (Appendix C);
(b) Free State, Department of Health; (Appendix D) and
(c) Health Sciences Research Ethics Committee, UFS (Appendix E) (UFS – HSD2018/1164/3010).

Ethical approval was deemed necessary for the study as patient data were accessed. The ethical considerations would ensure that no harm could come to any patients included in this study and that their identities would remain anonymous and thereby protected.

3.8. PLANNING TECHNIQUES

Two planning techniques and two different planning modalities were used to generate the 3D-CRT and IMRT plans, respectively. The 3D-CRT planning was executed as per the current departmental approach, whereas the IMRT planning was executed as a proposed new departmental approach to breast cancer treatment planning.

3.8.1. Planning technique for 3D-CRT plans

The programme used for the 3D-CRT planning was the XiO (V5.10.00.4) planning system from Elekta©. The planning system uses forward 3D-CRT to generate a plan for the patient. The planning radiation oncology radiographer (ROR) does all the planning and the planning system generates the plan according to the fields and dose entered by the planning ROR.

3.8.2. Planning technique for IMRT plans

The planning system utilised for IMRT planning was the Monaco (V5.11.02) planning system. The Monaco planning system uses a template based inverse planning technique to generate the plan, which in turn applies the Monte Carlo© algorithm to generate the dose distribution.

3.9. RESEARCH PROCESS

The flow of events for this research study was divided into four stages, as indicated in Figure 3.1.

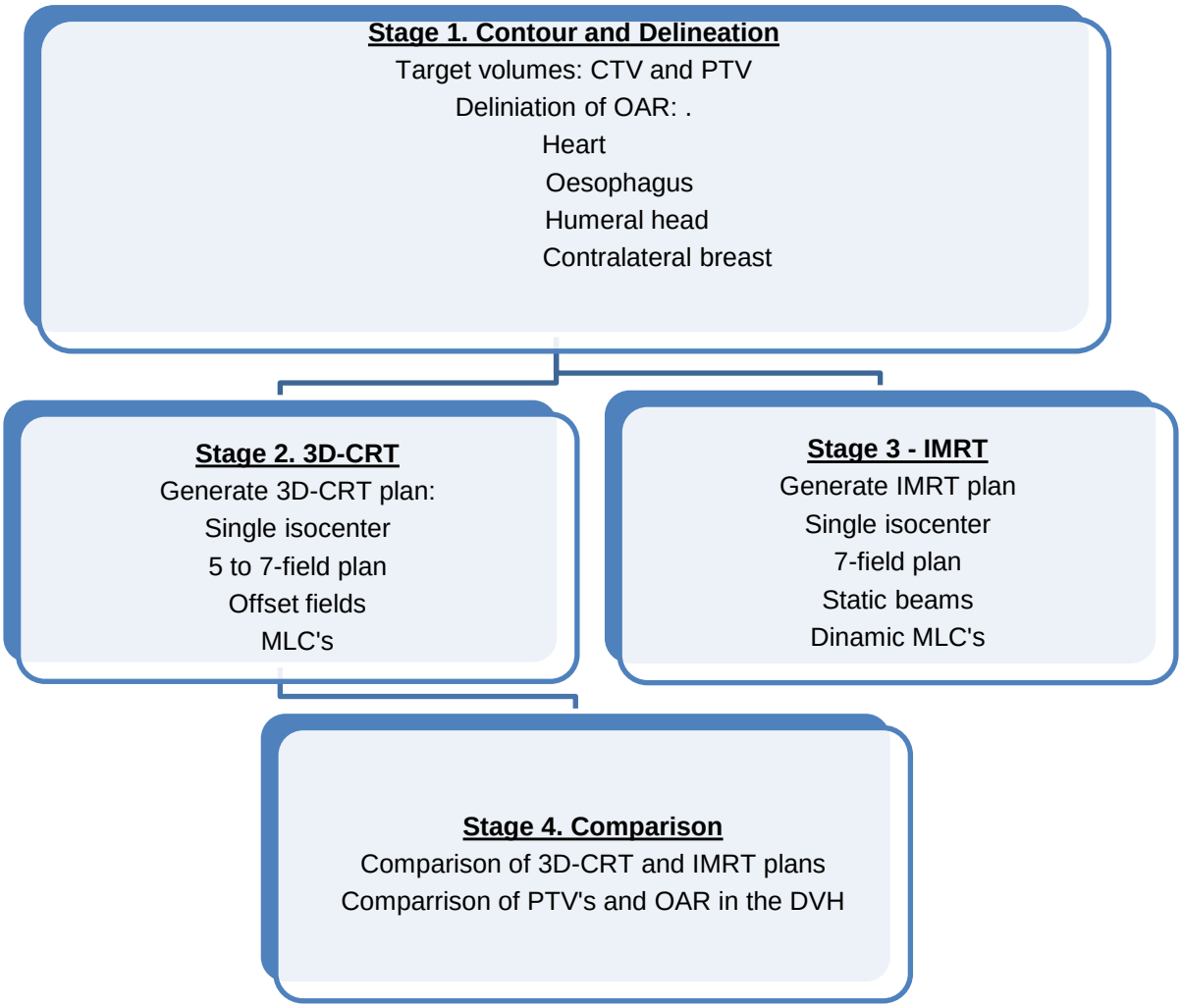

Figure 3.1 Research Stages.

3.9.1. STAGE 1: Contour and Delineation

The contouring and delineation of the additional structures were performed by the appointed oncologist. The clinical target volume (CTV) for both modalities (as the same patient scan with the same delineated structures was used) included the chest wall or breast tissue, as defined by the RTOG Breast Cancer Atlas (refer Appendix F), ipsilateral regional lymph nodes, interconnecting lymphatic drainage routes, and chest wall muscular tissue/skin. The mastectomy scar was also included in the CTV due to risk for microscopic disease.

The PTV for each patient included the supraclavicular area for the study. The PTV margins were as follows: 3-5 mm margin medially, 5-10 mm laterally, 3-5 mm posteriorly, and 5-10 mm superiorly, inferiorly and anteriorly (to include the skin surface), added to the CTV. The patients for this study were scanned with a 0.5cm superflab that functions as a bolus on the chest wall for tangential fields. Some of the patients were also scanned with the superflab on the supraclavicular area. The bolus is tissue equivalent and it allows the dose to be at the surface of the skin. The amount of lung was trimmed to the oncologist ‘s discretion. The lung is an OAR and having a large area of the lung in the PTV may cause the PTV coverage to become less or the lung dose to become too high (Ho & Powell, 2013). The PTV protocol was only used for this study; it is not the protocol for the Oncology Department, University of the Free State, since the department did not utilise the use of a PTV for breast cancer treatment at the time of the study. The OAR included the heart, lungs (left and right), spinal cord, oesophagus, humeral head and contra lateral breast.

The delineation of the OAR was based on the RTOG guidelines (White, *et al.*, 2018). The RTOG is widely used as a standard for delineation of structures for radiation therapy.

The amount of dose given to the normal tissue of the patient, that is tissue that is not included in the PTV or the OAR, was used to determine the patient toxicity as low dose radiation can lead to radiation-induced malignancies. With a larger area of normal tissue receiving low doses, the likelihood of secondary malignancies increases.

3.9.2. STAGES 2 AND 3: Creating Three-Dimensional Conformal Radiation Therapy-and Intensity Modulated Radiation Therapy Plans

The CT scan of each patient with the delineation of the PTV and OAR of stage one was used to create a 3D-CRT plan on the XiO treatment planning system© and the IMRT plan on the Monaco© planning system, retrospectively. After the first IMRT plan was created, the oncologist had to approve it. Once that was completed, the plan was saved as a template and used for creating the other IMRT plans in the study. Monaco is a template-based planning system and that made the planning of the following scans faster. However, small changes were made to the template as each patient’s anatomy was unique.

3.9.2.1 Three-Dimensional Conformal Radiation Therapy Planning

The 3D-CRT planning technique utilised a single isocenter plan. The isocenter was placed at the level of the sternal notch, anteriorly and laterally as needed per patient. The tan fields came in at angles to cover the maximum area of the PTV. The fields were 20cm offset fields, with the superior jaw at 0cm and the inferior jaw at 20cm. The collimator angles were kept close to 0°, as this rendered it possible to bring in the MLC's to cover areas of the lung and heart. The beam's eye view of the lateral tan field is illustrated in Figure 3.2. The MLC's were placed in the field to shield some dose to the OAR to keep the dose below tolerance. The use of a compensating field was necessary to get a more homogeneous dose distribution.

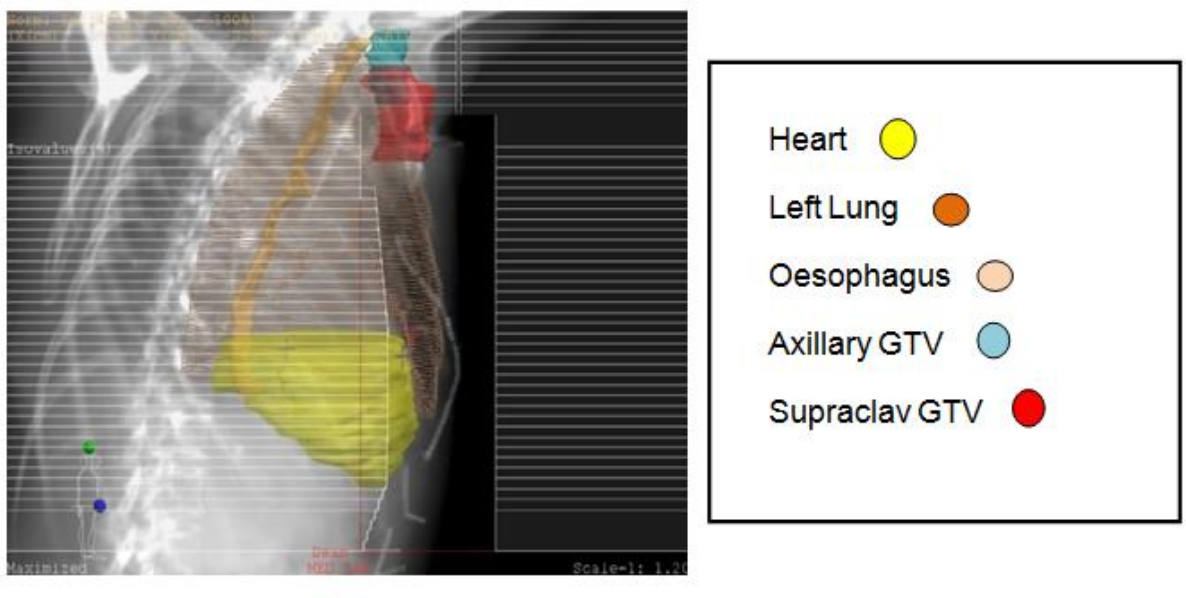

Figure 3.2 Beam's eye view of lateral tangential field (screenshot from XiO planning system).

The supraclavicular and axillary fields were offset superiorly to cover the PTV superior to the sternal notch (Figure 3.3). The axillary field was angled more posteriorly to spare more of the oesophagus. The humeral head was shielded with the MLC's in both the supraclavicular field and the axillary field. Five to seven fields were used to cover the PTV in order to obtain a homogeneous dose distribution. Virtual wedges were used where necessary. Filler or compensating fields were employed to compensate for cold and hot spots. Hotspots are areas with more than 105% of the dose and cold spots

are areas with less than 95% of the dose. Mastectomy scars that were not covered by the photon fields were treated with an additional electron field.

The use of offset fields rendered the dose spillage between the supraclavicular and tan fields less. Dose spillage occurs due to the penumbra of a dose of each field that can add a dose to an area of an adjacent field. In order to prevent this, the field is offset, meaning the one jaw is on the isocenter. The 20cm field limit caused by the single isocenter approach, led to the inferior part of the PTV to be cold and the dose less than 95% of the prescribed dose.

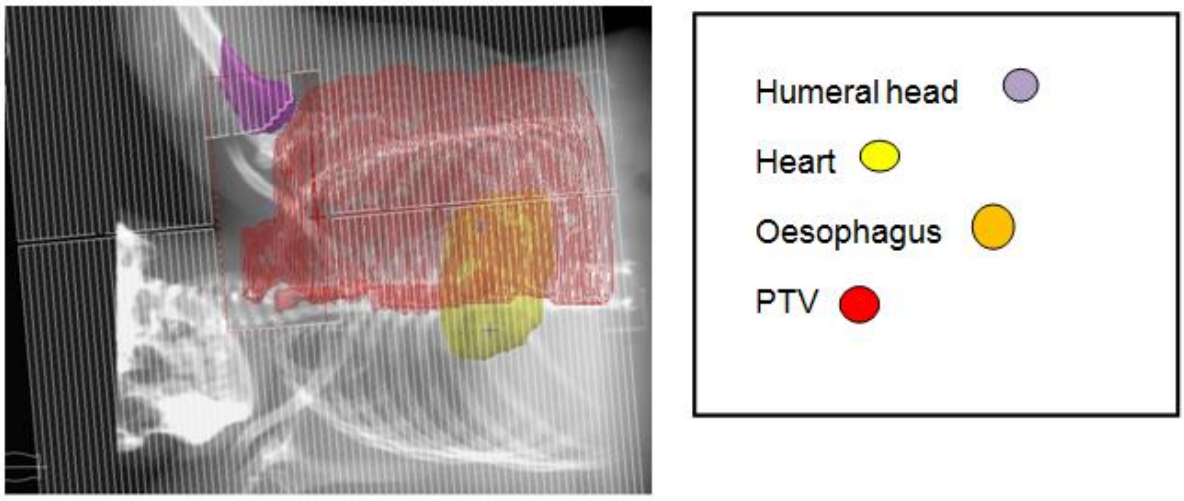

Figure 3.3 Beam's eye view of the supraclavicular field (screenshot from XiO planning system).

3.9.2.2 Intensity modulated radiation therapy planning

The planning technique used for IMRT planning was a single isocenter, seven-field plan utilising a dynamic multi leaf collimator (DMLC) IMRT plan. The seven fields used to deliver the dose to the PTV did come in at similar angles to that of the 3D-CRT TAN fields. The fields are static beams at a specific angle with the collimator rotation at a specific angle of 0°. The seven fields came in at 300°, 320°, 340°, 0°, 100°, 120°,140°, respectively. The beam orientation and isocenter placement is presented in Figure 3.4.

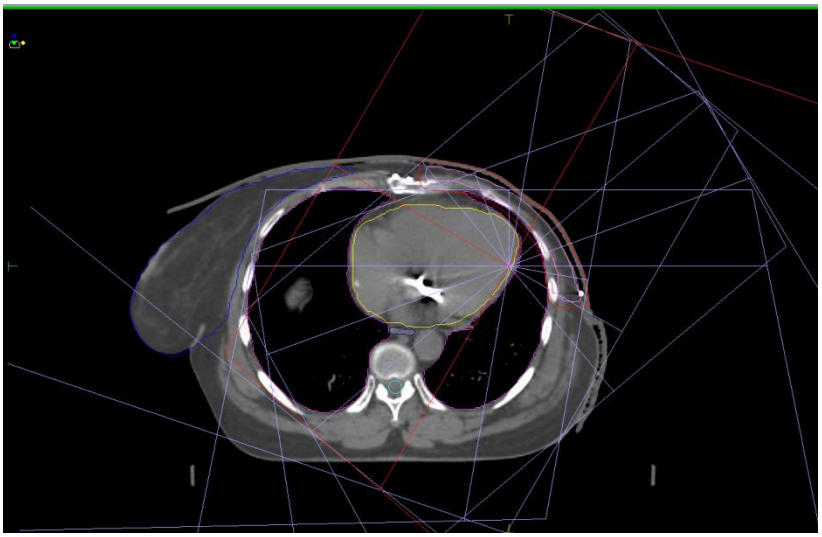

Figure 3.4 Example of beam orientation and isocenter placement (screenshot from Monaco planning system).

The isocenter was positioned in the centre of the PTV. This was done to ensure that the linear accelerator limitations in field size would not influence the delivery of the optimal dose; a hemogenic dose distribution. The dose prescription was to the PTV with constraints to overdosing and underdosing. Areas of not more than 2% of the PTV should receive more than 107% and no areas of 2% less than 95% of the prescribed dose. The OAR was constrained in order to prevent overdosing of the OAR, but also to restrict the dose to the OAR as far as possible. Parallel and serial dose constraints were used. The patients received individual plans with similar approaches. The approach of some patients' plans was "parieto", meaning PTV first and others received "constrained", meaning OAR first. The approach was adjusted in order to obtain the best possible PTV coverage with the OAR dose within tolerance.

The DVH and DVH statistics were used to evaluate the plan, the dose distribution and the homogeneity. The data form both the 3D-CRT and IMRT plans for each patient were placed on the same DVH so as to compare the plans.

3.9.3. STAGE 4: Comparison of three-dimensional conformal radiation therapy and intensity modulated radiation therapy plans

The 3D-CRT and IMRT plans on the Monaco© planning system was compared, because this system is equipped to compare both 3D-CRT and IMRT plans. The XiO planning system can only compare 3D-CRT plans and not the Monaco® IMRT plans.

The plans for each patient were compared side by side with the DVH displaying the different structures' doses. In addition, the DVH statistics were used to compare the dose administered to the structures at different percentages and to evaluate the tolerances for each structure. Utilising the DVH statistics, the PTV coverage was also compared by evaluating the hot and cold areas, while scrutinising the dose homogeneity.

The IMRT plans were compared to the 3D-CRT plans for each of the parameters. The parameters are presented in Table 3.2. The dose was compared for each patient between the two different planning techniques. Thereafter the results were tabulated in an Excel spreadsheet and analysed.

Table 3.2 Dose parameters for OAR

PTV	98% coverage of 38.5Gy	No areas of more than 42.85Gy	
Lungs	V18,87Gy< 30%		
Left lung	V18,87Gy < 35%		
Heart	V22Gy < 10%	Mean dose < 5Gy	Max dose < 43.5Gy
Spine	V20Gy < 20%	Mean dose< 10Gy	Max dose < 43.5Gy
Oesophagus			Max dose of < 53.1Gy
Humeral head			Max dose of < 35Gy
Contra lateral breast	V5 < 15%		Max dose of < 30Gy
Patient	V5 < 20%		

Planned treatment volume (PTV) V = Volume, Gy = Gray, Max = Maximum.

*Dose tolerances derived from (Milano, Constine & Okunieff: 2007). The dose constraints were adapted from 2Gy fractions to 2.67Gy fractions by the departmental medical physicists.

3.10. DATA COLLECTION

Data collection was done after each IMRT plan had been approved by the appointed radiation oncologist of the Oncology Department. The 3D-CRT and IMRT plans were compared and the DVH created. The DVH included the data from both the 3D-CRT and IMRT plans. The data from the compared DVH were entered into an Excel spreadsheet (see Appendix B). The spreadsheet included the following: Maximum-, minimum- and mean doses for all the structures, the hot and cold spot areas for the PTV and the dose constraints for the specific OAR.

3.11. STATISTICAL ANALYSIS

The data from the DVH statistics were controlled and reviewed before being added to the Excel spreadsheet. Thereafter the data were controlled for any typing errors before the data was saved.

The data analysis was performed by a statistician by means of SAS Version 9.2. Descriptive statistics, namely frequencies and percentages, were calculated for categorical data and means, and standard deviations or medians and percentiles were calculated for numerical data. In order to compare the data from the 3D-CRT and IMRT plans, the appropriate analytical statistics were used. Specifically, the chi-square test was used to compare proportions and the t-test (or Mann-Whitney U-test) was used to compare mean (or median) values. A significance level (α) of 0.05 was applied.

3.12. CONCLUSION

This section described the methods and methodology employed to collect the data for the study to compare the 3D-conformal and IMRT plans of post-mastectomy, left-sided breast radiation therapy patients. The data collected in the study from the methods used are presented in Chapter 4.

CHAPTER 4

RESULTS

4.1 INTRODUCTION

In this chapter, the results of the comparative research study of 3D-CRT versus IMRT planning for post-mastectomy, left sided breast radiation therapy (including the supraclavicular fossa), of 30 randomly selected patients are presented. The results are derived from a comparison between the planned target volumes (PTVs), clinical target volumes (CTVs) dose to organs at risk (OAR), and the dose volume histograms (DVHs) of the generated 3D-CRT and IMRT plans. The comparisons between the 3D-CRT plans and the IMRT plans were evaluated according to (a) the minimum-, maximum- and standard deviations; (b) the specific goals set for each of the PTVs, CTVs and OAR. The PTV and CTV coverages for each patient's plan were compared between the 3D-CRT and IMRT plans. The stages listed in Figure 3.1 were followed to gather the data.

4.2 PATIENT COMPUTED TOMOGRAPHY IMAGE INCLUSION AND EXCLUSION

The archived CT scans of patients who received radiation therapy to the left chest wall and supraclavicular fossa (post-mastectomy) in the Oncology Department, University of the Free State were selected according to the inclusion criteria for this retrospective study. The CT images were selected from the most recent patients that met the inclusion criteria (see Table 3.1). Each patient's CT scan was used to create a 3D-CRT and IMRT plan, respectively. These plans included the structures required for the comparative study, namely the PTV, CTV and the following OAR: heart, lungs, spinal cord, oesophagus, left humeral head, contralateral breast (right breast) and unspecified tissue.

The created 3D-CRT and IMRT plans of 26 patients' CT images qualified in terms of the inclusion criteria of the study and were subsequently analysed, (see Table 1). Four of the newly created 3D-CRT and IMRT plans did not meet the inclusion criteria and were excluded from the study. The plans were excluded due to the following reasons:

- The dose to the heart for newly created IMRT plan for “patient 16” was high; the V22 was higher than 10% (14.8%) and a 95% dose coverage attempt to lower the dose to the heart, was inadequate at 78%.
- The IMRT treatment plan created for “patient 22” was excluded due to the fact that the medial scar was over the midline of the patient and therefore resulted in a higher dose to the contralateral breast of 24.8%. In the attempt to increase the dose to the PTV for the specific purpose of this study, the heart dose increased and the V22 was higher than 10% (16.2%). Likewise, during an effort to lower the dose to the contralateral breast and heart, the 95% dose coverage proved to be inadequate at 82.4%.
- Created IMRT plan for “patient 23” produced inadequate PTV coverage of the 95% dose (81.1%), with a heart dose of V22 over 10% (15.5%) and the left lung had a dose of more than 35% (47%) to the dose of 18.9Gy.
- Created IMRT plan for “patient 30”, who presented with a large separation of the chest wall and an extended mastectomy scar lateral-posteriorly, caused an increase in the CTV and PTV volumes, respectively. The mean heart dose was more than 5Gy (11Gy) and a dose of 18.9Gy to the left lung, proved to be higher than 35% (42%).

4.3 PLANNED TARGET VOLUME COVERAGE

The planned target volume coverage was used to determine the dosimetric differences between the 3D-CRT and IMRT plans. Table 4.1 illustrates the dosimetric differences between the 3D-CRT plans and the IMRT plans for the PTV coverage of 105%, 98% and 95% respectively for the 26 patients.

Table 4.1 PTV coverage of 3D-CRT versus IMRT plans (n=26)

Variable	3D-CRT	IMRT	Mean Difference	P - value
PTV 105%				
Mean % > 105%	0.2 %	1.1 %	-0.9%	p < 0.0001
Minimum % dose	0%	0%		
Maximum % dose	1%	2.2%		
Standard Deviation	0.3 %	0.6 %		
PTV 98%				
Mean % = 98%	67.1 %	92.3 %	-25.2%	p < 0.0001
Standard Deviation	7.3 %	2.4 %		
Minimum % dose	56%	86.4%		
Maximum % dose	85.6%	97.9%		
PTV 95%				
Mean % < 95%	32.9 %	7.7 %	25.2%	p < 0.0001
Minimum % dose	14.4%	2.1%		
Maximum % dose	44%	13.6%		
Standard Deviation	7.3%	2.4 %		

**3Dimensional-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), planned treatment volume (PTV).*

4.3.1 PTV 105% coverage

The PTV coverage of the 3D-CRT versus IMRT plans revealed that the areas that received 105% or more of the PD for the 3D-CRT, were less with 0.21% mean dose for the set goal of 105%. The PTV coverage of the IMRT plans was 1.1% over the set goal dose of 105%. Areas of 107% of the PD were not accepted. The mean difference of 0.9% indicated that the 3D-CRT plans had fewer areas of 105% than the IMRT plans.

The IMRT plans had superior PTV coverage compared to the 3D-CRT plans. The negative values in the mean difference column indicated that the value of the first column (3D-CRT) is smaller than the value in the second column (IMRT).

4.3.2 PTV 98% coverage

The PTV 98% coverage indicated that, for the area that should at least be covered by the 95% of the PD, the coverage of the 3D-CRT plan of 95% was less than the IMRT plans with 67.1% versus 92.3% for the IMRT plans. The maximum PTV coverage of the 3D-CRT plans was 85.6% whereas the IMRT plans had a maximum coverage of 97.9%, which was in proximity of the desired PTV coverage of 98%.

4.3.3 PTV 95% coverage

The mean difference of 25.2% indicated that the 3D-CRT plans had a 25.2% less coverage of the 95% PD than that of the IMRT plans. The areas not covered in the PTV by the 95% indicated that the 3D-CRT plans did have larger areas of 95% dose, less than the IMRT plans with 32.9% versus 7.7%. Although both plans did not achieve the desired 2% dose limit allowed for areas in the PTV with less than 95% dose coverage, the plans were accepted by the oncologist (the reasons for this are set out and discussed in Chapter 5). The mean difference of 25.2% indicated that the PTV coverage of the 95% was covered superiorly by the IMRT plans. The standard deviation from the 3D-CRT plans was smaller for the 105%, namely 0.3% versus 0.6%, but larger for the IMRT plans for the 98% and 95%, namely 7.3% versus 2.4% for both. This data on PTV coverage indicated that the 3D-CRT plans were more consistent in keeping the dose low for the 105% but were worse for having the desired 95% coverage to the PTV.

The p-value for the 105%, 98% and 95% PTV coverage of the 3D-CRT versus IMRT (n=26) was $p < 0.0001$. There is thus a statistically, significant difference in the PTV coverage between the 3D-CRT plans versus the IMRT plans.

4.4 CLINICAL TARGET VOLUME COVERAGE

The clinical target volume coverage of the 3D-CRT plans versus the IMRT plans is illustrated in Table 4.2.

Table 4.2 CTV coverage 3D-CRT versus IMRT plans (n=26)

Variable	3D-CRT	IMRT	Mean Difference	P-value
CTV 105%				
Mean % > 105%	0.3%	1.06 %	-0.8%	p < 0.0006
Standard deviation	0.4 %	0.8 %		
Minimum % > 105%	0%	0%		
Maximum % >105%	2.0%	2.8%		
CTV 95%				
Mean % < 95%	14.5 %	0.9 %	13.5%	p < 0.0001
Standard deviation	6.2%	0.7 %		
Minimum % < 95%	3.8%	0.2%		
Maximum % < 95%	24.7%	3.3%		

**3Dimensional-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), clinical treatment volume (CTV).*

4.4.1 CTV 105% coverage

The dose coverage for the CTV was well within the target goals for both 3D-CRT plans and the IMRT plans, with mean values of 0.3% and 1.1%, respectively for the 105%. The 3D-CRT plans had a mean difference of -0.8%; fewer areas of 105% to the PTV than the IMRT plans. The negative values in the mean difference column indicated that the value of the first column (3D-CRT) is smaller than the value in the second column (IMRT).

4.4.2 CTV 95% coverage

The areas of 95% or less were larger for the 3D-CRT plans than for the IMRT plans. The 3D-CRT plans produced areas of less than 95% dose with a mean of 14.5% whereas the IMRT plans had mean dose of 0.9%. The mean difference of 13.5% indicated that the CTV coverage of the IMRT plans was superior to the 3D-CRT plans. The IMRT plans achieved the 2% goal, thus had an improved CTV coverage over the 3D-CRT plans. The standard deviation for the 105% of the 3D-CRT plans were 0.4%

versus the 0.8% for the IMRT plans. However, for the 95% the standard deviation, the 3D-CRT plans were 6.2% versus 0.7% for the IMRT plans. This was an indication that the 105% for both planning techniques produced consistent 105% doses for each plan.

The p-value for the CTV 95% coverage was $p < 0.0006$ and CTV 105% was $p < 0.0001$. There was a statistically significant difference in the CTV coverage between the 3D-CRT plans and the IMRT plans. The IMRT plans did have, on average, smaller areas of low dose coverage. The IMRT plans also had larger areas of dose higher than 105% of the PD.

4.5 ORGANS AT RISK

The OAR each has a different dose tolerance to radiation. The dose for each OAR is listed and compared at certain values to indicate the OAR sparing.

4.5.1 Heart V_{22} and mean dose

Table 4.3 displays the percentage dose that the **V_{22}** of the heart received for the 3D-CRT and IMRT plans, respectively. The average mean dose to the heart is also demonstrated.

Table 4.3 Heart V_{22} and Mean dose 3D-CRT versus IMRT plans (n=26)

Variable	3D-CRT	IMRT	Mean Difference	P-value
V22				
Mean % to the **V_{22}**	7.7 %	2.1 %	5.5 %	p = 0.1222
Standard deviation	2.0 %	2.0 %		
Minimum % to **V_{22}**	3.0%	0%		
Maximum % to **V_{22}**	10.6%	6.3%		
Mean heart dose				
Mean dose to the heart	4.9Gy	5.4Gy	-0.6Gy	p <0.0006
Standard deviation	0.8Gy	0.6Gy		
Minimum Gy to heart	3.0Gy	4.2Gy		
Maximum Gy to Heart	6.9Gy	6.3Gy		

3Dimensional-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), volume receiving 22Gy (V_{22}**).*

4.5.1.1 Heart V22

The average percentage dose to V_{22} of the heart was less than 10% for 3D-CRT and IMRT plans. The IMRT plans on average had a lower percentage of **V_{22}** dose to the heart with a mean difference of 5.5%. The 3D-CRT plans had a maximum percentage dose to the **V_{22}** of the heart of 10.6%, which is just above the goal of 10%. The IMRT plans did reveal that there was a minimum dose of 0%, indicating that there was a plan where the **V_{22}** of the heart did not receive any dose above 22Gy. The p-value for the heart **V_{22}** was p = 0.1222. Statistically, there was no significant difference in the **V_{22}** of the heart between the 3D-CRT and IMRT plans. The standard deviation for these two planning techniques was 2%, indicating that the data could deviate by approximately 2%.

4.5.1.2 Mean heart dose

The mean dose to the heart for the IMRT plans was on average more than the target goal of less than 5Gy (5.4Gy). However, it was approved by the oncologist for inclusion in the study. The 3D-CRT plans had a mean minimum heart dose for all 26 patients of 3.0Gy, which was lower than the 4.2Gy of the IMRT plans. The 3D-CRT plans had a

higher maximum mean dose than the IMRT plans, with 6.9Gy versus 6.3Gy. The standard deviation for the mean heart dose was very similar for 3D-CRT versus IMRT with 0.8Gy versus 0.6Gy, respectively. However, with a p-value of p <0.0006, the mean dose to the heart indicated a statistically significant difference between the 3D-CRT and IMRT plans. The negative values in the mean difference column indicate that the value of the first column (3D-CRT) is smaller than the value in the second column (IMRT).

4.5.2 Oesophagus

Table 4.4 demonstrates the dose received by the oesophagus with the 3D-CRT and IMRT plans, respectively.

Table 4.4 Dose received by the oesophagus for 3D-CRT versus IMRT plans (n=26)

Variable	3D-CRT	IMRT	Mean Difference	P-value
Mean dose				
Mean dose to the Oesophagus	5.1Gy	9.3Gy	-4.2Gy	p< 0.0001
Standard deviation	1.9Gy	2.2Gy		
Maximum dose				
Maximum dose to the Oesophagus	34.6Gy	39.4Gy	-4.7Gy	p< 0.0001
Standard deviation	7.8Gy	5.6Gy		

**3Dimensional-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT).*

The IMRT plans produced a higher average of the maximum and mean dose to the oesophagus than the 3D-CRT plans with 39.4Gy versus 34.6Gy and 9.3Gy versus 5.1Gy, respectively. The reason for this is that a small part of the oesophagus was included in the PTV, and to avoid an area of under dosing in the PTV, the small area of a higher dose to the oesophagus was accepted by the oncologist. The standard deviation for the mean dose for both techniques was similar to 3D-CRT plans (1.9Gy) versus IMRT plans (2.2Gy), thereby indicating that the mean dose of the oesophagus was consistent for all 26 patients' CT images. The standard deviation for the maximum dose for 3D-CRT plans was 7.8Gy versus the 5.6Gy for the IMRT plans, thereby

indicating that the maximum dose can differ significantly for both techniques, but more for the 3D-CRT plans. The p-value for the oesophagus' mean and maximum dose was p< 0.0001. There was thus a significant difference in dose to the oesophagus between the 3D-CRT and IMRT plans. The negative values in the mean difference column indicated the value of the first column (3D-CRT) is smaller than the value in the second column (IMRT).

4.5.3 Lungs

The dose for the left and right lungs that received 18.9Gy is demonstrated as percentages in Table 4.5.

Table 4.5 Dose percentage for the left and right lungs for 3D-CRT versus IMRT plans (n=26)

Variable	3D-CRT	IMRT	Mean Difference	P-value
Mean dose				
Mean percentage of 18.9Gy to the lungs	16.1 %	13.7 %	2.4 %	p< 0.0001
Minimum mean dose	11.6 %	9.9 %		
Maximum mean dose	18.9 %	17.2 %		
Standard deviation	1.7 %	1.7 %		

**3Dimensional-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT).*

Due to a decrease in the dose to the heart, the dose to the lungs were also decreased. For the 3D-CRT plans, the MLC's that were moved in to shield the heart also shielded the lung tissue and thus decreased the dose to the lungs. The percentage of lungs that received 18.9Gy for 3D-CRT plans and IMRT plans were below 30% and within the goal for the lungs. The mean difference of 2.4% indicated that the IMRT plans had on average less dose of 18,87Gy to the lungs than the 3D-CRT plans. The standard deviation for both techniques was 1.7%, indicating that there was some consistency in the dose to the lungs. The p-value for the lungs mean was p< 0.0001, which indicates that there is a significant difference in dose to the lungs between the 3D-CRT and IMRT plans, respectively.

4.5.4 Left lung

The mean differences in the percentage of the dose to the left lung that received 18.9Gy for each planning technique is illustrated in Table 4.6

Table 4.6 Percentage of dose to the left-lung of 18.9Gy for 3D-CRT versus IMRT plans (n=26)

Variable	3D-CRT	IMRT	Mean Difference	P-value
Mean dose				
Mean percentage of 18.9Gy to the left lung	33.5 %	28.1 %	5.4 %	p< 0.0003
Minimum mean dose	14.1%	16.5%		
Maximum mean dose	40.7%	34.2%		
Standard deviation	5.7 %	4.7 %		

**3Dimensional-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT).*

The percentage of lung receiving 18.9Gy was less than 35% for both the 3D-CRT- and IMRT plans, which were within the set goal for the dose to the left lung. However, the IMRT plans had the lowest average dose of the two planning techniques. The 3D-CRT plans had a maximum of 40.7% in comparison with the IMRT's maximum that was 34.2%. The mean difference of 5.4% indicated that the IMRT plans had on average less dose of 18.9Gy to the left lung. The standard deviation for the mean percentage of 18.9Gy was 5.7% versus 4.7% for 3D-CRT and IMRT plans, respectively. The p-value for the left lung's mean was p< 0.0003. There is thus a significant difference in dose to the left lung between the 3D-CRT and IMRT plans, respectively.

4.5.5 Left humeral head

Table 4.7 demonstrates the mean maximum dose to the left humeral head for each of the planning techniques.

Table 4.7 Maximum dose to the left humeral head for 3D-CRT versus IMRT plans (n=26)

Variable	3D-CRT	IMRT	Mean Difference	P-value
Maximum dose				
Mean maximum dose to the humeral head	37.4Gy	34.6Gy	2.9Gy	p < 0.0001
Minimum dose	33.5Gy	32.7Gy		
Maximum dose	40Gy	38.3Gy		
Standard deviation	1.5Gy	1.5Gy		

**3Dimensional-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT).*

The maximum dose to the humeral head was higher on average for the 3D-CRT plans. It is important to note that this was not the dose the entire humeral head received (refer Fig. 3.3), but only the maximum dose to an area of the humeral head closest to the PTV. This was the case for some of the patients only, since the anatomy of each patient is unique, and therefore the size of the supraclavicular fossa CTV may be smaller for some patients resulting in a smaller PTV, thus the PTV is further away from the humeral head and vice versa. The IMRT plans had a mean difference of 2.9Gy less for the maximum dose to the left humeral head than the 3D-CRT plans. The standard deviation for both 3D-CRT and IMRT plans was 1.5Gy on the maximum dose, thereby indicating a small deviation between the plans on the dose to the left humeral head. The p value of the left humeral head was $p < 0.0001$. There is thus a significant difference in dose to the left humeral head between the 3D-CRT and IMRT plans, respectively.

4.5.6 Right breast

The mean percentage of 5Gy delivered to the right breast is illustrated for each planning technique in Table 4.8

Table 4.8 Percentage dose to R-breast 3D-CRT versus IMRT plans (n=26)

Variable	3D-CRT	IMRT	Mean Difference	P-value
Mean dose				
Mean percentage of 5Gy to the right breast	3.5 %	11.4 %	-7.8 %	p < 0.0001
Minimum % of 5Gy	0%	2.3%		
Maximum % of 5Gy	16.4%	22%		
Standard deviation	4.6 %	5.0 %		

**3Dimensional-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT).*

The average dose to the right breast was lower for the 3D-CRT plans with a mean difference of 7.84% in comparison to the IMRT plans. The higher dose to the right breast in the IMRT plans was as a result of (a) the volume of the breast tissue that was in close proximity to the PTV, and (b) to limit the areas receiving less than 95% of the PD in the medial aspect of the PTV the dose to the contralateral breast was higher.

The minimum percentage of 5Gy to the right breast for the 3D-CRT plan was 0% and that indicated that the right breast received 0% of the 5Gy. Therefore, this percentage could indicate that the 3 D-CRT plan has advantages in sparing the right breast when compared to IMRT. The mean difference of 7.8% indicated that the 3D-CRT plans had 7.8% less dose of 5Gy to the right breast. The standard deviation for 3D-CRT versus IMRT was similar with 4.6% versus 5.0%, respectively. Thereby, indicating that both planning techniques had similar deviations in the percentage of 5Gy delivered to the contralateral breast. The p value for the right breast was $p < 0.0001$. There is thus a significant difference in the mean dose of 5Gy to the right breast between the 3D-CRT and IMRT plans, respectively. The negative values in the mean difference column indicated the value of the first column (3D-CRT) is smaller than the value in the second column (IMRT).

4.5.7 Spinal cord

Table 4.9 presents the mean of all the maximum doses to the spinal cord of the 26 patients' CT images for both the planning techniques.

Table 4.9 Spinal cord maximum dose 3D-CRT versus IMRT plans (n=26)

Variable	3D-CRT	IMRT	Mean Difference	P-value
Maximum dose				
Mean maximum dose to the spinal cord	22.6Gy	13.3Gy	9.4Gy	p < 0.0006
Minimum dose	4.1Gy	10.6Gy		
Maximum dose	37.4Gy	14.2Gy		
Standard deviation	9.0Gy	1.4Gy		

**3Dimensional-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT).*

For both techniques the dose to the spinal cord was within the goal maximum dose for the spinal cord, that is a maximum dose < 43.5Gy. The 3D-CRT plans did have a minimum of 4.1Gy that was less than the 10.6Gy for the IMRT plans. The IMRT plans however, had a maximum dose of 14.2Gy that was less than the 37.4Gy for the 3D-CRT plans. The IMRT plans had a mean difference of 9.4Gy less maximum dose to the spinal cord than the 3D-CRT plans. The standard deviation for the 3D-CRT was larger than that of the IMRT plans with 9.0Gy versus 1.4Gy, respectively. This demonstrated that the 3D-CRT plans were less consistent with regard to the dose to the spinal cord in comparison with the IMRT plans. The p-value for the spinal cord was p < 0.0006. There is thus a significant difference in dose to the spine between the 3D-CRT and IMRT plans, respectively.

4.5.8 Normal and unspecified tissue dose

Table 4.10 demonstrates the mean dose to the normal- and unspecified tissues not delineated as a PTV or an OAR, respectively. It also illustrates the mean percentage of 5Gy that the unspecified tissue received for the 26 patients' CT images.

Table 4.10 Normal tissue dose for 3D-CRT versus IMRT plans (n=26)

Variable	3D-CRT	IMRT	Mean Difference	P-value
Mean dose				
Mean dose to the normal tissue	3.1Gy	4.9Gy	-1.8Gy	p < 0.0001
Standard deviation	0.7Gy	0.6Gy		
Percentage of tissue receiving 5Gy			-12.0%	
Mean percentage of 5Gy to the unspecified tissue	12.9 %	24.9 %		
Standard deviation	2.9 %	3.1 %		

**3Dimensional-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT).*

The 3D-CRT plans demonstrated lower doses and percentages of 5Gy concerning the normal/unspecified tissue of the IMRT plans (Table 4.11). The higher percentage doses for IMRT plans were the result of the intensity modulation of the IMRT beams that delivered an increase in dosage to the normal tissue of 12% for the V5 due to the beam orientation, beam modulation and exit dose, respectively. The standard deviation for the mean dose was similar for both the 3D-CRT and IMRT plans with 0.7Gy versus 0.6Gy, respectively. The standard deviation for the tissue receiving 5Gy was similar for the 3D-CRT and IMRT plans with 2.9% versus 3.1%, respectively. The p-value for the mean dose to the normal tissue was p < 0. 0001. There is thus a significant difference in dose to the normal tissue between the 3D-CRT and IMRT plans, respectively. The negative values in the mean difference column indicate that the value of the first column (3D-CRT) is smaller than the value in the second column (IMRT).

4.6 DOSE VOLUME HISTOGRAMS

The DVH's was created for each patient scan, and the data for both the 3D-CRT plan and the IMRT plan were displayed on the DVH. Data collected from the DVH's for both planning techniques are presented in Appendix I. The PTV coverage with the OAR

sparing of the created plans of “patient 18” was close to the ideal IMRT plan in this study. Although the plan of “patient 17” had a similar 95% coverage, the 105% was higher. The created 3D-CRT plans for “patients 17 and 18” demonstrated a superior PTV coverage in comparison with that of the IMRT plans. The lowest mean dose to the heart was produced with the 3D-CRT plan for “patient 7” with 3.0Gy. The V_{22} for the heart of the IMRT plan was 0.1%. The V_{22} for the created IMRT plan of “patient 20” was 0%, thereby indicating that the IMRT plan had no dose to the heart of 22Gy or more. The created 3D-CRT plan of “patient 10” indicated that no dose of 5Gy was received by the contralateral breast. The created 3D-CRT plan of “patient 6” had the lowest unspecified tissue dose of 10.1% receiving 5Gy.

4.7 COMPARATIVE CT IMAGES OF 3D-CRT VERSUS IMRT PLANS

The following images demonstrate the comparisons observed between the (a) dose conformity; (b) dose to the heart; and (c) the dose to the PTV of the 3D-CRT plans (bottom) and IMRT plans (top), respectively. This patient’s CT images were chosen randomly for illustration purposes and the specific CT slice was chosen to illustrate the structures of interest (OAR).

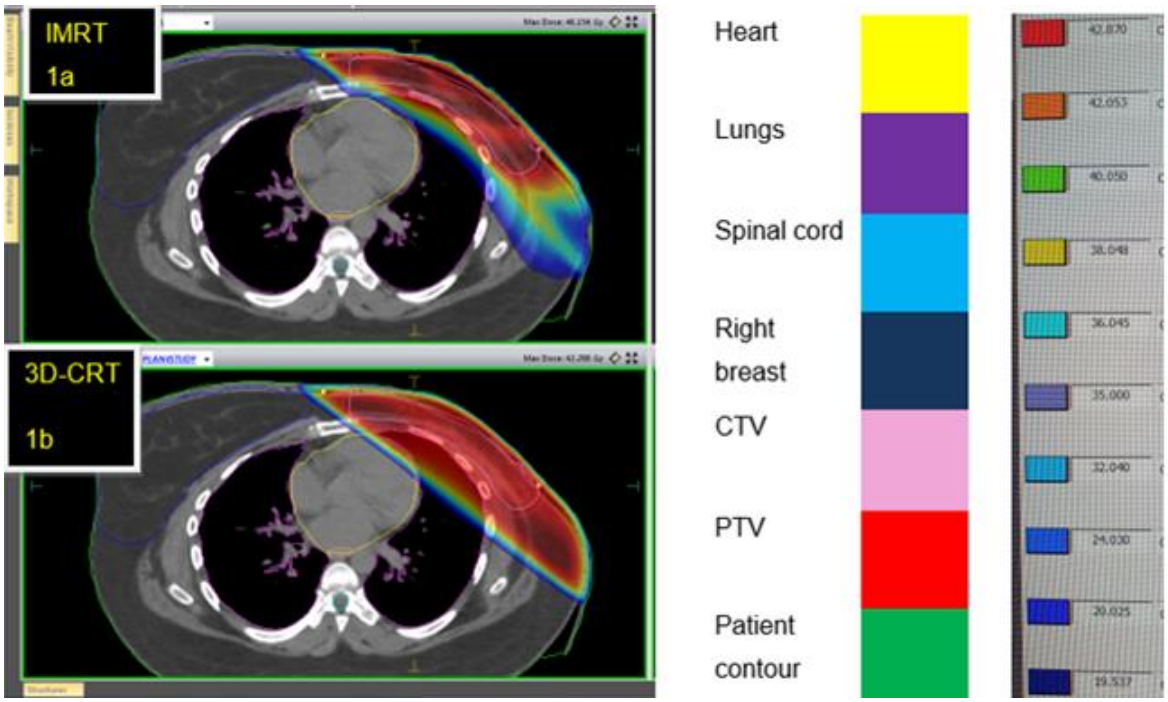

Figure 4.1 Transverse plane indicating dose coverage to the PTV

(CT Images: Courtesy of Oncology Department, University of the Free State, Monaco Planning, System, (V5.11.02).

Figure 4.1a demonstrates how the IMRT (top image) conforms superiorly to the PTV as opposed to the 3D-CRT in Figure 1b (bottom image). In Figure 4.1a the area in the medial aspect of the PTV can be seen to have less dose coverage of 95%, as indicated in orange in the image. The larger area of left lung covered by the higher dose in the 3D-CRT plan (bottom image) can be seen. Figure 4.1a also indicates that the dose to the heart is less than the dose to the heart in Figure 4.1b.

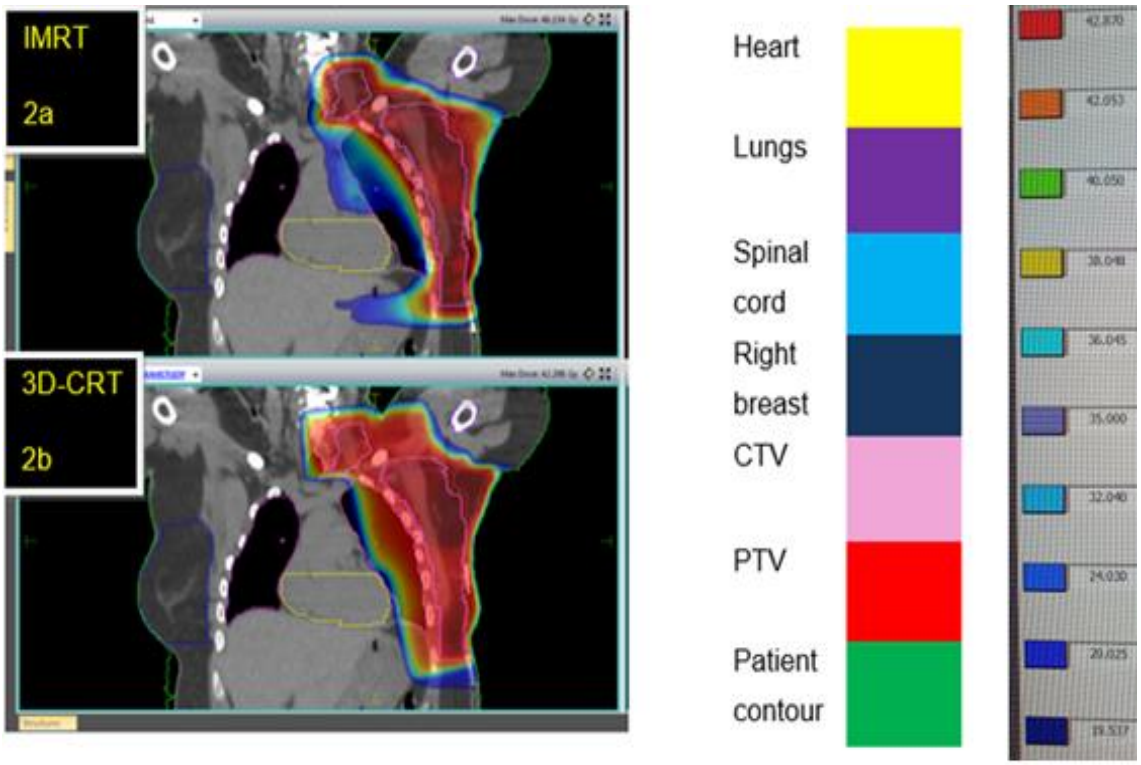

Figure 4.2 Coronal plane indicating dose to the heart

(CT Images: Courtesy of Oncology Department, University of the Free State, Monaco Planning, System, (V5.11.02).

Figure 4.2 demonstrates the dose to the heart for the 3D-CRT- and the IMRT plans, respectively. The dose in the IMRT plan (Fig 4.2a) conforms superiorly to the PTV and thus less dose to the heart and the left lung can be observed. In (Fig. 4.2b) the dose can be observed over a larger area of the left lung than in (Fig. 4.2a). The dark red areas in the IMRT plan (Fig. 4.2a) indicate a higher dose on the plan than the lighter red on the 3D-CRT plan (Fig. 4.2b). Figure 4.2a & b also demonstrate that the heart

does not receive a high dose in any of the planning techniques, as there is no yellow, red or dark red colour wash over the heart in the images.

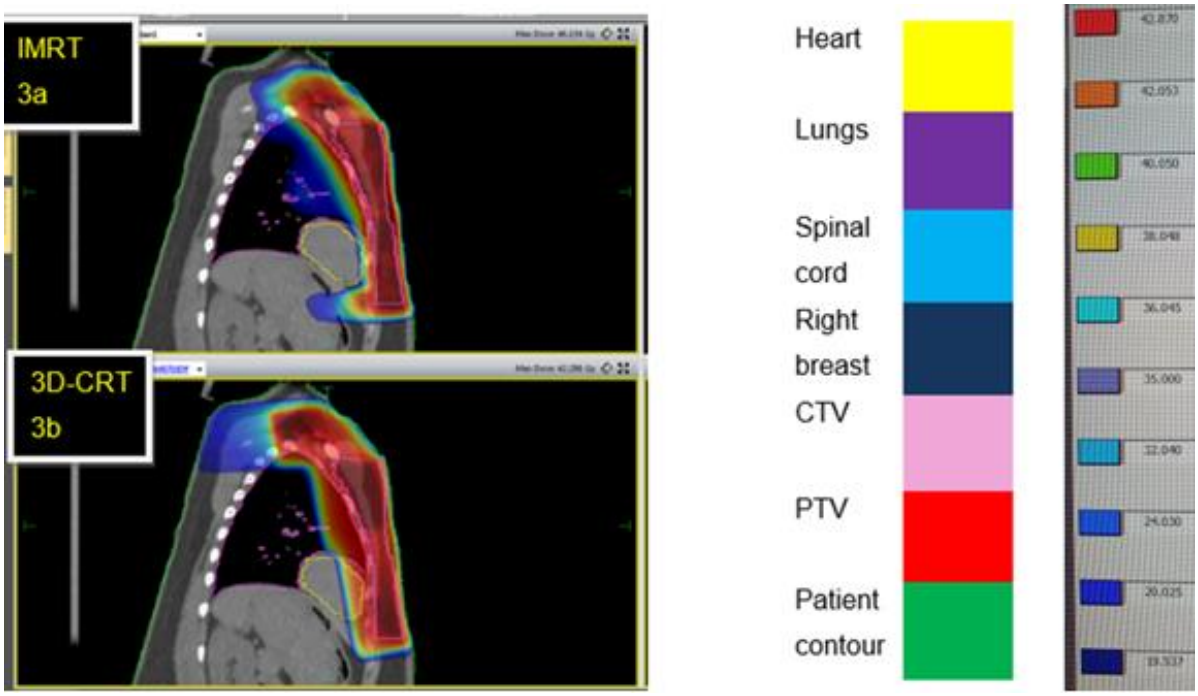

Figure 4.3 Sagittal plane indicating the dose conformity to the PTV

(CT Images: Courtesy of Oncology Department, University of the Free State, Monaco Planning, System, (V5.11.02).

Figure 4.3 demonstrates the dose conformity to the PTV and CTV. It is visible on the image that there is less dose over the heart and left lung in the IMRT plan (Fig. 4.3a) but there are areas of low dose indicated in blue. The straight lines in the dose distribution for the 3D-CRT (Fig. 4.3b) as opposed to the curved lines of the IMRT plan (Fig. 4.3a) indicate the conformity differences between the 3D-CRT and IMRT, indicating that the IMRT conforms superiorly to the PTV.

4.8 HETEROGENEITY INDEX AND CONFORMITY INDEX

The heterogeneity index (HI) and conformity index (CI) are indicators of the quality of the plan. These indicators are not solely used to verify a plan, but aid in the decision whether a plan is to be approved for the treatment of a patient or not. HI and CI are only reported in Monaco created plans, thus for the IMRT plans included in this study.

The HI describes the uniformity of dose within the PTV or target volume. The formula used is HI = (D5% - D95%), where the D5% is the dose delivered to the hottest 5% and 95% is the minimum dose delivered to the tissue.

The CI describes the degree to which the prescribed dose conforms to the shape and size of the PTV or target volume. Table 4.11 illustrates the HI and CI values for the IMRT plans that were created and used in this study.

Table 4.11 HI and CI minimum and maximum values

Variable	HI minimum	HI maximum	Mean	CI minimum	CI maximum	Mean
PTV	1.1	1.2	1.1	0.3	0.6	0.4
CTV	1.0	1.1	1.1	0.2	0.5	0.3

Heterogeneous index (HI), conformity index (CI), planned treatment volume (PTV), clinical treatment volume (CTV).

As indicated in Table 4.12, the CI and HI values indicate that the IMRT plans did conform to the PTV and CTV, respectively. The values also indicate that the dose was heterogeneous. Both the PTV and CTV did have values for the HI close to 1. The values for the CI are within 1 of the desired value of 1, thus indicating that the conformity was in the desired specifications.

4.9 CONCLUSION

The study aimed to provide 3D-CRT and IMRT plans with a heterogeneous and conformed dose to the PTV and CTV with no areas with a high dose of more than 105% and areas of low dose less than 95%. Moreover, it was important to keep the dose to the OAR below the goal dose for the plans. The results of the comparative research study of 3D-CRT versus IMRT plans of post-mastectomy patients have demonstrated both similarities and differences regarding the PTV-, CTV dose coverage and dose delivered to the OAR.

The 3D-CRT plans differed from the IMRT plans, with less PTV coverage and fewer areas of 105%. However, the dose conformity achieved with the IMRT plans was superior to the PTV and therefore minimal dose was administered to the heart and the left lung. The dose to the lungs and left lung were similar for both techniques, as both

techniques reflected the dose to the OAR within the goal dose. The dose to the heart was similar for both techniques, as both achieved the desired goal dose, as was the dose to the oesophagus and left humeral head. The dose to the contralateral breast was different as the 3D-CRT plans had less dose of 5Gy to the breast than the IMRT plans. There may be several reasons for these results, which are discussed in the next chapter.

CHAPTER 5

DISCUSSION

5.1 INTRODUCTION

The stages listed (see Fig. 3.1) led to the data collected for Chapter 4. A discussion of the resulting data are henceforth presented in this chapter. Technological advancements in cancer imaging and therapy planning techniques made it possible to deliver a precisely measured dose of irradiation to a defined tumour volume with as minimal radiation damage as possible to the surrounding OAR, resulting in eradication of the tumour. The current retrospective research study compared the "old" technology with the "new" to provide the best radiation therapy planning technique for post-mastectomy patients diagnosed with left breast, chest wall and supraclavicular fossa cancer. The outcome will demonstrate whether the 3D-CRT or IMRT planning technique delivered superior dose coverage of the PTV, CTV and minimal dose delivered to the OAR.

When considering how to achieve the best outcome from radiotherapy in the treatment of tumours, it is critical to understand the concept of therapeutic ratio. Barrett *et al*. (2009) defines the therapeutic ratio concept as follows: "Cure is always achieved at some cost in terms of normal tissue damage. There must be a balance between trying to ensure that all tumour cells receive a lethal dose of radiation and that acute and late effects are tolerable".

In the present study, the treatment plans were compared by utilising the DVH data. The PTVs and CTVs of the created 3D-CRT and IMRT plans were the targets and the dose coverage of these planning techniques was compared. The goal was to compare the 95% dose coverage for the PTV and CTV of both plans for possible underdosing and the 105% dose coverage for overdosing of the PTV and CTV. The dose delivered to the OAR was also compared and included the heart, left lung, both lungs, spinal cord, oesophagus, left humeral head, right breast and the normal tissue. The goal

doses (Chapter 3, Table 2) for each OAR were compared to identify which of the planning techniques provided a superior OAR sparing effect.

5.2 PLANNED TARGET VOLUME COVERAGE

The treatment of the PTV will have an influence in the overall tumour control. The desired PD should cover the PTV to have an acceptable plan for treatment.

5.2.1 Limiting factors of PTV coverage

The limiting factor for the PTV coverage of the 3D-CRT plans was the single isocenter approach, as per departmental protocol, which only allowed for a maximum field length of 20cm inferiorly. However, although a single isocenter approach was adopted for the PTV coverage of the IMRT plans, the isocenter placement was in the middle of the PTV and therefore the field length was not a limiting factor. Based on the researcher's experience with breast planning, the lateral aspect of the CTV and therefore the PTV, was not sufficiently included in the 95% dose coverage due to the mastectomy scar that needs to be included in the CTV of the treatment plan. In the researcher's experience, if the mastectomy scar is more posterior than the mid-axillary line, the coverage of the PTV becomes difficult.

In contrast, the lateral aspect of the CTV with the IMRT plans did cover the lateral-posterior aspect. The 3D-CRT plans covered the left chest wall and supraclavicular area with the axillary area sufficiently; the IMRT plans covered the entire PTV.

5.2.2 Dose coverage of PTV

The mean dose coverage of the 3D-CRT plans demonstrated that the 95% dose did not cover the lateral-posterior area of the PTV, while the IMRT plans did cover the lateral-posterior part of the PTV sufficiently. Figure 5.1 demonstrates the PTV dose coverages for 3D-CRT- and IMRT plans, respectively. The yellow circle indicates the area on the 3D-CRT plan where the 95% dose does not cover the PTV, where the same area is covered by the 95% for the IMRT plan. This research has established that for 24 of the 26 created 3D-CRT plans, where the mastectomy scar was not included with beam coverage lateral-posteriorly, the 95% dose did not cover the lateral-posterior area of the PTV.

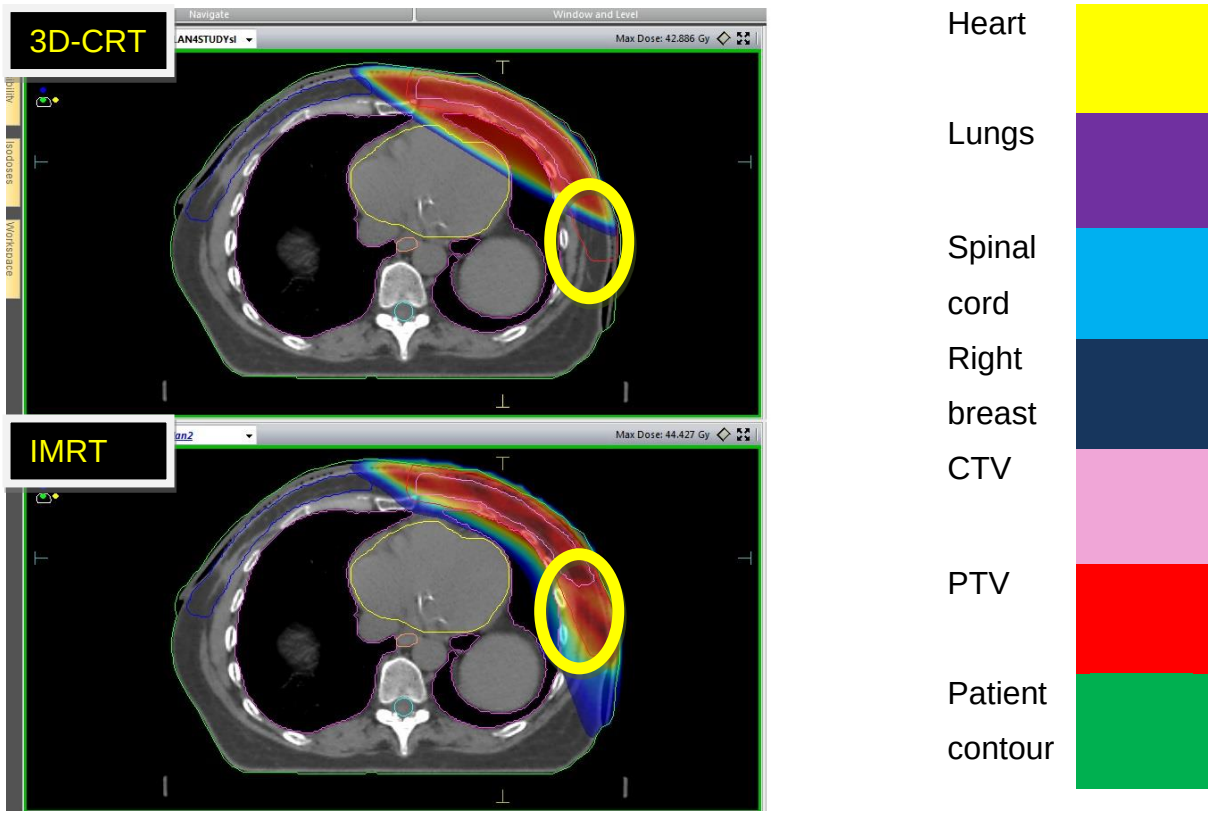

Figure 5.1 PTV Dose coverage

(CT Images: Courtesy of Oncology Department, University of the Free State, Monaco Planning, System, V5.11.02).

The study conducted by Schubert, *et al*. (2011) compared four different treatment planning techniques, which included 3D-CRT and Inverse IMRT. In their study, the IMRT plans had similar PTV coverage to the 3D-CRT plans. The 3D-CRT plans had a higher maximum dose (56.8Gy) than the inverse-IMRT plans (53.9Gy) for the PTV. The study used a PD of 50Gy in 25 fractions. The inverse-IMRT plans had superior PTV homogeneity to the 3D-CRT plans and had reduced the hotspots. However, his study was conducted on breast cancer patients who did not have a mastectomy but breast conserving surgery.

The current study has demonstrated that the IMRT plans, in comparison to the 3D-CRT plans, had a mean dose for the 105% coverage of 1.1%, which was higher than the 3D-CRT plans with a 105% coverage of 2%. However, this PTV coverage was within the 2% goal for the 105% margin. The 98% PTV dose coverage of the IMRT plans were 92.3%, which means the PTV was under dosed. The reason for the under dosage was due to the medial aspect of the PTV over the heart area. The underdosing

of the medial aspect of the PTV was necessary to keep the heart dose within the set goals of V22Gy < 10% and mean dose < 5Gy. There was also an area of under dose due to the effort to limit the dose to the right breast.

Haciislamoglu *et al*. (2015) published a study wherein the authors compared 3D-CRT with forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and volumetric arc therapy for whole breast irradiation of the left side. The authors concluded that the maximum dose to the PTV was higher than 107% of the PD and achieved 100% average coverage to the PTV. The high dose limitation of 105% did have an impact on the dose coverage of 95%. Should the high dose of 107% have been accepted as in the study by Haciislamoglu, *et al*. (2015), the 95% coverage to the 3D-CRT and IMRT plans would have been closer to the desired 98% coverage.

5.3 CLINICAL TARGET VOLUME COVERAGE

The clinical target volume (CTV) is a volume of tissue with suspected tumour tissue. The PTV denotes the CTV with margins for geometric uncertainties (Halperin, *et al.*, 2013). This indicates that the CTV is entirely inside the PTV and thus, should be covered with the prescribed dose (PD). The researcher created 3D-CRT- and IMRT treatment plans that covered the CTV with the PD of 40.05Gy, as per the departmental protocol. It was thus necessary to have 100% of the CTV with 95% dose or 38.04Gy and to have less than 2% of dose higher than 105% or 42.05Gy.

The CTV coverage of the 3D-CRT plans had a mean of 0.3% higher dose than 105% and 95% covered a mean of 85.5% of the CTV. In comparison, the CTV coverage of the IMRT plans had a mean of 1.1% higher than 105% and 95% covered a mean of 99.1% of the CTV. The underdosed area for the 3D-CRT plan of the 95% was also as a result of the mastectomy scar that was not included in the TAN fields and that was supplemented by a single electron field.

The p-value for the CTV 95% coverage was $p < 0.0006$ and CTV 105% was $p < 0.0001$. There is a statistically significant difference in the CTV coverage between the 3D-CRT plans versus the IMRT plans. The IMRT plans did have on average a smaller area of dose less than 95%, but did also have larger areas of dose higher than 105% of the PD. The IMRT plans for the 26 patients in this study proved superior CTV coverage over that of the 3D-CRT plans. The IMRT plans did cover more of the CTV with 95%

of the PD. The length of the mastectomy scar influenced both planning techniques, in decreasing the coverage to the CTV in the attempt to keep the OAR dose as low as possible.

5.4 DOSE TO ORGANS AT RISK

The dose to the OAR should be limited as there is a threshold to the dose an organ can tolerate before permanent or irreversible damage occur (Milano, *et al*., 2007). This damage can lead to irreversible long-term radiation damage, decrease the quality of life and eventually cause the death of the patient, depending on the organ. Each organ has a different tolerance to radiation damage. When the tolerance dose for an OAR is exceeded the probability of permanent organ damage or organ death increases. The dose given within the tolerances are considered safe practice.

5.4.1 Heart V_{22} and mean dose

Radiation damage to the heart can lead to radiation-induced cardiac disease and damage to the lungs, which can lead to radiation-induced pneumonitis and fibrosis. This is known as late radiation toxicity to the heart and will hereafter be discussed. The dose to the heart received from the 3D-CRT and IMRT plans in the study was one of the main areas of interest (see 2.3.2.1). The authors Darby, *et al.* (2010) indicated that radiation dose to the heart can lead to pericarditis, pericardial fibrosis, diffuse myocardial fibrosis and coronary artery disease. With maximum total dose over 20Gy, the evidence has revealed that radiation-related heart disease can occur (Darby, *et al.*, 2010). The goal of creating the treatment plans for left breast cancer patients was to indicate the dose received by the heart. The dose to the heart can be an area of difficulty when creating a plan for left sided breast cancer. In light of the aforementioned, it was necessary to achieve a mean total dose of less than 5Gy to the heart and a V_{22} less than 10% of the dose to the heart, as that is the tolerance dose levels for the heart.

The 3D-CRT plans had a mean dose for the V_{22} of 7.7%, with a standard deviation of 2%, which is within the goal for the heart dose. The mean doses to the heart for the 3D-CRT plans were 4.9Gy and were within the set goals for the study (see Table 4.3). The IMRT plans had a mean dose for the V_{22} of 2.1% and were 5.5% less than the dose for the V_{22} of the 3D-CRT plans. The mean dose to the heart of the IMRT plans

was 5.4Gy and therefore 0.6Gy more than the mean dose for the 3D-CRT plans. Additionally, the mean dose for all the IMRT plans to the heart was higher than the goal of 5Gy, but within an acceptable range. These results were similar to published findings of Beckham, *et al*. (2007). These authors indicated that the IMRT plans rendered less dose to the heart than the conventional treatment plan/s. The authors compared the IMRT plan with the conventional treatment plan or 3D-CRT, of which only the plans they considered to be the best of each modality was compared. Their study used 50Gy in 25 fractions for their PD.

The 3D-CRT plans had inferior OAR sparing compared to the IMRT plans for the V_{22} of the heart. However, the mean dose to the heart was inferior for the IMRT plans. As a result, the heart dose of the two plans was within the acceptable range.

5.4.2 Oesophagus

With regard to the maximum dose to the oesophagus, the main goal was to keep the maximum dose below 30Gy. In both the 3D-CRT and the IMRT plans, the maximum dose of the oesophagus was higher, with the mean of the 3D-CRT at 34.6Gy and the IMRT at 39.4Gy, respectively. The reason for the higher maximum dose delivered was due to a small part of the superior part of the oesophagus being within the PTV. The 3D-CRT plans did on average save more of the dose to the oesophagus than the IMRT plans.

The occurrence of secondary oesophageal cancer among breast cancer survivors is of concern because the oesophagus is within or near the border of several radiotherapy fields commonly used to treat breast cancer. The supraclavicular field with a medial border at or over the midline resulted in the highest mean doses to the oesophagus, particularly the upper region. With oesophageal tumour location, the risk was 8.3-fold increased when doses reached ≥35 Gy (Morton, *et al.,* 2012)

However, in an article published by Milano, Constine, and Okunieff (2007), the authors state that two-thirds of the oesophagus can receive a maximum of 58Gy and a third can receive 60Gy with a mean of more than 34Gy, indicating that the 39.4Gy is within acceptable doses.

5.4.3 Lungs

The lungs, which are located beneath the breasts, are among the most critical organs in radiation therapy in the treatment planning for breast cancer. As the essential organ for respiration, reduction of lung damage during breast cancer radiotherapy is vital. Radiation pneumonitis (RP), which decreases the quality of life (QoL), is the most common pulmonary complication in patients receiving breast irradiation (Lee, *et al.*, 2015).

The goal for both lungs (left and right lung contoured together) in this study was that V18.9Gy should be less than 30% of the lungs' dose (see Table 1.2). The lungs of the 3D-CRT treatment plans had a mean percentage of 16.1% to the 18.9Gy and the lungs of the IMRT plans had a mean of 13.7% to the 18.9Gy. The IMRT plans had superior OAR sparing of the lungs compared to the 3D-CRT plans.

5.4.4 Left lung

The left lung or ipsilateral lung had a goal that dose of 18.9Gy should be less than 35%. The 3D-CRT plans had a mean of 33.5% with a standard deviation of 5.7%. The IMRT plans had a mean of 28.1% with a standard deviation of 4.7%. Both techniques met the goals of V18.87 less than 35%. The IMRT plans did deliver plans with superior OAR sparing, with a mean difference of 5.4% less dose to the ipsilateral lung. This is similar to the results indicated by Ayata, *et al.*, 2011), with 3D-CRT techniques delivering a higher dose to the ipsilateral lung than the IMRT techniques. It must be noted though that their study compared patients that had breast-conserving surgery and not a mastectomy.

The study done by Wen, *et al*., (2017) indicated that their findings suggest a threshold for V20 of 39,8% and V30 of 2,7% being optimal cut-offs for symptomatic radiation pneumonitis (SRP). This is however derived from a limited number of patients and caution should be taken when applying these thresholds. The study employed 45-50Gy PD in 1.8-2Gy fractions.

5.4.5 Left humeral head

The maximum dose to the left humeral head should be less than 35Gy, which is applicable to the entire organ. In this study, the mean of the maximum doses for the 3D-CRT plans of the humeral head was 37.4Gy with a standard deviation of 1.5Gy. The IMRT plans had a mean of the maximum doses to the humeral head of 35.6Gy

and a standard deviation of 1.5Gy. The IMRT plans had a lesser mean dose of 2.9Gy to the humeral head compared to the 3D-CRT plans. In a study conducted by Ma, *et al.*, (2013) on post-mastectomy IMRT treatment of chest wall and regional nodes: dosimetry data and acute toxicities, the humeral head had a D_{mean} of 23.98 ± 9.25Gy. However, during this specific study a total dose of 50Gy in 25 fractions was utilised. This indicates that the dose to the ipsilateral humeral head can still be limited and be within the desired goal dose. The IMRT plans had lower maximum doses to the humeral head compared to the 3D-CRT plans.

5.4.6 Right breast

The contralateral breast or the right breast's goal dose was 5Gy less than 15% of the patients' plan. The 3D-CRT plans had a mean percentage of 5Gy to the breast of 3.5%, which is within the goal dose to the right breast. The IMRT plan had a mean dose of 5Gy to the breast of 11.4% and is lower than the pre-set goal dose, but higher than the 3D-CRT plans. The main reason for the higher contralateral breast dose is the loss of dose to the medial part of the PTV if the breast dose is to be within the set goal dose.

The absolute risk of contralateral breast cancer from modern radiotherapy should be well under 1%, and the risk of death from this late radiation effect should be smaller still (Taylor, *et al.*, 2017).

The higher dose to the right breast for the IMRT plans is similar to the findings of (Beckham, *et al.* (2007), who found that the IMRT plans had higher doses to the right breast than the conventional radiation therapy planning, with the IMRT delivering 29.2% versus 7.9% for the standard plan to the V5 of the right medial breast.

The study conducted by Ayata, *et al.* (2011), demonstrated that the plans for IMRT had higher doses to the contralateral breast. The authors mentioned that a higher dose to the contralateral breast is especially important for younger patients, as they have a statistically significant risk of contralateral breast cancer.

The larger percentage of tissue exposed to low doses of radiation will increase the risk of radiation-induced secondary cancers (Zhang, *et al*., 2020). According to the authors, approximately 80% of secondary cancers are located close to the treatment field or within the treatment field.

The 3D-CRT plans obtained superior dose sparing of the right breast when compared to the IMRT plans. The superior dose sparing in the contralateral breast can lead to a decrease in the chance for secondary malignancies in the contralateral breast, especially for younger patients.

5.4.7 Spinal cord

The spinal cord had a set dose for the maximum dose to be less than 43.5Gy, which is higher than the PD of the plan of 40.05Gy. Both the planning techniques achieved the goal dose of less than 43.5Gy. The 3D-CRT had a mean maximum dose of 22.6Gy and the IMRT had a mean maximum dose of 13.3Gy to the spine. The IMRT plans did prove to be superior to the 3D-CRT plans in delivering less dose to the spinal cord. The study conducted by Ma, *et al*. (2013) indicated that their study achieved a maximum dose of 36.1Gy. This suggests that the spinal cord is not a great risk of being overdosed.

5.4.8 Normal and unspecified tissue dose

The goal of this study was for the normal tissue or unspecified tissue to have a dose of 5Gy to be less than 20%. The mean dose to the unspecified tissue for the 3D-CRT plans was 3.1Gy and for the IMRT it was 4.9Gy, indicating that the mean was below the goal dose of less than 5Gy, but the volume of normal tissue receiving 5Gy is smaller for the 3D-CRT.

The percentage of normal tissue that received 5Gy for the 3D-CRT plans was 12.9% and for the IMRT plans it was 24.9%. These results are similar to the results of Beckham, *et al.* (2007), where their study indicated the percentage that received more than 5Gy was also larger for the IMRT than for the conventional treatment planning. The higher percentage of 5Gy to the IMRT patients can be contributed to the modulation of the beams and the beam orientation used in this study.

Abo-Madyam, *et al*. (2014) investigated doses to normal tissue that received low doses of more than 2Gy, by comparing the doses to the normal tissue of 3D-CRT, IMRT and VMAT. The results of that study revealed that in those models created, the 3D-CRT had a 34% and 50% lower risk, respectively for secondary cancers occurring, compared to multi-beam IMRT and volumetric intensity arc therapy (VMAT).

The 3D-CRT did deliver smaller areas of low dose to the unspecified tissue than the IMRT plans. This may indicate a lower risk for secondary malignancies for the 3D-CRT plans opposed to the IMRT plans.

5.5 DATA COLLECTED FROM DOSE VOLUME HISTOGRAMS

DVHs may aid selection of the superior plan but these histograms do not indicate which part of the organ is receiving a high or low dose; DVHs of the PTV, CTV are needed to indicate the possible clinical outcome (Barrett, *et al*., 2009). In order to access the plan, the DVH's created for each plan were compared, the dose to the PTV and CTV were evaluated, as were the dose to each OAR. The information from the DVH determined whether the plan could be accepted or if there were areas of improvement to consider.

The data collected from the DVH's indicated that the main trends for the 3D-CRT plans were less PTV coverage than for the IMRT plans. By complying to the tolerated doses for the OAR, the dose to the PTV was under dosed. The area of PTV that was not covered sufficiently by the TAN fields was supplemented by an additional electron field. The 3D-CRT plans had lower percentages of low doses to the patient's normal tissue than the IMRT plans. The low dose to the right breast tissue was also less than for the IMRT plans. This was as a result of the beam angle manipulation of the 3D-CRT plans.

The trends for the IMRT plans were superior coverage on the PTV and CTV. IMRT plans had superior dose conformity to the PTV and CTV compared to the 3D-CRT, which was indicated by the data from the DVH's. IMRT had lower doses for some of the OAR, such as the ipsilateral lung, lungs, and heart, but with much higher percentages of low doses to the contralateral breast and the normal tissue of the patients, as indicated by the DVH comparisons.

5.6 COMPARATIVE CT IMAGES OF 3D-CRT VERSUS IMRT PLANS

The transverse plane's images (Chapter 4.1) of the PTV coverage revealed that the IMRT plans had conformed superiorly to the PTV, as opposed to the 3D-CRT plans, which proved to be similar to the results published by Beckham, *et al*. (2007), where they compared conventional TAN plans with IMRT plans. On the coronal plane images of the OAR the dose to the left lung and the heart could be seen to be less in the IMRT

plan as compared to the 3D-CRT plan. Also, a larger area of a low dose in the IMRT plan was observed when compared with the OAR of the 3D-CRT image. On the sagittal plane (see Fig. 4.3), the low dose to the lung can be observed in blue for the IMRT plan. The linear dose distribution as well as the larger area of high dose to the lung for the 3D-CRT plan can be observed, as indicated in red.

5.7 CONCLUSION

The outcome of this comparative research study has provided an argument for each technique in order to produce/generate a feasible planning and treatment option for post-mastectomy, left breast cancer patients that include the supraclavicular fossa.

The comparison between the 3D-CRT plans and the IMRT plans yielded results that can be interpreted as both planning techniques being beneficial. However, in order to produce a viable plan, the dose to the PTV should be acceptable as well as the dose to the OAR. A viable plan is one that adheres to most or all the goals set out for the plan. In this study, one area of special interest was to establish whether the dose delivered to the heart will be less for IMRT versus 3D-CRT, while still having a feasible plan that can be used.

The PTV coverage was one facet of the study where the data suggests that the IMRT plans conformed superiorly to the PTV coverage of the breast when compared with the 3D-CRT plans. However, this needs to be clarified, as the 3D-CRT plans proved to produce limited coverage inferiorly as a result of beam length limitations and the placement of the isocenter. The lateral-posterior aspect of the PTV that was not covered by the desired dose for the 3D-CRT plans was due to the long mastectomy scars. The PTV could have been covered by the photon beams by changing the size of the field or by changing the beam angles. However, by doing that the dose to the left lung and dose to the heart will increase. The 3D-CRT plans were created to cover the PTV and CTV and the areas that could not be covered by the 95% dose lateral posteriorly were supplemented with an electron field, which was adjacent to the photon field. This adjustment cannot be done with the IMRT plans, as the IMRT plans have small beamlets and the exact field end cannot be determined in order to add the electron field. In addition, the IMRT treatment planning technique does not allow the

planning radiographer to exclude a certain area of the PTV without changing the actual PTV.

The low dose to the unspecified tissue or normal tissue can lead to radiation-induced secondary malignancies. The goal for this study was determined by the researcher, which states that V5Gy should be less than 20% of the tissue volume. The mean dose to the normal tissue was less than 5Gy for both techniques. The 3D-CRT had a lower percentage of 5Gy than the IMRT plans. Therefore, the 3D-CRT planning technique proved to be superior in the limitation of low dose to the unspecified tissue.

The next chapter will conclude the results and discussion of this study. Chapter 6 will also provide recommendations for clinical practice and future research. In addition, the chapter will include comments on the limitations of the present study.

CHAPTER 6

CONCLUSION

6.1 INTRODUCTION

The aim of radiation therapy is to administer maximum dose to the tumour and limit the radiation dose to OAR and adjacent normal structures. Both 3D-CRT and IMRT planning techniques have valid reason to be used in the Oncology Department, University of the Free State.

The objectives of the research study were:

(a) To generate an IMRT plan from archived images of patients who already had a 3D-CRT plan in order to draw a comparison with the existing 3D-CRT plan.
Both 3D-CRT and IMRT plans were generated for 30 patients (see Chapters 3.8.2.1, 3.8.2.2. and 4.1).

(b) To compare the dosimetric dose distributions administered to the PTV by comparing the hot spots (areas receiving ≥ 107% of the prescribed dose) and cold spots (areas receiving ≤ 95% of the prescribed dose).
The results of the dosimetric dose distributions for the PTV and CTV were provided (see Chapter 4.3 and 4.4).

(c) To compare dosimetric dose distributions administered to the OAR, such as the heart, lungs, spinal cord, oesophagus and contralateral breast.
The dosimetric dose distributions to the OAR was provided (see Chapter 4.5).

(d) To compare the DVH of both treatment modalities. The DVH data and statistics for each patient's plan was compared for both 3D-CRT and IMRT (see Chapter 4.6).

The comparison between 3D-CRT and IMRT treatment techniques will be concluded in this chapter. The recommendations for clinical application and future research, as well as the limitations of the research study will follow in the next section.

6.2 DEDUCTIONS

It is important to note that each patient requires an individual approach to radiation therapy. Individual risk assessment and strict normal tissue constraints should be applied when a treatment plan is to be generated (Ma, *et al.*, 2013). No patient is the same. For some the dose to the OAR might be within the goal doses, whereas the same approach for a different patient may have doses to the OAR far above the desired doses. This may be the result of many factors, such as the length of the mastectomy scar, the size of the contralateral breast or even the shape of the chest wall, which can all influence the dose distribution. The choice of a unique planning technique to be used should be considered for each patient and department.

6.3 COMPARISON OF 3-DIMENSIONAL CONFORMAL RADIATION THERAPY AND INTENSITY MODULATED RADIATION THERAPY

The use of 3D-CRT for post-mastectomy, left sided breast cancer patients that include the supraclavicular fossa, remains a challenge. The dose to the heart and left lung remains a concern, due to the proximity of the heart and lung to the chest wall (refer Chapter 2.3.2.1). In this study, the dose to the PTV was compromised, but only where the dose could be supplemented with an electron field to ensure the PTV is covered (refer Table 4.1). The use of IMRT proved to be favourable for post-mastectomy, left sided breast cancer patients (see Table 4.1), but the higher percentage of low dose to the OAR and normal tissue is a concern for secondary malignancies (see Table 4.10).

The planning techniques used for comparison in this study has indicated that both techniques, 3D-CRT and IMRT can be used for patient treatment (see Chapter 4.9), but the following factors should be considered: (a) the 3D-CRT plans need careful consideration in terms of the PTV coverage; (b) 3D-CRT plans warrant that the OAR are within the dose limits; (c) the IMRT plans have indicated that the OAR can receive even less dose as the 3D-CRT plans; (d) IMRT plans provide improved conformed dose to the PTV, although a low dose to the OAR and the normal tissue is of concern. The availability of technology, such as linear accelerators that can deliver IMRT, planning systems that can plan IMRT and the availability of inspiration gating technology may influence the outcome of the decision to plan and treat the patient.

The delineation of the OAR for both treatment techniques was done by the appointed oncologist, while all the plans were created by the researcher. Each patient scan was individually compared and evaluated and approved by the oncologist. All the data from the plans' DVH statistics were recorded and verified by the researcher.

Gathering the archived data proved to be challenging, as it was difficult to retrieve only patient data from the left-sided breast cancer patients that received radiation therapy with the supraclavicular fossa included. Another challenge proved to be the contouring and standardisation of the structures, since it was performed by one person only. The initial IMRT planning was problematic as there was no specific departmental approach for IMRT breast cancer treatment.

6.3.1 Planning target volume comparison

The PTV coverage for the planning techniques was compared by evaluating the doses from the DVH's. The percentage of dose that exceeded 105% of the PD was superior for the 3D-CRT planning technique compared to the IMRT planning technique, though both were within the 2% of the allowed dose. The area of 95% dose coverage was superior for the IMRT planning technique, indicating the 3D-CRT plans had underdosage to the PTV compared to the IMRT plans. The dose homogeneity could not be compared.

6.3.2 Organs at risk comparison

6.3.2.1 Heart dose

The mean dose to the heart was better for the 3D-CRT planning techniques as the mean heart dose was lower compared to the IMRT planning technique. The percentage of the dose received by the volume of heart receiving 22Gy was superior for the IMRT planning technique. The minimum dose to the heart was achieved by the 3D-CRT planning technique. The maximum dose to the heart was higher for the 3D-CRT planning technique.

6.3.2.2 Oesophagus dose

The mean dose to the oesophagus was lower for the 3D-CRT plans as opposed to the IMRT plans. The maximum dose to the oesophagus was higher for the IMRT plans. The 3D-CRT plans achieved superior organ sparing compared to the IMRT plans.

6.3.2.3 Lungs dose

The percentage of dose to both lungs receiving 18,87Gy was less for the IMRT plans compared to the 3D-CRT plans. The minimum mean dose was less for the IMRT plans and the maximum mean dose were lower for the IMRT plans as well. The IMRT plans achieved superior organ sparing compared to the 3D-CRT plans.

6.3.2.4 Left lung dose

The percentage dose for the left lung receiving 18,87Gy was less for the IMRT plans compared to the 3D-CRT plans. The IMRT did have superior organ sparing compared to 3D-CRT plans.

6.3.2.5 Left humeral head dose

The maximum dose to the humeral head was less for the IMRT plans. Thus, the IMRT plans had superior organ sparing comparing to the 3D-CRT plans.

6.3.2.6 Right breast dose

The mean percentage dose to the right breast that received 5Gy was less for the 3D-CRT plans compared to the IMRT plans. The 3D-CRT planning technique did however exhibit superior organ sparing.

6.3.2.7 Spinal cord dose

The maximum dose to the spinal cord was lower for the IMRT planning technique. Both planning techniques displayed doses lower than the goal dose for the spinal cord. The IMRT planning technique had superior organ sparing compared to the 3D-CRT planning technique.

6.3.2.8 Normal tissue dose

The mean dose to the normal tissue was less for the 3D-CRT planning technique. The percentage of dose that received 5Gy was less for the 3D-CRT planning technique. The 3D-CRT plans displayed superior normal tissue sparing compared to the IMRT planning technique.

6.4 RECOMMENDATIONS

Recommendations are offered for clinical practice, future studies and finally, an IMRT planning manual for the department.

6.4.1 Clinical practice

The use of deep inspiration breath-hold (DIBH) or inspiration gating (IG) is recommended to ensure the proper coverage of dose to the PTV and the sparing of the OAR for IMRT planning and treatment (Chi, *et al.*, 2015). The implementation of a breathing protocol when implementing IMRT for breast cancer treatment is deemed to be an advantage.

There are concerns about the breathing movement of the chest wall during the treatment and techniques to minimise the possible underdosing of the PTV and overdosing of the OAR should be considered. Techniques such as deep breath hold have been used in other studies with desirable results. A study conducted by Vuong, *et al*. (2019) indicated that the DIBH technique better lowers the mean and maximum dose to the heart compared to the free-breathing treatment.

The use of IG has displayed positive results as an alternative to DIBH. The patients are only treated during a specific phase of breathing with IG; the use of 4-dimensional CT is necessary for the data to do the planning. The use of IG has shown a reduction of dose to the heart (Fung & Hendry, 2012). However, several studies have reported that some patients do comply poorly and therefore the use of IG and DIBH is deemed to be complicated.

6.4.2. IMRT planning manual for the department

The researcher is in the process of compiling an IMRT planning manual for the Oncology Department, University of the Free State, specifically for post-mastectomy, left breast, chest wall and supraclavicular fossa cancer patients. This manual will include recommendations on dose limits and dose constraints. It will also include planning-cost-function recommendations for the Monaco planning system. The manual will include the RTOG breast contouring Atlas as guideline for contouring of the structures. It is recognised that the treatment planning of left side breast cancer patients for IMRT and 4D planning techniques where respiratory gating during CT-simulation is performed, should be incorporated.

6.4.3. Future studies

In this study the higher percentage of low dose to the normal tissue with the IMRT plans was found to be of concern. Several studies have reported that an increase in

low dose can lead to an increase in radiation-induced secondary malignancies (Dracham, *et a*l., 2018). There exists potential for future studies that have a long follow-up on patients that received IMRT radiation therapy for left breast cancer.

Radiation pneumonitis (RP), which decreases the quality of life (QoL), is the most common pulmonary complication in patients receiving breast irradiation (Lee, *et al.*, 2015). A study that compares follow-up patients who received 3D-CRT and IMRT radiation therapy for breast cancer to evaluate the late toxicities of the patients may indicate the future use for IMRT in breast cancer treatment.

6.5 LIMITATIONS

During this study it was found that he high dose of 105% was a limiting factor, as the PTV could have been covered by the desired 98% of the 95% dose. Should the maximum allowed dose have been 107% or even 110% of the PD the 95% dose coverage could have been improved.

The use of one approach to the planning of the IMRT plans was limiting, as several studies compare the differences between seven-field, nine-field and even eleven-field IMRT plans (Ayata, *et al*., 2011).

The use of a single isocenter for the 3D-CRT plans was found to be a limiting factor in the inferior aspect of the PTV, as the field could not cover the inferior aspect of the PTV. By moving the isocenter more inferior to correct this problem, the dose from the supraclavicular field increased the dose to the left lung.

6.6 CONCLUDING REMARKS

The question of how 3D-CRT planning compares with IMRT planning for post-mastectomy patients receiving radiation therapy to the left chest wall and supraclavicular fossa is most relevant. 3D-CRT planning for post-mastectomy patients receiving radiation therapy to the left chest wall, including the supraclavicular fossa, compares well with IMRT planning. 3D-CRT is a viable planning technique to be used in clinical practice. The sparing of the OAR can be achieved with careful planning technique and skills, the heart dose can be limited to be within the tolerance dose while delivering acceptable dose to the PTV. IMRT has the potential to be superior to PTV coverage and OAR sparing when compared to 3D-CRT planning. However, the use of

either technique remains individualised, as there are trade-offs for both techniques that include PTV coverage for 3D-CRT and low dose irradiation to OAR for IMRT. IMRT for breast cancer treatment should be accompanied with a controlled breathing technique.

In addition, one needs to address the question whether proton therapy will become the next normal for left breast cancer patient treatment. A prospective clinical trial done by McDonald, *et al.*, (2013), has indicated that proton therapy for breast cancer patients can be feasible and is well tolerated by the patients. The study achieved an average mean dose to the heart of 0.44Gy and the average volume to heart receiving 20Gy was 0.01%. For the lung they achieved an average of 6Gy for the mean dose and the mean volume that received 20Gy was 12.7%. They did have a PD of 50.4Gy. The authors did not indicate any long-term toxicities. Artificial Intelligence (AI) has advantages in the radiation therapy treatment planning process. AI saves time in automated delineation of structures, increases consistency and improves dose-volume parameters. AI could also assist in contouring of the OAR and the target volumes. In addition, AI has provided promising clinical applications for automated treatment planning for cervical and prostate cancer (Poortmans, *et al.*, 2020).

CLOSING STATEMENT

Working closely with the oncologist and focussing on problem solving, as there was no protocol for IMRT breast cancer treatment in the department at the time of the study, was an unforgettable learning experience. The use of new technology to improve patient treatment delivery is always a personal achievement. The opportunity to have a positive impact on the outcomes of future post-mastectomy left breast cancer patients who will receive radiation therapy is rewarding.

Thomas A. Edison said: "There is a better way for everything. Find it." Thomas A. Edison. I echo the words and add: If there is a better way to treat breast cancer, I want to find it.

"*As we conquer peak after peak we see in front of us regions full of interest and beauty, but we do not see our goal, we do not see the horizon; in the distance tower still higher peaks, which will yield to those who ascend them still wider prospects, and deepen the feeling, the truth of which is emphasized by every advance in science, that 'Great are*

the Works of the Lord'." Joseph John Thomson. After this study there are more peaks for me to climb to discover the beauty and widen my prospects.

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APPENDIX A

Treatment Policy for Conservative Management of Early Stage Invasive Breast Cancer courtesy of (Halperin *et al*., 2013).

Treatment Volume	Indication	Fraction Size/Technique	Total Dose	Comment
Early Stage Invasive Breast Cancer				
Whole breast	Routinely following BCS	200 (prefer) or 180cGy/ tangents with wedges or dynamic wedges to optimise homogeneity	4,500 - 5040cGy	Consider omission of RT in elderly with stage I (oestrogen receptor positive) and comorbidities
Boost	Routinely following whole breast	200 or 1 80 cGy (prefer 200)/En face electrons	1,000–1,600cGy to bring total dose to >6,000	May consider no boost for widely negative margins in women over 60
Accelerated whole breast	Patient convenience	266 cGy tangents with no nodal fields/no boost	4,250cGy	
Accelerated partial breast	On protocol	3.4–3.8 Gy/ext. beam conformal,	3,400 – 3,850cGy	

		interstitial, or Mamo Site		
Treatment Policy for Regional Nodes				
Supraclav	Clinical N2 or N3 disease >4 +LN after axillary dissection 1 –3 +LN with high risk features Node + sentinel lymph node with no dissection unless risk of additional axillary disease is very small High risk no dissection	180–200 (Prefer 200)/AP or AP-PA	4,500 – 5,040cGy	May omit with 1 –3 positive nodes in select cases
Axilla	N+ with extensive ECE SN+ with no dissection Inadequate axillary dissection	180–200/AP —consider posterior axillary boost if suboptimal coverage with AP only	4,500 – 5,040cGy	Axilla may be intentionally included with use of “high tangents”

	High risk with no dissection			
Internal mammary	Individualised but consider for: Positive axillary nodes with central and medial lesions Stage III breast cancer +SLN in the IM chain +SLN in axilla with drainage to IM on lymphoscintigraphy	180 - 200/Partially wide tangents or separate IM electron/photon	4,500–5,040 [mb85]cGy	

APPENDIX B

Patient	PTV 105% Dose	PTV 95% Dose	PTV 98% coverage	Heart Mean	Heart V22	Oesophagus Mean Dose	Oesophagus Max Dose
Nr.1) 3D			100				
IMRT			100				

Patient	% Lungs Dose = 18.87Gy	% Left Lung Dose = 18.87Gy	Humeral head Max Dose	Right Chest wall / Breast 5Gy	Spine Max Dose	Patient Mean Dose
Nr.1) 3D						
IMRT						

APPENDIX C

Department of Oncology

Universitas Academic Hospital

Bloemfontein

9300

Prof A Sherriff

HOD

Department of Oncology

RE: Permission to conduct a research project at Universitas Hospital Annex

Dear Prof Sherriff

I, Stephan Loots, am currently employed at Universitas Academic Hospital Annex Bloemfontein as a Radiation Therapy Radiographer. I am also studying towards attainment of a Masters degree in Radiation Therapy. As part of the outcomes for attaining the above mentioned qualification, it is an obligation to conduct research on a topic of my choice. My research project's main objectives will compare the dose volume histograms of the three dimensional conformal radiation therapy (3D-CRT) planning of left sided breast patients with a supraclavicular field, with the dose volume histogram of an intensity modulated radiation therapy (IMRT) plan of the same patient. I will make use of the patient archiving system and the Monaco planning system. It will not influence the patient negatively, because the 3D-CRT plan will be retrieved from the archive and no active patients will be used for the study, the IMRT plan will only be used for comparison in the study. I hereby request your permission on using the Monaco planning system and the archived patient data at the Oncology department as the site for my research project. If needed, I shall furnish you with the specifics of the research project.

I hope that my request receives your kind and urgent attention.

Yours Sincerely

S Loots

Approval / No approval

Prof. A. Sherriff (HOD)

14 · 8 · 15

Date

APPENDIX D

health
Department of Health
FREE STATE PROVINCE

26 November 2018

Mr. S Loots
Dept. of Radiography
CUT

Dear Mr. S Loots

Subject: THREE-DIMENSIONAL CONFORMAL VERSUS INTENSITY-MODULATED RADIOTHERAPY PLANNING FOR LEFT BREAST, CHEST WALL AND SUPRACLAVICULAR FOSSA OF CANCER PATIENTS.

- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary
- A written consent by each participant must be obtained.
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** [redacted] **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are required to present your study findings/results at the Free State Provincial health research day

Trust you find the above in order.
Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 26/11/18

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APPENDIX E

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

11-Oct-2018

Dear Mr Stephan Loots

Ethics Clearance: THREE-DIMENSIONAL CON FORMAL VERSUS INTENSITY-MODULATED RADIOTHERAPY PLANNING FOR LEFT BREAST, CHEST WALL AND SUPRACLAVICULAR FOSSA OF CANCER PATIENTS

Principal Investigator: Mr Stephan Loots

Department: Radiography - CUT

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2018/1164/3010**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784

APPENDIX F

Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions

RTOG
RADIATION THERAPY ONCOLOGY GROUP

Collaborators

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[1]Medical College of Wisconsin, [2]Virginia Commonwealth University, [3]M.D. Anderson Cancer Center, [4]Massachusetts General Hospital, [5]University of North Carolina, [6]University of Michigan, [7]Beth Israel Deaconess Medical Center Hospital, [8]University of Colorado, [9]William Beaumont Hospital

Content

- → Overlying principles: slides 4 - 6
- → Consensus definitions of anatomical boundaries: slides 7 - 12
- → Illustrative cases:
  - A: Stage I intact post-lumpectomy left breast (slides 13 - 30)
  - B: Stage III post-mastectomy left breast (slides 32 - 51)
  - C: Stage III intact post-lumpectomy right breast (slides 54 - 71)

Overlying principles: Breast Contour

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

Lumpectomy GTV: Includes seroma and surgical clips when present

Overlying principles: Chestwall Contour

Chestwall CTV:
- Considers referenced clinical chestwall at time of CT
- Incorporates consensus definitions of anatomical borders (see table)
- Includes the mastectomy scar *(may not be feasible for occasional cases where the scar extends beyond the typical borders of the chestwall)*

Overlying principles: Nodal volumes

Regional nodal CTV:
- Nodal volumes contoured for targeting will depend on the specific clinical case
- Considers consensus definitions of anatomical borders (see table)
- The three levels of the axilla can overlap caudal to cranial
- "Axillary apex" was considered level III of the axilla

Breast and Chestwall Contour: Anatomical Boundaries

	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Breast[1]	Clinical Reference + Sternal rib interface[2]	Clinical reference + loss of CT apparent breast	Skin	Excludes pectoralis muscles, chestwall muscles, ribs	Clinical Reference + mid axillary line (typically, excludes latissimus dorsi)[3]	Sternal rib junction[4]
Breast + Chestwall[2]	Same	Same	Same	Includes pectoralis muscles, chestwall muscles, ribs	Same	Same
Chestwall[3]	Caudal border of the clavicle head	Clinical reference + loss of CT apparent ipsilateral breast	Skin	Glenohumeral interface. (Includes pectoralis muscles, chestwall muscles, ribs)	Clinical Reference mid axillary line (typically, excludes latissimus dorsi)[3]	Sternal rib junction[4]

Contouring Comments: Breast and Chestwall

1. Breast: After appropriate lumpectomy for breast only treatment
2. Cranial border is highly variable depending on breast size and patient position. The lateral aspect can be more cranial then the medial aspect depending on breast shape and patient position.
3. Lateral border is highly variable depending on breast size and amount of ptosis.
4. Medial border is highly variable depending on breast size and amount of ptosis. Clinical reference needs to be taken into account. Should not cross midline.

Contouring Comments: Breast and Chestwall

1. Breast-Chestwall: CTV after appropriate lumpectomy for more locally advanced cases includes these:
   - With clinical stage IIb, III who receive neoadjuvant chemotherapy and lumpectomy
   - Who have sufficient risk disease to require post-mastectomy radiation had mastectomy done
2. Chestwall: CTV after appropriate mastectomy:
   a. Lateral border meant to estimate the lateral border of the previous breast. Typically extends beyond the lateral edge of the pectoralis muscles but excluded the latissimus dorsi muscle
   b. Clinical reference marks need to be taken into account. The chestwall typically should not cross midline. Medial extent of mastectomy scar should typically be included

Regional Nodal Contours: Anatomical Boundaries

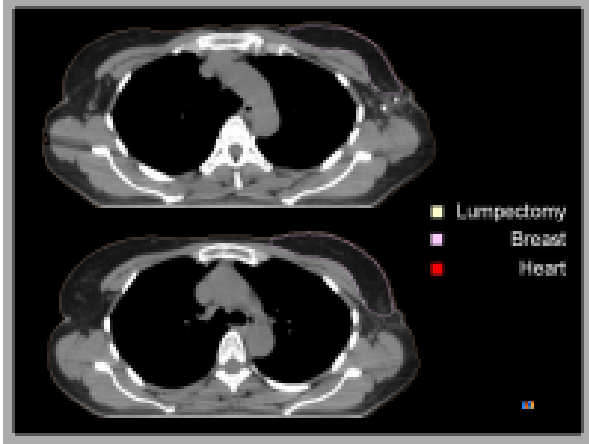
	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Supra-clavicular	Caudal to the cricoid cartilage	Junction of brachiocephalic, axillary vein and caudal edge clavicular head [a]	Sternocleido-mastoid (SCM) muscle (ms)	Anterior aspect of the scalenus ms.	Cranially, lateral edge of SCM ms. Caudally, junction 1st rib, clavicle	Excludes thyroid and trachea
Axilla-Level I	Axillary vessels, cranial lateral edge of Pec. Minor ms.	Pectoralis (Pect) major muscle (insert onto ribs) [b]	Base defined by: anterior surface of Pec. Maj., ms and Lat. Chest ms.	Anterior surface of subscapularis ms.	Medial border of lat. dorsi ms.	Lateral border of Pec. minor ms.
Axilla-level II	Axillary vessels cross medial edge of Pec. Minor ms.	Axillary vessels cross lateral edge of Pec. Minor ms. [c]	Anterior surface Pec. Minor ms.	Ribs and intercostal muscles	Lateral border of Pec. Minor ms.	Medial border of Pec. Minor ms.
Axilla-level III	Pec. Minor ms. insert on coracoid	Axillary vessels cross medial edge of Pec. Minor ms. [d]	Posterior surface Pec. Major ms.	Ribs and intercostal muscles	Medial border of Pec. Minor ms.	Thoracic inlet
Internal mammary	Superior aspect of the medial 1st rib.	Cranial aspect of the 3rd rib	[e]	[e]	[e]	[e]

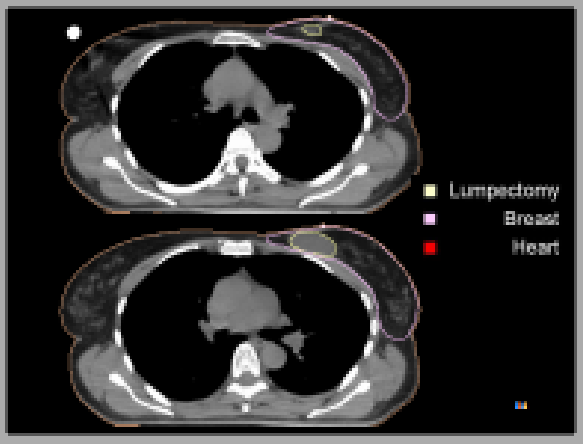
Contouring Comments: Regional Nodal Volumes

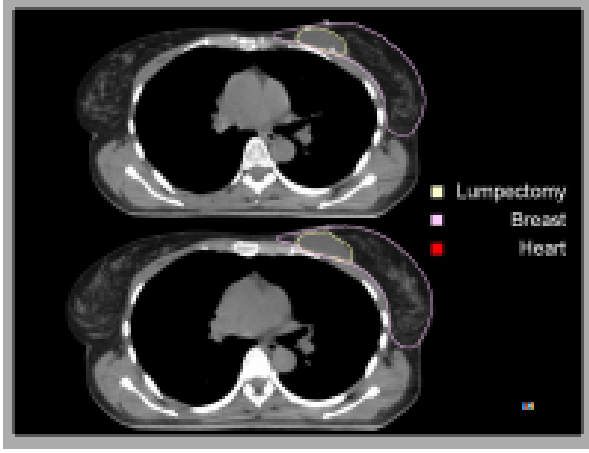
a. Supraclavicular caudal border meant to approximate the superior aspect of the breast/ chestwall field border
b. Axillary level I caudal border is clinically at the base of the anterior axillary line
c. Axillary level II caudal border is the same as the cranial border of level I
d. Axillary level III caudal border is the same as the cranial border of level II
e. Internal Mammary lymph nodes: encompass the internal mammary/ thoracic vessels

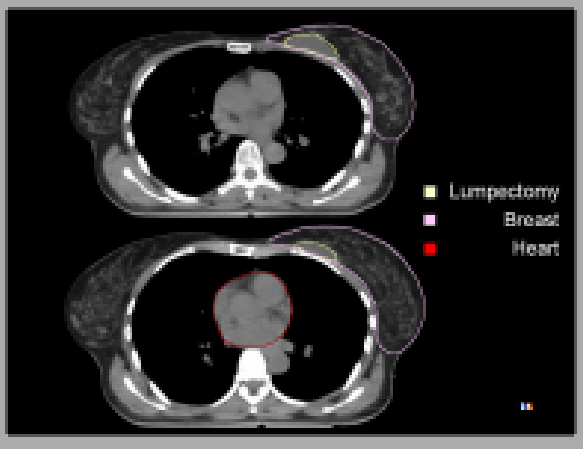
Case A- Intact post lumpectomy breast

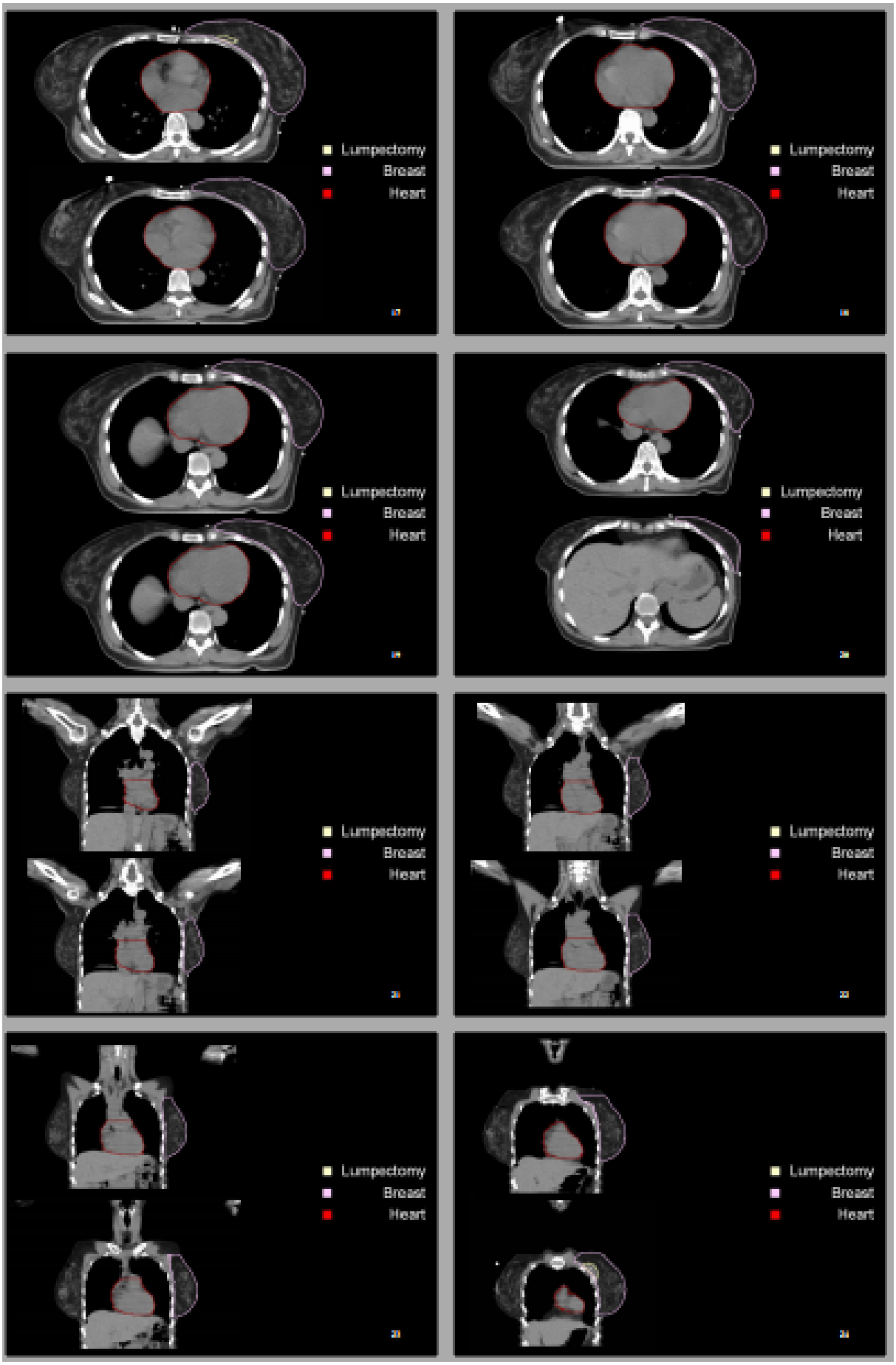
- Stage I (T1c, N0, M0) Left breast cancer
- Surgery: Lumpectomy and sentinel node biopsy
- Radiation: Breast
- Six surgical clips placed at lumpectomy site
- External markers placed at time of CT:
  - BB at AP set-up point
  - 4 wire markers for clinical estimate of cranial, caudal, medial, and lateral extent of anticipated tangents
  - Wire extending from 9-3 o'clock around the infra-mammary fold
  - Wire over the lumpectomy scar

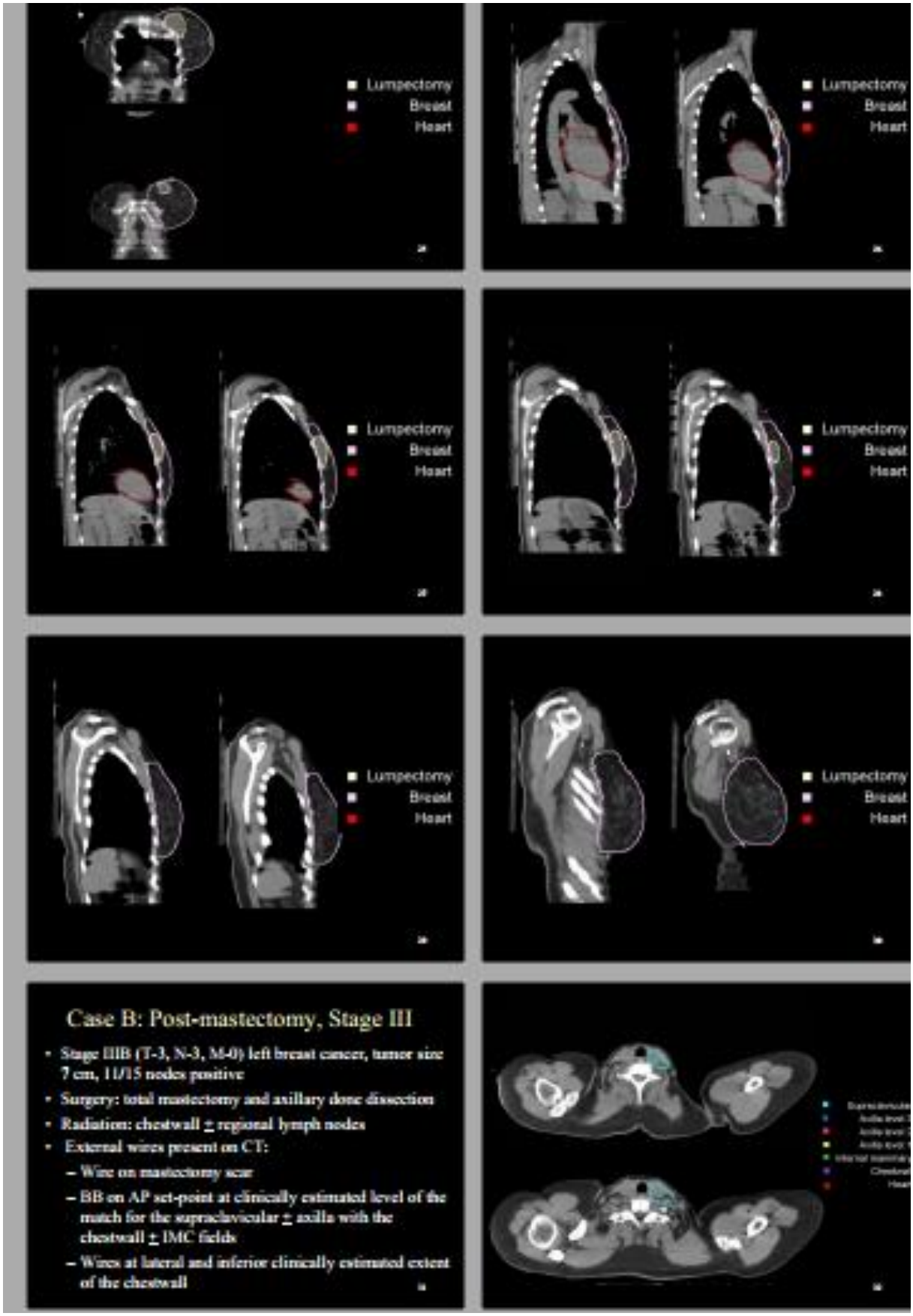


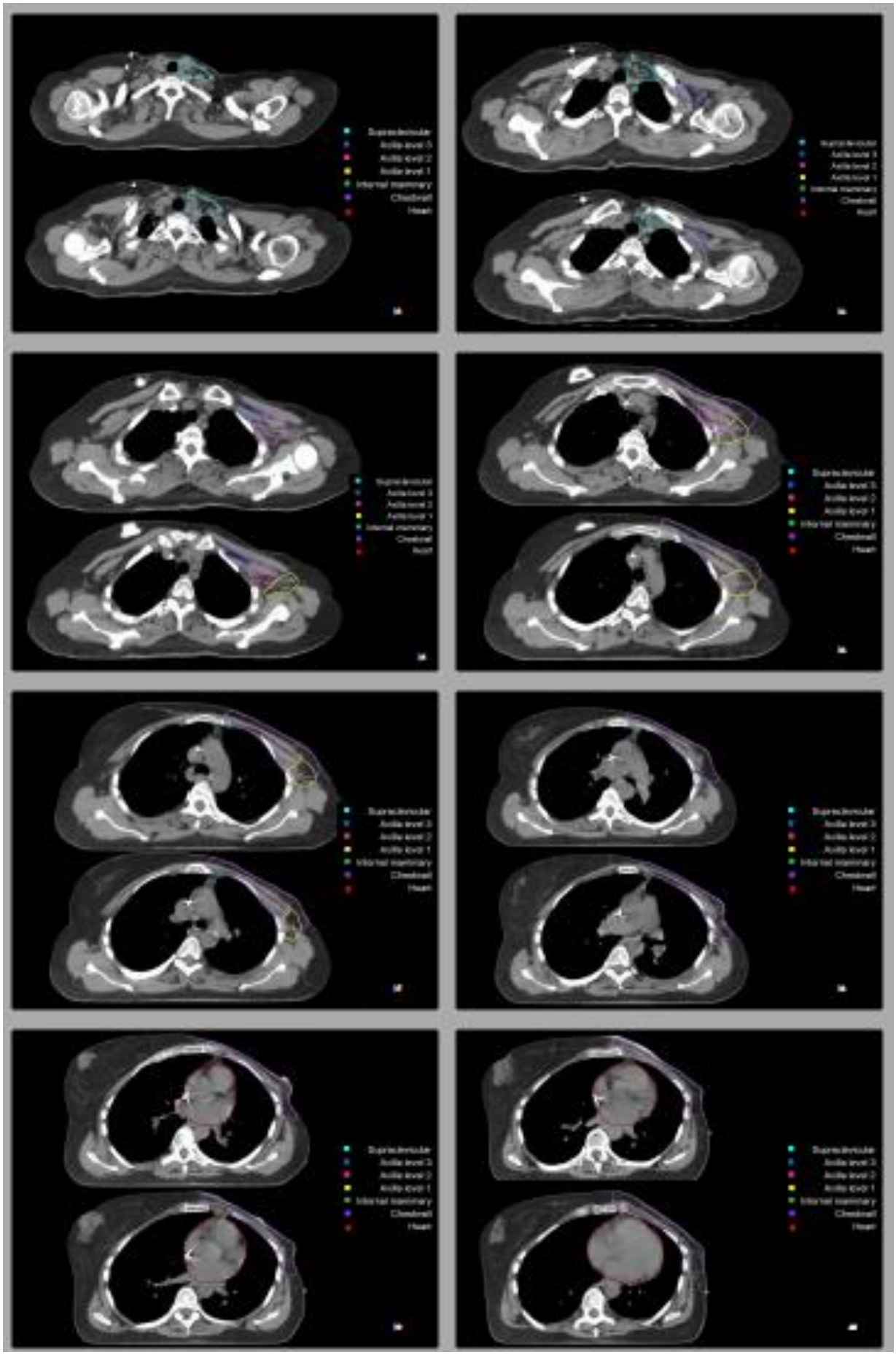


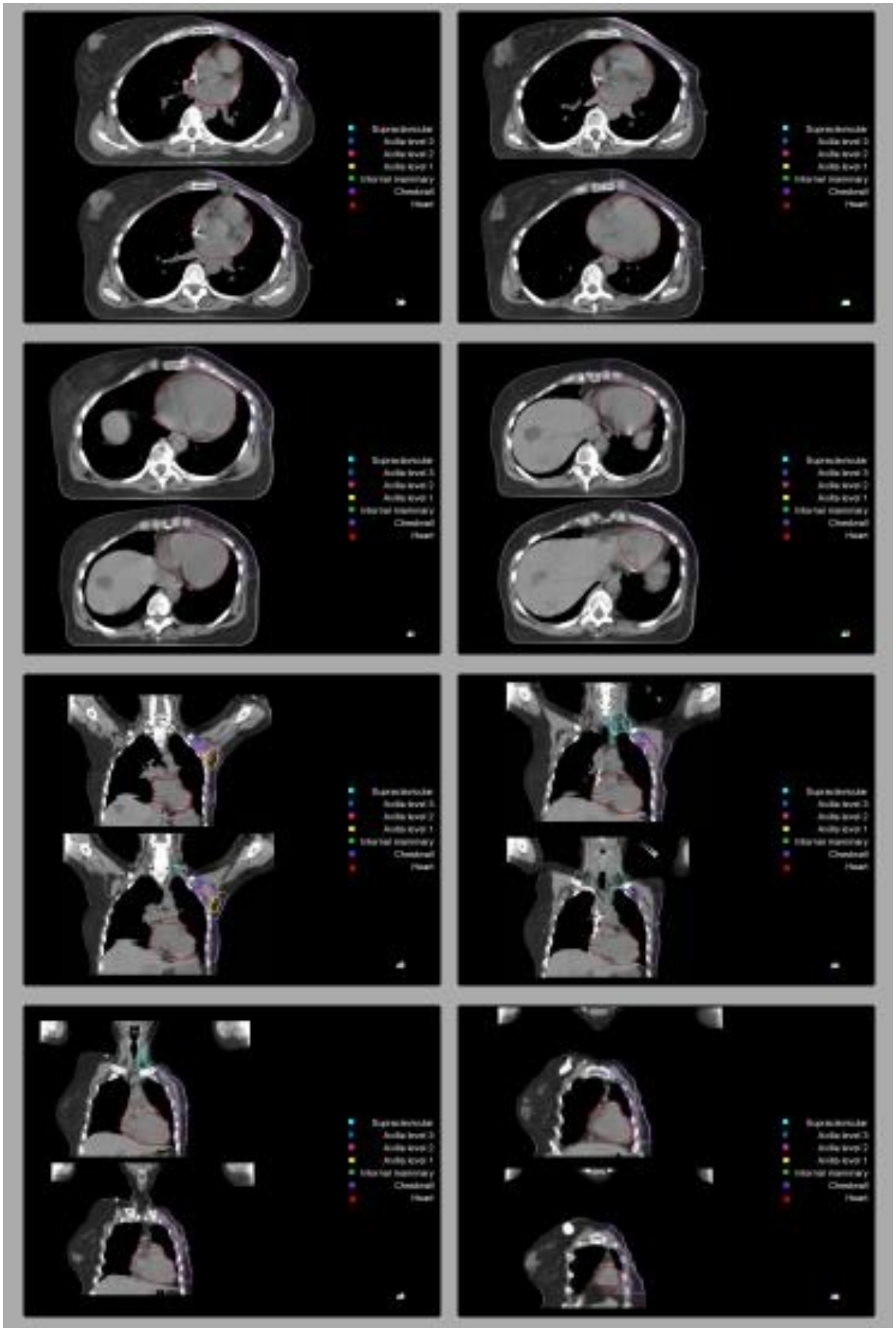


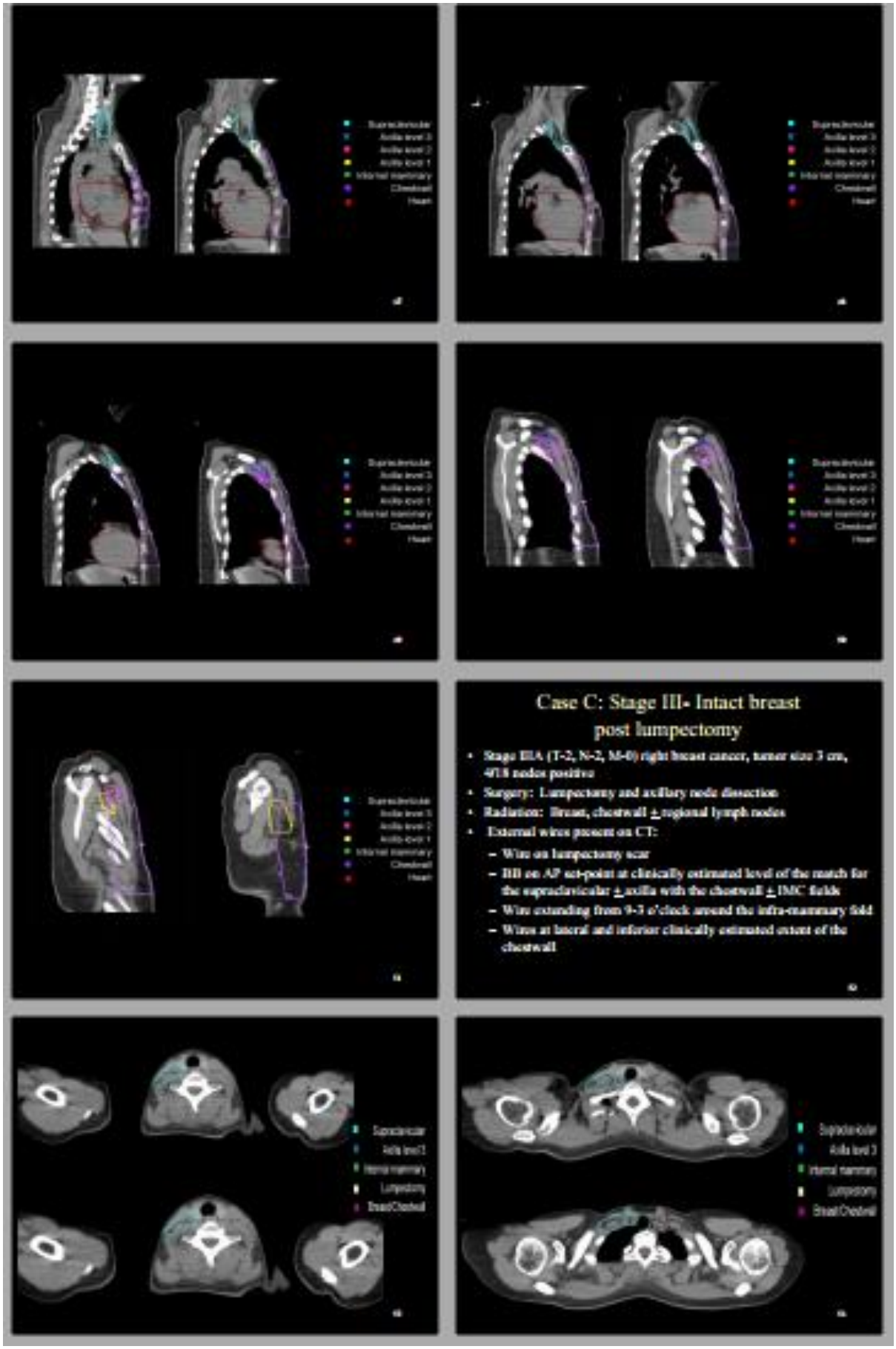


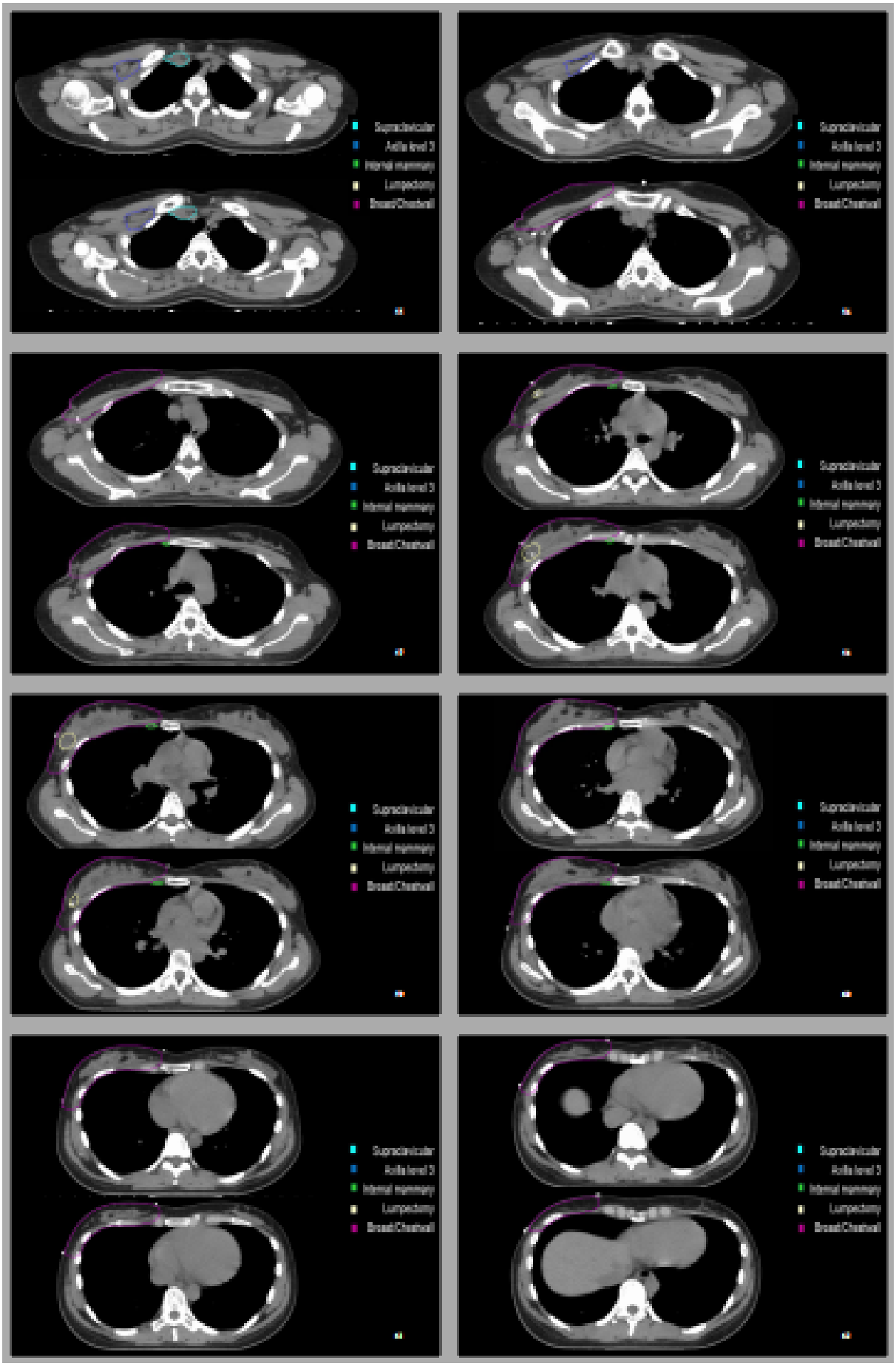


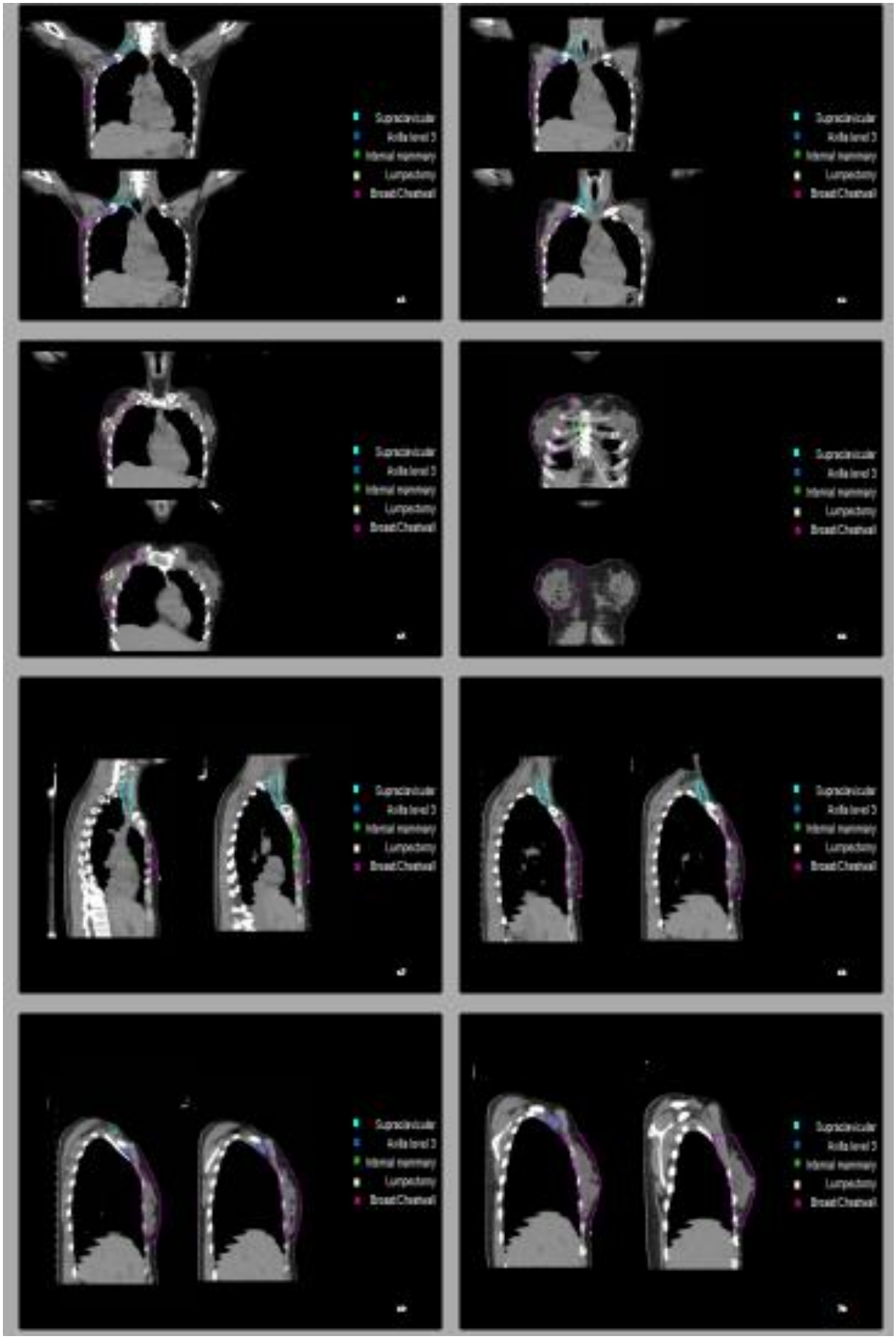


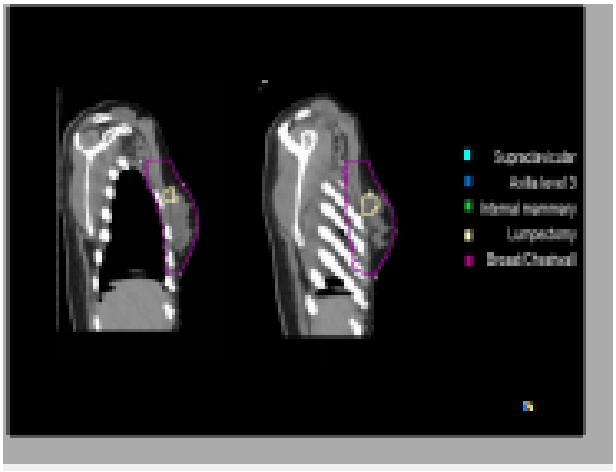












APPENDIX G

Patient	PTV 105% Dose	PTV 95% Dose	PTV 98% coverage	CTV 105% Dose	CTV 95% Dose	Heart Mean	Heart V22	Oesophagus Mean Dose	Oesophagus Max Dose	% Lungs Dose = 18.87Gy
Nr.1) 3D	0,28	14,38	85,62	0,4	3,84	4,9	8,35	7,95	39,58	15,79
IMRT	1,42	8,93	91,07	0,72	3,28	5	0,41	10,93	40,84	12,86
2) 3D	0,24	29,28	70,72	0,34	8,12	5,12	9,05	1,46	11,08	17,46
IMRT	1,08	9,13	90,87	1,59	0,73	5,97	1,13	5,62	13,23	13,51
3) 3D	0,15	34,51	65,49	0,23	14,12	5,15	9,04	5,8	37,74	16,87
IMRT	0,33	9,31	90,69	0,07	0,76	5,99	1,98	10,22	40,18	15,3
4) 3D	0,07	33,42	66,58	0,13	10,39	4,26	6,49	4,63	34,73	17,36
IMRT	1,56	13,6	86,4	1,76	0,91	6,31	3,54	8,8	38,21	15,37
5) 3D	0,34	36,21	63,79	0,43	6,01	4,74	7,15	5,8	39,37	18,75
IMRT	0	8,48	91,52	0	0,2	5,85	2	10,39	41,11	16,59
6) 3D	0,04	33,66	66,34	0,03	15,18	5,87	10,6	3,43	34,24	16,56
IMRT	1,35	9,16	90,84	1,08	1,57	6,11	4,86	8,26	40,79	14,09
7) 3D	0,35	27,83	72,17	0,13	10,28	2,99	2,95	4,75	35,09	13,45
IMRT	0,57	8,77	91,23	0,41	0,59	4,17	0,1	7,35	37,95	9,83
8) 3D	0,58	22,47	77,53	0,06	5,03	5,8	9,72	6,5	40	18,05
IMRT	1,76	8,96	91,04	1,43	2,03	6,2	5,34	8	41,8	14,52
9) 3D	0	32,8	67,2	0	15,17	5,3	8,8	6,5	36,5	15,8
IMRT	1,86	9,85	90,15	2,75	1,78	6,2	5	10,4	41,7	13,4
10) 3D	1	25,2	74,8	1,99	4,87	5,1	8	7,1	41,1	16,87
IMRT	0,95	6,7	93,3	1,28	0,16	5,7	4,35	8,4	39,5	13,9
11) 3D	0,1	43,75	56,25	0,16	22,99	5	8,3	7,1	41,3	16,5

IMRT	1,25	9,6	90,4	0,81	0,68	6	5,5	11,6	40	15
12) 3D	0,03	42,05	57,95	0	24,68	5,4	5,4	6,2	37,1	14,56
IMRT	0,99	8,6	91,4	0,65	2,18	5,6	3,2	7,6	41,3	12,85
13) 3D	0,08	26,17	73,83	0,08	12,59	4,66	7,66	3,4	36,4	16,81
IMRT	1,19	4,61	95,39	0,88	0,5	5,35	1,35	10,22	40	14,85
14) 3D	0,31	33,99	66,01	0,51	14,49	6,8	10,6	7,3	38,3	15,3
IMRT	1,15	9,8	90,2	1,72	0,86	5,1	0,91	10,5	40,5	11,88
15) 3D	0,78	39,26	60,74	1,13	19,1	5,56	6,91	5,8	37,2	16,54
IMRT	1,51	6,64	93,36	1,59	1,58	5,87	0	8,3	40,2	13,05
16) 3D	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
IMRT	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
17) 3D	0,18	26,6	73,4	0,28	13,7	3,59	4,18	1,14	10,4	16,61
IMRT	2,24	2,13	97,87	1,97	0,63	5,08	0,3	6,8	41,9	12,61
18) 3D	0,29	21,5	78,5	0,15	11,85	5,22	9,88	4,3	36,8	15,67
IMRT	1,07	2,07	97,93	0,16	0,47	4,5	0,41	9,7	43,6	13,75
19) 3D	0,06	30,7	69,3	0,12	9,83	4,3	6,5	3,1	30,7	13,9
IMRT	0,7	5,9	94,1	0,68	0,26	5,1	1	12,5	41,2	12,2
20) 3D	0,09	44	56	0,021	22,69	5,2	9,11	6,6	35,8	18,87
IMRT	2,02	9,09	90,91	2,47	0,69	6,1	0	15,3	41,6	16,96
21) 3D	0,04	40,41	59,59	0,03	23,98	3,6	5,49	5,6	37,12	13,35
IMRT	1,46	5,76	94,24	2,36	0,21	5,06	0,73	11,02	39,85	14,01
22) 3D	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
IMRT	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
23) 3D	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
IMRT	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
24) 3D	0	35,25	64,75	0	18,03	4,8	8,7	6,7	39,1	15,43
IMRT	0,93	8,03	91,97	1,18	0,56	5,47	4,61	8,3	41,3	13,45
25) 3D	0	40,9	59,1	0	22,9	4,85	7,2	5,7	38,3	16,23
IMRT	0,54	6,8	93,2	0,03	0,56	4,89	1,2	4,8	38,8	12,91

26) 3D	0	35,3	64,7	0	16,7	4,4	7,7	5,3	37,9	16,75
IMRT	1,26	6,9	93,1	1,6	0,95	5,2	5,8	8,6	41,6	11,49
27) 3D	0	39,5	60,5	0	18,57	5,05	9,99	2,5	30,4	16,14
IMRT	0,1	8,09	91,91	0,11	0,95	5,14	0,87	10,1	35,8	12,14
28) 3D	0,4	35,2	64,8	0,44	19,21	3,45	4,75	2,4	25,7	17,61
IMRT	1,31	6,26	93,74	0,2	0,73	4,35	0,54	9,4	39,8	12,57
29) 3D	0	31,9	68,1	0	11,9	5,1	6,6	4,7	38,2	11,6
IMRT	0,05	6,6	93,4	0,03	0,7	4,8	0,45	8,8	40,7	17,18
30) 3D	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
IMRT	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Patient	% Left Lung Dose = 18.87Gy	Humeral head Max Dose	Right Chestwall / Breast 5Gy	Spine Max Dose	Patient 5Gy %	Patient Mean Dose	HI CTV	CI CTV	HI PTV	CI PTV
Nr.1) 3D	32,16	38,28	1,49	35,03	15,57	4,15				
IMRT	26,21	34,11	12,13	13,93	23,99	4,84	1,07	0,33	1,14	0,4
2) 3D	40,71	36,64	15,59	22,19	13,08	3,28				
IMRT	32,08	34,96	18,38	14,16	22,77	4,74	1,06	0,28	1,14	0,31
3) 3D	37,33	38,3	0,19	22,46	10,1	2,41				
IMRT	34,06	38,3	3,94	11,64	24,04	4,4	1,06	0,19	1,12	0,38
4) 3D	32,33	36,43	1,21	14,2	12,59	3,04				
IMRT	17,36	34,36	10,1	13,95	21,73	4,3	1,06	n/a	1,19	n/a
5) 3D	36,37	35,97	0	30,15	20,01	3,34				
IMRT	32,18	33,58	13,06	14,06	26,58	5,06	1,04	0,19	1,11	0,26
6) 3D	36,49	40	4,88	6,4	11,96	3,05				
IMRT	31,73	34,61	8,61	11,85	27,61	5,37	1,08	0,25	1,13	0,38
7) 3D	26,47	36,17	16,36	23,57	14,31	3,18				

IMRT	19,42	35,26	12,48	10,61	18,15	3,54	1,05	0,33	1,13	0,41
8) 3D	39,27	38,1	0,89	37,4	19,4	4,65				
IMRT	31,9	35,6	3,4	14,78	31,3	6,2	1,07	0,28	1,13	0,48
9) 3D	34,2	39,5	5,3	25,1	13,71	3,3				
IMRT	29	36,8	14,2	11,4	26,95	5,2	1,06	0,47	1,16	0,59
10) 3D	35,3	37,8	0,6	33,2	17,87	4,7				
IMRT	29,1	33	13,2	13,6	28,28	5,6	1,06	0,4	1,11	0,41
11) 3D	33,5	38,9	0,6	27,4	10,52	2,5				
IMRT	16,5	34,1	10,4	12,4	23,36	4,7	1,07	0,27	1,14	0,4
12) 3D	32,14	36,7	0,08	22,5	13,18	3,3				
IMRT	28,38	38,3	9,52	12,36	25,93	5,4	1,06	0,4	1,15	0,5
13) 3D	37,58	38,66	0,89	18,8	8,86	2,2				
IMRT	33,2	33,65	16,65	13,6	24,37	4,8	1,06	0,19	1,09	0,36
14) 3D	35,4	38,9	3,49	31,45	15,35	3,25				
IMRT	27,6	33,7	4,14	13,9	29,81	5,8	1,07	0,36	1,14	0,39
15) 3D	36,41	36,4	9,3	26,4	12,83	2,8				
IMRT	28,75	33,2	8,13	14,89	22,75	4,6	1,06	0,35	1,12	0,43
16) 3D	n/a	n/a	n/a	n/a		n/a				
IMRT	n/a	n/a	n/a	n/a		n/a	n/a	n/a	n/a	n/a
17) 3D	36,89	36,19	2,41	4,05	12,58	3,22				
IMRT	28,01	33,9	10,46	13,59	27,73	5,52	1,07	0,35	1,08	0,49
18) 3D	32,8	37,2	1,82	30,69	11,79	2,9				
IMRT	28,7	33,7	12,33	14,39	22,92	4,4	1,06	0,3	1,07	0,43
19) 3D	29,2	37,7	5,85	11,8	9,8	2,5				
IMRT	25,9	35,5	12,1	13,5	20,77	4,1	1,06	0,2	1,1	0,33
20) 3D	38,23	37,03	0,01	25,14	11,9	2,78				
IMRT	34,23	36,5	2,26	11,48	26,83	5,05	1,06	0,3	1,14	0,43
21) 3D	29,22	38,2	7,58	26,04	10,81	2,6				
IMRT	30,97	33,7	20,38	14,02	22,94	4,4	1,06	0,31	1,1	0,54

22) 3D	n/a	n/a	n/a	n/a		n/a				
IMRT	n/a	n/a	n/a	n/a		n/a	n/a	n/a	n/a	n/a
23) 3D	n/a	n/a	n/a	n/a		n/a				
IMRT	n/a	n/a	n/a	n/a		n/a	n/a	n/a	n/a	n/a
24) 3D	34,1	38,7	0,6	29,8	11,59	2,8				
IMRT	30,1	35,06	10,38	16,2	24,03	4,8	1,07	0,35	1,13	0,48
25) 3D	33,85	33,5	2,77	22,9	12,19	2,8				
IMRT	23,93	33,4	8,2	10,98	29,9	5,5	1,05	0,23	1,11	0,33
26) 3D	37,87	37,1	8,01	16,2	12,38	3,06				
IMRT	26	34,7	22,02	13,05	25,47	5,1	1,06	0,37	1,12	0,5
27) 3D	14,08	34,1	1,23	7,4	10,21	2,3				
IMRT	26,65	32,7	13,25	12,5	22,32	4,2	1,05	0,25	1,12	0,32
28) 3D	36,8	38,2	0	11,29	9,35	2,2				
IMRT	26,21	32,7	17,7	13,9	22,37	4,3	1,06	0,25	1,11	0,46
29) 3D	21,6	38,6	0,15	26,7	12,93	3,5				
IMRT	32,1	33,3	7,7	14,3	23,87	4,9	1,05	0,33	1,11	0,41
30) 3D	n/a	n/a	n/a	n/a		n/a				
IMRT	n/a	n/a	n/a	n/a		n/a	n/a	n/a	n/a	n/a

APPENDIX H

Breast cancer staging (Courtesy of: Halperin *et al*., 2013).

Staging: Primary tumour (T), Regional Lymph nodes (N), Distant Metastasis (M).	
T1	Tumour 2cm or less in greatest dimension.
T2	Tumour greater than 2cm, but less than 5cm in greatest dimension.
T3	Tumour more than 5cm in greatest dimension.
T4	Tumour of any size with direct extension to chest wall or skin.
N0	No regional lymph node metastasis histologically.
N1	Metastasis in 1 to 3 axillary lymph nodes and or internal mammary nodes with microscopic disease.
N2	Metastasis in 4 to 9 axillary lymph nodes or in clinical apparent internal mammary nodes in the absence of axillary lymph node metastasis.
N3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes, or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes or in ipsilateral supraclavicular lymph nodes.
MX	Distant metastasis cannot be assessed.
M0	No distant metastasis.
M1	Distant metastasis.

APPENDIX I

The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

*The START Trialists' Group**

Summary

Background The international standard radiotherapy schedule for early breast cancer delivers 50 Gy in 25 fractions of 2·0 Gy over 5 weeks, but there is a long history of non-standard regimens delivering a lower total dose using fewer, larger fractions (hypofractionation). We aimed to test the benefits of radiotherapy schedules using fraction sizes larger than 2·0 Gy in terms of local-regional tumour control, normal tissue responses, quality of life, and economic consequences in women prescribed post-operative radiotherapy.

Methods Between 1999 and 2001, 2215 women with early breast cancer (pT1-3a pN0-1 M0) at 23 centres in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2·0 Gy over 5 weeks or 40 Gy in 15 fractions of 2·67 Gy over 3 weeks. Women were eligible for the trial if they were aged over 18 years, did not have an immediate reconstruction, and were available for follow-up. Randomisation method was computer generated and was not blinded. The protocol-specified principal endpoints were local-regional tumour relapse, defined as reappearance of cancer at irradiated sites, late normal tissue effects, and quality of life. Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN59368779.

Findings 1105 women were assigned to the 50 Gy group and 1110 to the 40 Gy group. After a median follow up of 6·0 years (IQR 5·0–6·2) the rate of local-regional tumour relapse at 5 years was 2·2% (95% CI 1·3–3·1) in the 40 Gy group and 3·3% (95% CI 2·2 to 4·5) in the 50 Gy group, representing an absolute difference of –0·7% (95% CI –1·7% to 0·9%)—i.e., the absolute difference in local-regional relapse could be up to 1·7% better and at most 1% worse after 40 Gy than after 50 Gy. Photographic and patient self-assessments indicated lower rates of late adverse effects after 40 Gy than after 50 Gy.

Interpretation A radiation schedule delivering 40 Gy in 15 fractions seems to offer rates of local-regional tumour relapse and late adverse effects at least as favourable as the standard schedule of 50 Gy in 25 fractions.

Introduction

The international standard radiotherapy regimen after breast conservation surgery or mastectomy for early breast cancer delivers 25 daily doses (fractions) of 2·0 Gy to a total dose of 50 Gy over 5 weeks.1–4 Alternative schedules based on a lower total dose delivered in fewer, larger fractions (hypofractionation) were introduced in the UK and Canada several decades ago5 on an empirical basis, and 40 Gy in 15 fractions over 3 weeks is a commonly used regimen.5,6 Results of retrospective studies of hypofractionated radiotherapy in early breast cancer suggest satisfactory outcomes in terms of tumour control and late adverse effects if modest increases in fraction size are combined with appropriate downward adjustments to total dose.7–14 The first results of a Canadian randomised trial testing 42·5 Gy in 16 fractions against 50 Gy in 25 fractions are consistent with these findings, suggesting equivalence in terms of local

control and breast cosmesis for the 16-fraction regimen.15 Fractions of more than 2·0 Gy caused unacceptable rates of late adverse effects when inadequate downward adjustments to total dose were applied several decades ago. 16–20 Despite widespread empirical use in the UK, 40 Gy in 15 fractions has never been formally compared with standard fractionation, raising concerns in the mid-1990s that it could be less effective or less safe than 50 Gy in 25 fractions. To address this uncertainty, the Standardisation of Breast Radiotherapy (START) Trials were initiated by the then UK Coordinating Committee for Cancer Research (now National Cancer Research Institute) to test the effects of radiotherapy schedules using fraction sizes larger than 2·0 Gy. START Trial A21 tested two dose levels of a 13-fraction regimen delivered over 5 weeks in order to measure the sensitivity of normal and malignant tissues to fraction size. START Trial B compared 40 Gy in 15 fractions of 2·67 Gy in 3 weeks with a control group of 50 Gy in 25 fractions of 2·0 Gy over 5 weeks. This paper presents the results of Trial B.

Methods

Participation was open to all UK centres that provided radiotherapy treatment to patients with early breast cancer. With START Trials A and B running in parallel, centres chose to participate in either Trial A (17 centres) or B (23 centres).

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See Comment page 1050
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*Trialists listed at end of paper
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Patients Women with operable invasive breast cancer (International Union Against Cancer stage pT1-3a pN0-1M0) requiring radiotherapy after primary surgery (breast conserving surgery or mastectomy, with clear tumour margins ≥1 mm) were eligible for the trial if they were aged over 18 years, did not have an immediate reconstruction, and were available for follow-up. Patients from 21 of the centres participating in Trial B were also recruited into the quality of life and health economics studies (health economics data not presented here, baseline quality of life data have been published elsewhere22). 20 of the centres participating in the quality of life study recruited patients with breast conserving surgery into the photographic assessment of Trial B. Patients from 17 centres also consented to donate a 20 ml blood sample and to complete an associated family history questionnaire (sub study not reported here). The START Trials were approved by the South Thames Multi-Research Ethics Committee in September, 1998, and by the local ethics committees of all participating centres. Written informed consent was obtained for all patients. Procedures START Trial B patients were randomised to 50 Gy in 25 fractions over 5 weeks or to 40 Gy in 15 fractions over 3 weeks. Randomisation was arranged via telephone at the Clinical

Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU), Sutton, UK, where patient details were recorded and treatment was allocated. Randomisation was not blinded. Computer-generated random permuted blocks were used as the method of allocation, with patients stratified by hospital, type of surgery (breast conserving surgery or mastectomy), and intention to give a tumour bed boost dose or not. Use of adjuvant systemic treatment was recorded, with a requirement of at least a 2-week gap between exposure to chemotherapy and radiotherapy. Patients lay in a supine treatment position. The planning target volume was defined as the whole breast with a 1 cm margin to palpable breast tissue; where regional radiotherapy was indicated, the planning target volume was supraclavicular nodes with or without axillary chain with a 1 cm margin. Most patients were treated with 6 MV x-rays, although treatment with higher energies or cobalt γ-rays was allowed after discussion with the START Trial radiotherapy quality assurance team. Planning protocols were specified at the time of notification of participation into the study and had to conform to the minimum quality criteria described in the protocol. Planning protocols varied slightly between centres, but within each centre they were identical in each fractionation group. Doses were prescribed to international reference points. 23 Departments were required to have a protocol specifying whether patients who had had breast conserving surgery would receive a boost to the tumour bed, and to use an electron field of appropriate energy to deliver 10 Gy in five daily fractions to the 100% isodose, after initial radiotherapy. All centres submitted details of the standard radiotherapy technique, after which a visit by the quality assurance team checked dosimetric measurements in a 2D and 3D breast phantom, including the junction region between supraclavicular fossa and tangential breast or chest wall fields. 24–27 The mean difference between prescribed and measured dose in a phantom was 2·1%. Additionally, a third of the radiotherapy treatment plans were collected and analysed by the quality assurance team to ensure compliance with the protocol in terms of prescription point, dose homogeneity, and lung depth, and a random sample of patients had in-vivo thermo luminescent dosimeter measurements done. 28–30 The protocol allowed for a dose variation (in the planning target volume) between 95% and 105% of that at the reference point on the central axis. Lung depth data was obtained by the radiotherapy quality assurance programme, and analysis indicated that most patients had less than 2 cm of lung within the treatment volume. These results confirmed a good compliance with the technical aspects of the trial protocol. The principal endpoints specified in the protocol were local-regional relapse, normal tissue effects, and quality of life. Local-regional tumour relapse was defined as local 2215 patients randomised 1105 allocated 50 Gy in 25 fractions over 5 weeks 1110 allocated 40 Gy in 15 fractions over 3 weeks1091 received allocated treatment* 6 treatment stopped early 5 refused allocated treatment 1 opted for mastectomy (no radiotherapy given) 1 had chicken pox after 4 fractions so treatment delayed (56 Gy given in total) 1 second primary in lung, so no breast radiotherapy given 1103 received allocated treatment* 4 given non-allocated treatment 1 refused allocated treatment 1 had subarachnoid haemorrhage so treatment abandoned after 1 fraction 1 breast lump was found to be secondary to bowel cancer 10 with baseline data only 7 withdrew consent to follow-up after randomisation 3 ineligible 9 with baseline data only 5 withdrew consent to follow-up after randomisation 2 moved 2 unknown 1105 included in analysis 1110 included in analysis *Figure 1:* Trial profile for START Trial B *Only major treatment deviations listed. Minor deviations due to public holidays, machine service days, and machine breakdowns not included. Articles 1100 www.thelancet.com Vol 371 March 29, 2008 relapse in breast or chest wall, and regional relapse in ipsilateral axilla or supraclavicular fossa if it had been

within an irradiated target volume. Any ipsilateral regional relapse outside the radiotherapy target volume was excluded from the analysis of local-regional relapse. Normal tissue effects in the breast, arm, and shoulder were assessed by photographic comparison with baseline, patient self-reported assessments, and physician assessments. Other endpoints were disease-free and overall survival, second primary cancers, and health economic consequences. Disease-free survival was defined as time to any breast cancer-related event (local-regional or distant relapse, contralateral breast cancer, or death from breast cancer). Data relating to five key breast normal tissue effects from the patient quality of life self-assessments are presented here. Separate papers will present the full analysis of all self-assessments and physician assessments of normal tissue effects, and of quality of life. Cases of ischaemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis were recorded during follow-up; incidence with and without confirmation of diagnosis (e.g., using imaging and further investigation) was included. Brachial plexopathy was reported if damage to the brachial plexus was suspected and the patient had symptoms of pain, paraesthesia, numbness, or other sensory symptoms (graded on a 4-point scale). Suspected cases of brachial plexopathy were subject to confirmation by neurophysiological assessment and MRI. Patients were reviewed every year for tumour relapse and radiotherapy-induced normal tissue effects. Clinical data were recorded on pre-printed case report forms and sent to the coordinating clinical trials office at the ICR-CTSU, Sutton, UK. Photographs were taken at baseline (post-surgery and pre-radiotherapy) and then at 2 and 5 years to assess changes to the breast based on change in size, shrinkage, and shape, and scored on a 3-point graded scale. Changes in breast appearance (photographic) were scored by three observers blind to patient identity, treatment allocation, and year of follow-up, and a final agreed score reached by consensus. Breast size and surgical deficit were both defined from the baseline photographs by the same three observers applying 3-point graded scales. Quality of life data were obtained using standardised questionnaires31–34 at baseline and at 6 months, 1, 2, and 5 years. Post-baseline quality of life questionnaires included an additional four protocol specific items relating to changes in the affected breast after radiotherapy (skin changes in the area of the affected breast, overall change in breast appearance, firmness to touch of the affected breast, and reduction in size of the affected breast). Of these four items, patients who had had mastectomy only rated change in skin appearance after radiotherapy. Details of the quality of life study protocol and baseline data have been published elsewhere.22 The trial was coordinated by the ICR-CTSU, Sutton, UK. The trial was overseen by a Steering Committee of several independent experts joined by members of the ICR-CTSU, START Trial Management Group, and representatives of the funding bodies (as observers). The Trial Management Group was responsible for the day-to-day management of the trial, and the emerging safety and efficacy data was reviewed regularly by the Independent Data Monitoring Committee. Central statistical monitoring of data was done by ICR-CTSU, supplemented by selected on-site source document verification. Statistical analysis A 5-year local-regional tumour relapse rate of 10% in the 50 Gy group was predicted, based on the earlier Fractionation schedule Total n=2215 50 Gy in 25 fractions n=1105 40 Gy in 15 fractions n=1110 Age (years) 20–29 7 (0·6) 0 (0·0) 7 (0·3) 30–39 62 (5·6) 39 (3·5) 101 (4·6) 40–49 179 (16·2) 170 (15·3) 349 (15·8) 50–59 427 (38·6) 447 (40·3) 874 (39·5) 60–69 304 (27·5) 327 (29·5) 631 (28·5) 70–79 117 (10·6) 119 (10·7) 236 (10·7) 80– 9 (0·8) 8 (0·7) 17 (0·8) Mean (SD) 57·0 (10·4) 57·8 (9·5) 57·4 (10·0) Time from surgery to randomisation (weeks); median (IQR) [range] 7·3 (4·9–12·3) [0·9–45·3] 7·1 (4·9–11·9) [0·6–49·3] 7·3 (4·9–12·0) [0·6–

49·3] Primary surgery Breast conserving surgery 1020 (92·3) 1018 (91·7) 2038 (92·0) Mastectomy 85 (7·7) 92 (8·3) 177 (8·0) Histological type Invasive ductal 865 (78·3) 843 (75·9) 1708 (77·1) Invasive lobular 122 (11·0) 132 (11·9) 254 (11·5) Mixed ductal/lobular 20 (1·8) 25 (2·3) 45 (2·0) Other 95 (8·6) 103 (9·3) 198 (8·9) Not known 3 (0·3) 7 (0·6) 10 (0·5) Pathological node status Positive 238 (21·5) 266 (24·0) 504 (22·8) Negative 831 (75·2) 804 (72·4) 1635 (73·8) Not known (no axillary surgery) 36 (3·3) 39 (3·5) 75 (3·4) Not known (missing data) 0 (0·0) 1 (0·1) 1 (0·04) Tumour size (cm) <1 151 (13·7) 167 (15·0) 318 (14·4) 1– 552 (50·0) 542 (48·8) 1094 (49·4) 2– 287 (26·0) 288 (25·9) 575 (26·0) 3– 113 (10·2) 107 (9·6) 220 (9·9) Not known 2 (0·2) 6 (0·5) 8 (0·4) Tumour grade 1 306 (27·7) 311 (28·0) 617 (27·9) 2 518 (46·9) 532 (47·9) 1050 (47·4) 3 261 (23·6) 248 (22·3) 509 (23·0) Not known (not applicable)* 15 (1·4) 15 (1·3) 30 (1·3) Not known 5 (0·4) 4 (0·4) 9 (0·4) (Continues on next page) Articles www.thelancet.com Vol 371 March 29, 2008 1101 Royal Marsden Hospital/Gloucestershire Oncology Centre (RMH/GOC) pilot trial. 35 A target sample size of 1840 patients was defined in Trial B to provide 95% power to exclude an increase of 5% in the local-regional relapse rate for the 40 Gy group compared with 50 Gy (one-sided α=0·025). The protocol specified that if the true 5-year local-regional relapse rate in the 50 Gy group was lower than expected (e.g., 5%), this sample size would give more than 95% power to detect an increase of 5% in the local-regional relapse rate in the 40 Gy group. Survival analysis methods were used to compare rates of each endpoint between the fractionation schedules. Length of follow-up was calculated as time from randomisation until time of first event or last follow-up assessment, whichever occurred first. Patients were still evaluable for local-regional relapse after distant relapse but were censored at date of death. For the photographic endpoint, patients were no longer evaluable for change in breast appearance after local-regional relapse. Kaplan-Meier estimates of 5-year relapse rates, rates of normal tissue effects, rates of any breast-cancer related event, and mortality rates were calculated (with 95% CIs). For the patient quality of life self-assessments of normal tissue effects an event was defined as the first occurrence of a moderate or marked symptom (graded “quite a bit” or “very much”). The scores from the photographic assessments of change in breast appearance at 2 and 5 years were dichotomised as none versus mild or marked change, and the first occurrence of such a change was taken as the endpoint for the survival analysis. There were too few patients with marked change in breast appearance to be able to analyse this category separately. The log-rank test was used to compare fractionation schedules. Crude hazard ratios (with 95% CIs) comparing fractionation schedules for each endpoint were obtained from Cox proportional hazards regression models. The proportionality assumption of the Cox model was tested using Schoenfeld residuals and was found to be valid for all of the analyses. Since point estimates of differences in event rates can, by chance, be atypical of the overall pattern of differences between schedules, estimates of the absolute difference in 5-year event rates taking the whole range of observation times into account were obtained by applying the hazard ratios obtained from the Cox model to the Kaplan-Meier estimate of the rate in the 50 Gy control group. 36 Both one-sided and two-sided 95% CIs were calculated for the absolute difference in local-regional relapse rates at 5 years, since the upper limit is of greater clinical interest, in view of concern about a possible excess risk caused by hypofractionated schedules. Kaplan-Meier survival curves and Nelson-Aalen cumulative hazard functions were plotted according to fractionation schedule. Plots were censored at the median length of follow-up (rounded to nearest year). Analysis included all randomised patients on an intention-to-treat basis. This study is registered as an International Standard

Randomised Controlled Trial, number ISRCTN59368779. Role of the funding source The funding sources provided peer-reviewed approval for the trial and have had representation (as observers) on the Trial Steering Committee, but had no other role in the design, conduct, data collection, data analysis or interpretation of the study or the results. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between January, 1999, and October, 2001, 2215 patients were enrolled in START Trial B at 23 centres in the UK (figure 1). A total of 1079 patients were enrolled in the quality of life study and 1094 in the photographic assessment study (with 930 patients enrolled in both sub studies). Fractionation schedule Total n=2215 50 Gy in 25 fractions n=1105 40 Gy in 15 fractions n=1110 (Continued from previous page) Adjuvant therapy None 37 (3·3) 47 (4·2) 84 (3·8) Tamoxifen/no chemotherapy 782 (70·8) 810 (73·0) 1592 (71·9) Chemotherapy/no tamoxifen 77 (7·0) 78 (7·0) 155 (7·0) Tamoxifen+chemotherapy 181 (16·4) 155 (14·0) 336 (15·2) Other endocrine therapy† 16 (1·4) 11 (1·0) 27 (1·2) Not known 12 (1·1) 9 (0·8) 21 (0·9) Lymphatic treatment None 32 (2·9) 36 (3·2) 68 (3·1) Surgery/no radiotherapy 980 (88·7) 984 (88·6) 1964 (88·7) Radiotherapy/no surgery 5 (0·4) 3 (0·3) 8 (0·4) Surgery+radiotherapy 74 (6·7) 79 (7·1) 153 (6·9) Not known 14 (1·3) 8 (0·7) 22 (1·0) Boost (BCS patients only) n=1020 n=1018 n=2038 Yes 422 (41·4) 446 (43·8) 868 (42·6) No 584 (57·3) 565 (55·5) 1149 (56·4) Not known 14 (1·4) 7 (0·7) 21 (1·0) From baseline photographs n=522 (%) n=514 (%) n=1036 (%) Breast size Small 49 (9·4) 42 (8·2) 91 (8·8) Medium 377 (72·2) 390 (75·9) 767 (74·0) Large 96 (18·4) 82 (16·0) 178 (17·2) Surgical deficit Small 307 (58·8) 286 (55·6) 593 (57·2) Medium 164 (31·4) 177 (34·4) 341 (32·9) Large 51 (9·8) 51 (9·9) 102 (9·8) Data are n (%) unless otherwise stated. BCS=breast conserving surgery. *Lobular and other histological types. †Other endocrine therapies include combinations of tamoxifen/anastrozole/letrozole/goserelin mostly within randomised trials.

Table 1: Demographic and clinical characteristics at randomisation of the 2215 patients in START Trial B

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1102 www.thelancet.com Vol 371 March 29, 2008 Demographic and clinical characteristics were well balanced between the treatment groups (table 1). Of the women prescribed chemotherapy, 59·1% (290/491) received an anthracycline-containing regimen, which was balanced between randomised radiotherapy schedules (154/258 [59·7%] for 50 Gy and 136/233 [58·4%] for 40 Gy). Cyclophosphamide, methotrexate, and fluorouracil combination therapy alone was prescribed in 196 women (39·9% of those receiving chemotherapy), which was similarly balanced between randomised groups (103 [39·9%] for 50 Gy and 93 [39·9%] for 40 Gy). Nine women (three allocated 50 Gy and six allocated 40 Gy) received an adjuvant taxane. Of the 1955 women prescribed tamoxifen or another endocrine therapy, almost all were continuing treatment at randomisation (956/979 [97·6%] for 50 Gy and 963/976 [98·7%] for 40 Gy). The quality of life subgroup included 12·3% women who had undergone mastectomy. There were only 21 major treatment deviations (including early stopping of treatment, patient refusal of allocated treatment, and patients found to be ineligible for reasons including presence of second primaries), resulting in 99·0% compliance with allocated treatment (figure 1). Compliance with completion of quality of life questionnaires over 5 years was more than 90%. Median follow-up of surviving patients was 6·0 years (IQR 5·0 to 6·2), with a maximum follow-up of 8·0 years. At the time of analysis, 1872 patients (84·5%) were alive and without relapse, 34 (1·5%) were

alive with local-regional relapse (without distant relapse), 45 (2·0%) were alive with distant relapse (including four with local-regional relapse), 245 (11·1%) had died (including 27 with local-regional relapse), and 19 (0·9%) had no follow-up (figure 1). At the time of analysis, 65 (2·9%) patients had experienced a local-regional relapse. The hazard ratio for local-regional relapse after 40 Gy compared with 50 Gy was 0·79 (95% CI 0·48–1·29; table 2). The estimated absolute difference in local-regional relapse rates for 40 Gy compared with 50 Gy at 5 years was –0·7% (–1·7% to 0·9%), which indicates that the absolute difference between schedules is likely to be at worst 0·9% higher and at best 1·7% lower after 40 Gy in 15 fractions than after 50 Gy in 25 fractions. Since the main concern over hypofractionation is an excess risk rather than a possible benefit, a more precise estimate of the potential excess risk of local-regional relapse is obtained from the upper limit of the one-sided 95% CI for the absolute difference in 5-year local-regional relapse rates. This calculation indicated an upper limit of 0·6% excess risk associated with the 15-fraction schedule. The Kaplan-Meier and cumulative hazard rate plots for local-regional relapse according to fractionation schedule (figure 2) illustrate the low event rate in both randomised groups. The 5-year rate of distant relapse was lower in the 40 Gy group (hazard ratio 0·69, 95% CI 0·53–0·91), which contributed to the higher rates of disease-free survival and overall survival than in the 50 Gy group (table 2). Analysis of the Kaplan-Meier and cumulative hazard rate plots indicated that the divergence in distant relapse Events/total (%) Estimated % with event by 5 years (95% CI) Crude hazard ratio (95% CI) Log-rank test p value Local relapse* 50 Gy 34/1105 (3·1) 3·3 (2·2–4·4) 1 40 Gy 25/1110 (2·2) 2·0 (1·1–2·8) 0·72 (0·43–1·21) 0·21 Local-regional relapse 50 Gy 36/1105 (3·2) 3·3 (2·2–4·5) 1 40 Gy 29/1110 (2·6) 2·2 (1·3–3·1) 0·79 (0·48–1·29) 0·35 Distant relapse 50 Gy 122/1105 (11·0) 10·2 (8·4–12·1) 1 40 Gy 87/1110 (7·8) 7·6 (6·0–9·2) 0·69 (0·53–0·91) 0·01 Any breast cancer-related event† 50 Gy 164/1105 (14·8) 14·1 (12·0–16·2) 1 40 Gy 127/1110 (11·4) 10·6 (8·7–12·4) 0·75 (0·60–0·95) 0·02 All-cause mortality 50 Gy 138/1105 (12·5) 11·0 (9·1–12·9) 1 40 Gy 107/1110 (9·6) 8·0 (6·4–9·7) 0·76 (0·59–0·98) 0·03 *Local relapse defined as ipsilateral local tumour relapse in breast parenchyma/breast skin/chest wall skin. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer (“disease-free survival”).

www.thelancet.com Vol 371 March 29, 2008 1103 between the schedules began at around 1 year after randomisation (figure 3). Change in breast appearance (photographic) was assessed on a 3-point graded scale (none, mild, marked) in 923 patients with a baseline and at least one follow-up image (461 for 50 Gy and 462 for 40 Gy). Not all patients had photographs available at both 2 and 5 years, for reasons including the 5-year assessment not yet being done at the time of scoring and analysis, patient refusal, and withdrawal from the photographic study due to relapse. There were no associations between score for change in breast appearance (photographic) at 2 years or patient demographic or treatment characteristics and whether or not the patient had a 5-year assessment (data not shown). Mild change was graded for 284 (30·8%) patients and marked change for 28 (3·0%) patients, by 5 years. Change in breast appearance (photographic) was less likely after 40 Gy than after 50 Gy, with a hazard ratio of 0·83 (95% CI 0·66–1·04, p=0·06; figures 4 and 5). Adjusting for breast size and surgical deficit made little difference to these results. Figure 4 shows that the treatment differences were evident at the first time point of 2 years, and persisted to 5 years. Patient quality of life self-assessments of normal tissue effects were available for 1037 (96·1% of all patients in the quality of life study) patients with baseline information and at least one completed follow-up questionnaire (511 for 50 Gy and 526

for 40 Gy). Changes in breast appearance and breast hardness (patients with breast conserving surgery) were the most common changes recorded. Analysis of patient self-assessments of five key normal tissue effects on the breast and breast area showed that rates of moderate or marked effects by 5 years tended to be lower after 40 Gy than after 50 Gy, with a significantly lower rate of change in skin appearance after radiotherapy for 40 Gy than after 50 Gy (p=0·02; figure 5). The results of the various assessments of normal tissue effects were consistently in favour of the 40 Gy group compared with 50 Gy (figure 5). The incidence of ischaemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis was low at this stage during follow-up, and balanced between the schedules (table 3). There were no cases of brachial plexopathy in the 82 women given 40 Gy in 15 fractions or in the 79 women given 50 Gy in 25 fractions to the supraclavicular fossa, axilla, or both. An unusually marked acute reaction during radiotherapy was recorded for 16 (0·7%) patients (13 after 50 Gy [1·2%], three after 40 Gy [0·3%]). Of these, 14 cases were severe skin reactions (extensive moist desquamation), one was an infected seroma in the scar area, and one had severe pain in the breast tissue and ribs. There were 36 (1·6%) contralateral breast cancers (19 after 50 Gy (1·7%), 17 after 40 Gy [1·5%]), and 58 patients [2·6%] had other second primary cancers (32 after 50 Gy [2·9%], 26 after 40 Gy [2·3%]), the most frequent being lung (ten), endometrial (ten), ovarian (eight), and colon (five). The remaining 25 incidences of second primary cancers consisted of one or two cases of several different types.

Discussion

START trial B aimed to provide a robust evidence base for clinical practice in breast radiotherapy by comparing 50 Gy (122/1105) 40 Gy (87/1110)

Years since randomisation

Figure 4: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 923 patients with
breast conserving surgery