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FACILITY-BASED OPTIMISATION AND STANDARDISATION OF VMAT BREAST CANCER TREATMENT PLANNING: A DOSIMETRIC AND QUALITY ASSURANCE STUDY

BY

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DECLARATION

This dissertation is my own work produced from original research undertaken under supervision of Prof. Francis Hasford, Dr. Samuel Nii Adu Tagoe and Prof. Ernest Osei.

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ABSTRACT

Variations in planning protocols can compromise treatment plan quality, impacting patient outcomes. The study analyses systematic approach in improving the overall Volumetric Modulated Arc Therapy (VMAT) breast cancer treatment plan quality through a 'plan-overview' optimisation approach. The main objective of the study was to conduct confirmatory studies to evaluate current VMAT breast treatment planning, which will subsequently inform and justify the development of standardised facility-based VMAT breast treatment planning optimisation criteria. The objective was achieved through four distinct phases aimed at investigating structured approaches to enhance overall plan quality and at developing clinical tools to standardise VMAT breast treatment planning optimisation. Results from eleven respondents during the National Breast Cancer EBRT survey identified minor inter-protocol variations from adopted international guidelines and the recognition of improvements in plan quality through new techniques as vital. From the plan acceptability criteria established, acceptable plans can be developed even though plan acceptability deviations from the planning objectives were observed. The criteria for intact breast cases had a mean target volume that received 95% of the prescribed (50 Gy dose) to be 95.08 ± 1.11% and 94.95 ± 1.19% for the chest-wall cases. Significant low doses in contralateral volumes were observed with absolute doses of 7.64 Gy and 7.28 Gy recorded in the contralateral breast volumes for intact breasts and chest-wall VMAT plans, respectively. The current facility protocol tends to improve target conformity at the expense of increasing low doses of contralateral organ volumes. The proposed planning optimisation criteria were established based on results from the plan overview analysis. Comparing the analysed dosimetric parameters between the automated plans with its manual training plan cohort, the mean intact breast target volume that received the 95% of the prescribed dose were 95.81 ± 0.64% and 95.46 ± 0.40%, respectively with a percentage

difference of 0.37 ± 0.79%. A mean volume of 95.11 ± 0.72% and 95.04 ± 0.61%, respectively for the chest-wall cases with a percentage difference of 0.07 ± 0.99% also evaluated. The proposed optimisation criteria, however, produced VMAT plans with significantly reduced low doses to the contralateral organ volumes for both intact breast and chest-wall cases. There were no significant differences in the gamma index analysed during intact breast (p-value = 0.962 and p-value = 0.742) and chest-wall (p-value = 0.925 and p-value = 0.779) cohort plans pretreatment QA measurements using both the Octavius 4-D phantom and EPID-based EPIbeam software respectively. There was no statistically significant difference in all dosimetric parameters evaluated between the three cohort plans and among any pair of cohort plans compared during the validation phase of the study. This is a positive demonstration of the clinical feasibility of the proposed optimisation criteria as optimal VMAT breast plans can be consistently reproduced by other treatment planners. This study undoubtedly introduces a new optimisation approach, grounded in a sufficiently extensive dosimetric, quality assurance and radiation therapy efficiency comparative study. Innovative clinical research focusing on standardising local evidence-based outcomes should be encouraged to derive maximum patient treatment benefits. The radiotherapy facility should incorporate the plan acceptability criteria into its planning protocols, and adherence to these criteria must be ensured.

DEDICATION

This research work is dedicated to my wife, Mrs. Stella Acquah, my father, Mr. Edward Ofori Acquah, my mother Mrs. Joyce Naa Norkor Acquah and my children, Gretchen Gwen Acquah, Sterling McGreg Acquah, Greyson Myles Acquah and George Felix Acquah Jr. for their support and prayers. This work is also dedicated to my siblings, Mrs. Gladys Nora Blankson and Mrs. Alice Joycelyn Acquah; and to Mr. Edward Ocran, and uncle, Rev. Charles Lokko, in recognition of your enduring concern and unwavering support.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

2-D	Two-Dimensional
3-D CRT	Three-Dimensional Conformal Radiotherapy
AAA	Analytical Anisotropic Algorithm
AAPM	American Association of Physicists in Medicine
ACR	American College of Radiology
ACS	American Cancer Society
AI	Artificial Intelligence
AJCC	American Joint Committee on Cancer
ANOVA	Analysis of Variance
a-Si	Amorphous-Silicon
BCRT	Breast Cancer and Radiation Therapy
BCS	Breast-Conserving Surgery
BCSS	Breast Cancer Symptom Scale
BCTOS	Breast Cancer Treatment Outcome Scale

Brst_opt	Intact Breast Volume for Optimisation
BS	Breast Separation
CAX	Central Axis
CB	Contralateral Breast
CBCT	Cone Beam CT
CCC	Collapsed Cone Convolution
Chst_opt	Chest-wall Volume for Optimisation
CI	Conformity Index
CICL	Centre International de Cancerologie de Lomé
CL	Contralateral Lung
Co-60	Cobalt-60
CT	Computed Tomography
CTV	Clinical Target Volume
DD	Dose Difference
DIBH	Deep Inspiration Breath Hold
DICOM	Digital Imaging and Communications in Medicine
DMPO	Direct Machine Parameter Optimisation
DNA	Deoxyribonucleic Acid

DRRs	Digitally Reconstructed Radiographs
DTA	Distance-To-Agreement
DVH	Dose Volume Histograms
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EBRT	External Beam Radiation Therapy
ECBAS	Ethics Committee of the Basic and Applied Sciences
EORTC	European Organization for Research and Treatment of Cancer
EPID	Electronic Portal Imaging Device
EUD	Equivalent Uniform Dose
FACT-B	Functional Assessment of Cancer Therapy-Breast
FFF	Flattening Filter Free
FMC	Fluence Map Complexity
FP-FIF	Forward Planning Field-In-Field
FPPs	Fixed-Physical Properties
GLOBOCAN	Global Cancer Observatory
GTV	Gross Tumour Volume
Gy	Gray
HI	Homogeneity Index

HT	Helical Tomotherapy
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
IBCSG	International Breast Cancer Study Group
ICRU	International Commission on Radiation Units and Measurements
IEC	International Electrotechnical Commission
IMNs	Internal Mammary Nodes
IMRT	Intensity Modulated Radiation Therapy
KBP	Knowledge-Based Planning
kV	Kilovoltage
Linac	Linear Accelerator
LKB	Lyman-Kutcher-Burman
MC	Monte Carlo
MCO	Multi-Criteria Optimisation
MCS	Modulation Complexity Score
MI	Modulation Index
MLC	Multileaf Collimator
MPs	Medical Physicists

MRI	Magnetic Resonance Imaging
MV	Megavoltage
nC	Nano Coulomb
NCI	National Cancer Institute
NDI	Nano Dose Iteration
NEMA	National Electrical Manufacturers Association
NRONMC	National Radiation Oncology and Nuclear Medicine Center
NTCP	Normal Tissue Complication Probability
OARs	Organs at Risk
OC	Optimisation Criteria
OD-KATH	Oncology Directorate – Komfo Anokye Teaching Hospital
OQM	Optimisation Quality Metrics
PAC	Plan Acceptability Criteria
PB-AIO	Protocol-Based Automatic Iterative Optimisation
PBC	Pencil-Beam Convolution
PBT	Proton Beam Therapy
PD	Prescribed Dose
PDD	Percentage Depth Dose

PET	Positron Emission Tomography
PMMA	Poly Methyl Methacrylate
POC	Planning Optimisation Criteria
POI	Points of Interest
PQM	Plan Quality Metric
PROMIS	Patient-Reported Outcomes Measurement Information System
PSQA	Patient-Specific Quality Assurance
PTV	Planning Tumour Volume
PTV_opt	Planning Target Volume for Optimisation
PTQA	Pretreatment Quality Assurance
QA	Quality Assurance
QC	Quality Control
QI	Quality Index
QUANTEC	Quantitative Analyses of Normal Tissues Effects in the Clinic
RBE	Relative Biological Effect
RF	Radiofrequency
RNI	Regional Nodal Irradiation
ROI	Region of Interest

ROs	Radiation Oncologists
RP	Radiotherapy Plan
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
RTTs	Radiation Therapy Technologists
RVS	Record and Verifying System
RW3	Water-Equivalent Phantom
SAD	Source-Axis Distance
SBRT	Stereotactic Body Radiation Therapy
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
SGMC	Sweden Ghana Medical Center
SIB	Simultaneous Integrated Boost
SID	Source-to-Isocentre Distance
SSD	Source-to-Surface Distance
TCP	Tumour Control Probability
TNM	Tumour size, Nodes and Metastasis
TPS	Treatment Planning System

UI	Uniformity Index
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organisation
XVI	X-ray Volume Imaging

CHAPTER ONE

INTRODUCTION

Chapter One gives the general background of the thesis and an overview of the research problem of the study. It also outlines the main research objective and specific study objectives, as well as the justification and scope of the study.

1.1 BACKGROUND

The current global cancer statistics report (GLOBOCAN 2020) ranked breast cancer as the most prevalent cancer worldwide with higher incidence and mortality rates among African women (Ferlay *et al*., 2020). In the year 2020, breast cancer accounted for 16.8% of all newly diagnosed cancer cases across Africa, encompassing both sexes and all age groups. In the West African sub-region, 49,339 new breast cancer cases were recorded, representing 33.5 percent of all new female cancer cases of all ages. Ghana is projected to record approximately 4,600 new breast cancer diagnoses in 2030 among women under 60 years, accounting for a fraction of the estimated 19,900 new cases across all cancer types for both sexes based on a projected 38 million population in 2030 (Ferlay *et al*., 2020) (Gaisie *et al*., 2014). African women are diagnosed with breast cancer at a significantly younger mean age, under 50 years, compared to their Caucasian counterparts (Brinton *et al*., 2014).

Breast cancer treatment and management often rely on external beam radiation therapy (EBRT) delivered by specialised machines. EBRT is an indispensable component of the whole breast cancer care process, required at a point for maximum therapeutic outcome either post-breast cancer surgical procedures (breast conserving surgery (BCS) or full breast removal) (EBCTCG, 2005).

Standard radiation therapy for breast cancer typically involves delivering curative dose fractionation of either 50 Gy in 25 fractions, or 42.56 Gy in 16 fractions to achieve optimal tumour control (Henry *et al*., 2020). In contrast to other cancers, breast cancer irradiations often employ moderate dose levels, which have proven effective in disease control without requiring dose escalation. To effectively manage the disease, the treatment may combine radiation therapy, surgery, and chemotherapy to improve survival (Henry *et al*., 2020). Ensuring effective breast cancer radiation therapy requires addressing patient anatomy irregularities, standardising dose planning, minimising toxicity risks, and protecting critical organs (Darby *et al*., 2013). Post-surgical radiation therapy is essential for reducing tumour regrowth (cancer relapse) and preventing advanced breast cancer with distant spread (metastasis), regardless of risk classification, after lumpectomy (surgical excision of cancerous cells) or mastectomy (surgical removal of whole breast) (Osei *et al*., 2020). Evidence from randomised clinical trials indicates that adjuvant radiation therapy enhances local control and reduces recurrence in low-risk, early-stage I and II breast cancer patients who have undergone lumpectomy (referred to as intact breast in this study) and mastectomy (referred to as chest-wall in this study) (EBCTCG, 2005). The treatment strategy of breast cancer is stage-dependent and often involves a combination of modalities, such as surgical intervention, chemotherapy, and radiation therapy to optimise disease management and treatment outcomes. Radiation therapy following BSC lowers the susceptibility of tumour relapses and cancer-related mortality, potentially improving survival rates. However, radiation-related side effects, including cardiotoxicity and secondary malignancies, can offset these benefits and increase mortality risk (Cuzick *et al*., 1994). Therefore, treatment plans must consider each patient's unique risk profile to optimise outcomes and minimise harm.

The quality of radiation treatment may differ due to the availability of required resources and technical know-how (both human and technology) based on the patient's geographic location. Sub-Saharan Africa faces disproportionately high breast cancer mortality rates, with approximately 51.9% of cases resulting in death (Ferlay *et al*., 2020). Limited access to high-quality cancer care and radiotherapy services in the region likely plays a significant role in this disparity. Internationally, clinical research and trials in breast cancer radiation therapy have significantly advanced evidence-based treatments, enhancing the effectiveness and safety of breast cancer management. These studies have led to improved patient outcomes and minimised potential side effects. Notable studies include the recognition of external beam radiation therapy as a crucial post-surgical step. Additional key developments include hypofractionation regimes, which shorten treatment duration, partial breast irradiation for targeted tissue treatment, tumour bed boost doses for enhanced local control, and optimised axillary node irradiation for improved regional management (EBCTCG, 2005; Cuzick *et al*., 1994; Thompson *et al*., 2018). External beam radiation therapy is the predominant radiation therapy modality, relying on precise treatment planning using computerised treatment planning system (TPS) to simulate and optimise treatment plans, ensuring personalised dose delivery (Karunakaran *et al*., 2016).

Radiotherapy facilities in the developed world are focusing on developing new treatment planning strategies, techniques and technology aimed at providing maximum tumour coverage with minimal radiation doses to surrounding healthy structures (Thompson *et al*., 2018). This is mainly achieved through conducting various clinical research/trials into the advanced intact breast and chest-wall radiation treatment planning simulations (Zeverino *et al*., 2018). The advent of Computed Tomography (CT) scanners revolutionised radiotherapy treatment planning, paving the way for sophisticated simulation techniques. While parallel-opposed tangential treatment planning is

widely regarded as the gold standard, recent advancements have led to the increasing adaptation of arc therapy or tomotherapy techniques as viable alternatives (Teoh *et al*., 2011). Advanced radiation techniques such as the Three-Dimensional Conformal Radiotherapy (3-D CRT), the Forward Planning Field-in-Field (FP-FIF), Intensity Modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT) or helical techniques, hybrid planning technique and proton therapy have transformed radiation treatment (Tanaka *et al*., 2015; Lauche *et al*., 2016; Zeverin *et al*., 2018). Image guidance and respiratory motion management, including respiratory gating and Deep Inspiration Breath Hold (DIBH), minimise heart exposure in left-sided breast cancer, reducing cardiac risks and improving patient outcomes (Dodul *et al*., 2016).

Treatment planning automation and advanced treatment planning techniques like VMAT planning offer better breast plan quality during the treatment simulation processes (Hussein *et al*., 2018; Ueda *et al*., 2018; Teoh *et al*., 2011). VMAT technology facilitates dynamic intensity-modulated radiotherapy through advanced multileaf collimator (MLC) leaf sequencing, ensuring precise tumour coverage and efficient treatment delivery. This is coupled with simultaneous gantry rotations to provide beam intensity modulations and achieve better dose coverage to the tumour volume and reduction of doses to organs at risk. VMAT revolutionised treatment delivery with faster, more efficient, and precise dose conformity. It also enables differential dosing and simultaneous integrated boost (SIB) delivery, streamlining treatment for multiple target volumes (Teoh *et al*., 2011). A significant obstacle in providing uniform, high-quality breast cancer care is the variability in radiation treatment planning processes across different facilities and even among individuals within the same institution. This inconsistency can lead to disparities in treatment outcomes, inefficient resource utilisation, and compromised patient care. Therefore, it has become ever more important for the development of local resource-stratified site-specific treatment plan

acceptability criteria based on facility's data to minimise significant variations in patient treatment plans and maximise the overall treatment plan quality.

Hence, evaluation of current facility breast treatment guidelines is key in assessing the clinical suitability of planned doses and overall plan quality expected from treatment plans. To optimise patient outcomes, systematic collection and analysis of clinical data is crucial. This data-driven approach facilitates evidence-based practice, improving patient outcomes and advancing radiation oncology. This involves prospective data collection, retrospective data analysis, and individualised patient treatment plan evaluation. Clear guidelines for evaluating treatment plans effectively should be developed, informed by the evidence-based findings from clinical data analysis. (Osei *et al*., 2020; Osei *et al*., 2015). This is to maintain uniformity in breast cancer treatment planning acceptability criteria in the radiotherapy facility and ultimately improve the overall plan quality. By leveraging data-driven protocols, facilities can predict treatment efficacy, identify potential toxicities, inform personalised treatment decisions, and enhance quality of care. These established Plan Acceptability Criteria (PAC) (Acquah *et al*., 2023) would be assessed for further improvement by proposing new Planning Optimisation Criteria (POC) using established facility-based plan Optimisation Quality Metrics (OQM) (Vaniqui *et al*., 2020; Hernandez *et al*., 2020).

1.2 STATEMENT OF PROBLEM

One significant challenge is the lack of local treatment planning standards, and even variations within the radiotherapy facility. International organisations, professional bodies and researchers have made huge investments and committed resources into conducting and publishing task group reports, recommendations and guidelines in ensuring consistency in workflow (EBCTCG, 2005; Thompson *et al*., 2018; Van der Laan *et al*., 2010; Cuzick *et al*., 1994). Clinical research and trials

are usually conducted by some of these working groups (Parulekar *et al*., 2019; Mamounas *et al*., 2014; Chen *et al*., 2011) collectively in providing well-defined breast treatment criteria through consensus building whereby establishing international, regional, and national standardised guidelines. These have over the decades helped improve the quality of clinical practices by establishing breast Quality Assurance (QA) procedures. Unfortunately, in Africa, there has been very minimal work on oncology research particularly in the standardisation of EBRT local protocols at facility level (Odedina *et al*., 2020). Without local conducted research, whether at the national or facility level, institutions tend to adopt international guidelines as local protocols which mostly lack data diversity (equipment, technology and patient-type data) and may even be lacking in our local clinical practice (Emami *et al*., 1991; Bradley *et al*., 2007; ICRU 83, 2010). Adopting international guidelines without proper evaluations leading to local protocols may introduce unnecessary criteria variations that may lead to treatment inefficiencies and inferior treatment outcomes.

Also, studies have found VMAT breast plans to improve dose coverage of the target at the expense of increased low doses to the critical organs, which in rare cases can increase the risk of secondary cancer (Hall *et al*., 2003; Stovall *et al*., 2008; Keller *et al*., 2012). This study, therefore, seeks to establish a facility-based OQM relative scoring method to develop new planning optimisation criteria for breast cancer treatment planning that will improve the overall VMAT plan quality (achieve both target coverage and organ sparing). The radiation treatment plans produced from the two optimisation criteria (OC); PAC-based cohort (automated plans) and POC-based cohort (manual plans) would be dosimetrically, and radiobiologically compared as well as other VMAT desirable qualities quantified (Hernandez *et al*., 2020; Vaniqui *et al*., 2020).

1.3 OBJECTIVE OF STUDY

The overall objective of this study is to conduct confirmatory studies to evaluate current VMAT breast planning, which will subsequently inform and justify the development of standardised facility-based treatment planning optimisation criteria for intact breast and chest-wall irradiations during external beam radiotherapy.

1.3.1 Specific Objectives

The primary objective was to be achieved through the underlisted specific study objectives:

1. To gain insights into adopted external beam radiotherapy breast cancer treatment guidelines across multi-facilities by conducting a national survey.
2. To determine if the current facility's automated VMAT planning guidelines for breast cancer meet institutional treatment goals (plan quality) through clinical suitability estimation.
3. To create a clear benchmark for acceptable plans, reduce variations and ensure the same quality of care by establishing Plan Acceptability Criteria (PAC).
4. To enhance overall plan quality (driving continuous improvement) by developing new VMAT Planning Optimisation Criteria (POC) using an established user-defined plan Optimisation Quality Metric (OQM).
5. To validate and demonstrate the consistency of the proposed optimisation criteria by assessing its clinical performance and standardisation.

1.4 JUSTIFICATION

1.4.1 Relevance and Rationale

In the era of personalised data, targeted and evidence-based clinical practice, it is no longer adequate to assume that adopting international protocols and treatment guidelines will be best in managing all breast cancer types. Facility-based breast VMAT treatment planning objectives/constraints and optimisation criteria developed by adopting these established international guidelines (Thompson *et al.*, 2018; ICRU 83, 2010; Van der Laan *et al.*, 2010; Ueda *et al.*, 2018; Keller *et al.*, 2012) need to be evaluated. To effectively streamline breast cancer radiation treatment planning process, clinical research purposely to investigate institutionally EBRT intact breast and chest-wall treatment planning need to be conducted and standardised guidelines established. These guidelines are useful tools for translating clinical research and institutional experience into harmonising breast cancer patient treatment and eliminating unnecessary variations that may lead to inefficiency and inferior outcomes. As radiation oncology healthcare professionals, this will help minimise variations in treatment plans, improve workflow, enhance safety associated with treatment delivery, and provide the same best quality of breast cancer care within the facility.

1.5 SCOPE OF STUDY

A major part of the research was carried out within the radiotherapy department at Centre International de Cancerologie de Lomé (CICL) in Lomé, Togo during the period of January 2021 to June 2023. This research was conducted to systematically review and establish facility-based (CICL) automated VMAT treatment planning protocols for intact breast and chest-wall cases. Specific areas investigated were the establishment of the facility-based plan acceptability criteria

(by analysing available clinical breast plan data), exploring the use of user-defined scoring method to establish new breast planning optimisation criteria. Planning optimisation methods and strategies for establishing treatment plans to meet the required improved facility-based planning objective criteria or a 'wish-list' established through team consensus were also investigated. All quality assurance (QA) and quality control (QC) requirements to ensure clinical implementation of the proposed approaches and developed planning guidelines, problems and proposed solutions to problems were all conducted.

CICL was chosen as the main study site because of the advanced breast treatment planning technique (automated VMAT inverse planning) it uses in planning, treating and managing its breast cancer patients. It was the only facility in the sub-region that utilised such advanced technology in the management of breast cancer. The radiotherapy department of the cancer facility is equipped with a 64-slice CT scanner, a Pinnacle treatment planning system and a medical linear accelerator (LINAC) with 160 MLCs of 0.5-cm thickness. The LINAC is equipped with cone beam CT (CBCT) and megavoltage (MV) imagining capabilities. The TPS was server-based and connected remotely to the other five radiotherapy facilities worldwide. PTW water phantom (BEAMSCAN), PTW water-equivalent phantom (RW3), PTW Octavius 4-D 1500 phantom with BEAMSCAN software (v3.4) and Verisoft software (v8.0), EPID-based EPIbeam system were employed for experimental measurements and analysis, respectively.

However, as a prerequisite in establishing the above facility-based comprehensive external beam breast cancer treatment planning guideline, two surveys (Acquah *et al.*, 2022) were conducted to understand the extent of perceived variations in the adopted international guidelines across radiotherapy facilities in Ghana.

1.6 ORGANISATION OF THESIS

This PhD dissertation is in chronological order of five main chapters. Chapter one is an introduction to the study which covers the objectives, problem statement, relevance and scope of the work. In Chapter two, a critical analysis of the existing body of literature and relevant theories were undertaken. Chapter three covers the materials and experimental methods used in undertaking the study. The results and findings obtained from the study and the relevant discussions have been presented in Chapter four. Finally, Chapter five deals with the study conclusion and suggested recommendations to various stakeholders. References and appendices are presented after the final chapter.

CHAPTER TWO

LITERATURE REVIEW

This chapter focuses on the relevant literature and theories covering all the principles that were utilised in the study.

2.1 BREAST CANCER

Cancer is characterised by the abnormal growth of cells that divide uncontrollably and have the potential to invade and destroy nearby healthy tissues. Cancer most often also can spread throughout the entire human body. Cancer is ranked as a leading cause of death worldwide and tends to reduce life expectancy in many countries (Bray *et al.*, 2021). It is estimated to be the second leading cause of death among people below the age of 70 years in 112 countries (out of 183) according to the World Health Organization (WHO) in 2019 (World Health Organization, 2023). One in five people worldwide develop cancer during their lifetime but survival rates in the developed countries are higher due to improvements in screening, prevention and treatment policies and guidelines (World Health Organization., 2023). Breast cancer is a type of cancer that starts in the breast (either in one or both breasts) and mainly occurs in women but very few men have also been diagnosed and treated for breast cancer. Most lumps that develop in the female breasts may be benign and not cancerous (malignant) (Henry *et al.*, 2020).

The current global cancer statistics report (GLOBOCAN 2020, produced by the International Agency for Research on Cancer (IARC)) ranked breast cancer as the most prevalent cancer worldwide (as captured in Table 2.1 for the top 10 cancers) with higher incidence and mortality rates among women in Africa (Ferlay *et al.*, 2020). Approximately 17% of all new cancer cases recorded in Africa (for both sexes and all ages) in 2020 were breast cancer. In the West African

region, 49,339 new breast cancer cases were recorded, representing 33.5 percent of all new female cancer cases for all ages (Ferlay *et al.*, 2020).

Table 2.1: New number of cancer cases and deaths per site recorded for the top 10 cancers according to the GLOBOCAN 2020 report (Ferlay *et al.*, 2020)

Cancer Site	Number of new cases (% of all sites)		Number of new deaths (% of all sites)	
Female breast	2,261,419	(11.7)	684,996	(6.9)
Lung	2,206,771	(11.4)	1,796,144	(18.0)
Prostate	1,414,259	(7.3)	375,304	(3.8)
Non-melanoma of skin	1,198,073	(6.2)	63,731	(0.6)
Colon	1,148,515	(6.0)	576,858	(5.8)
Stomach	1,089,103	(5.6)	768,793	(7.7)
Liver	905,677	(4.7)	830,180	(8.3)
Rectum	732,210	(3.8)	339,022	(3.4)
Cervix uteri	604,127	(3.1)	341,831	(3.4)
Esophagus	604,100	(3.1)	544,076	(5.5)
All sites	**19,292,789**		**9,958,133**	

There were an estimated 19.3 million new cancer cases reported, and 10 million cancer deaths recorded worldwide in 2020. The report also estimated 4,600 new cases (out of a total estimated 19,900 new cases of all cancers for both sexes) to occur among Ghanaian women less than 60 years for a projected population of 38 million in 2030 (Ferlay *et al.*, 2020; Gaisie *et al.*, 2014).

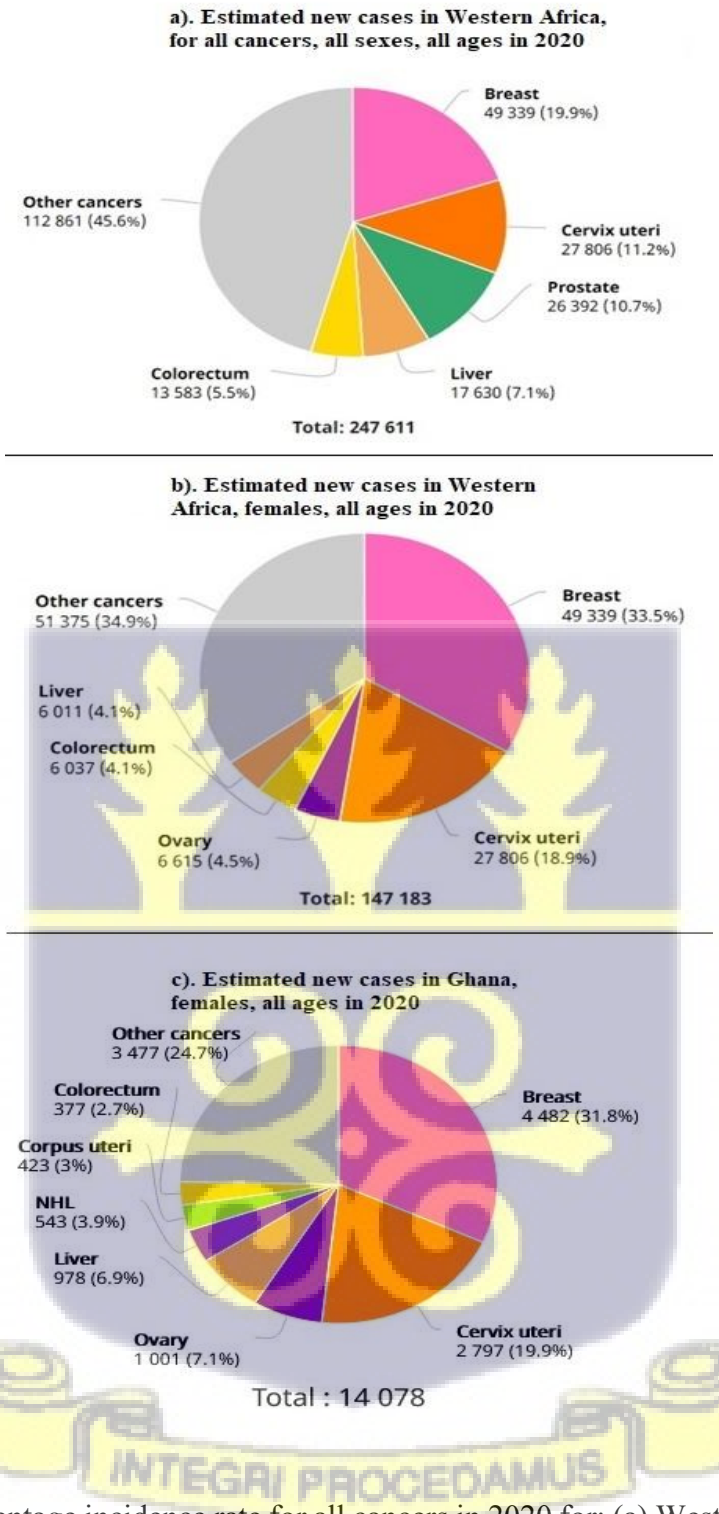


Figure 2 1: The percentage incidence rate for all cancers in 2020 for: (a) Western Africa, all sexes, all ages, (b) Western Africa, females, all ages and (c) Ghana, females, all ages (Ferlay *et al*., 2020)

Figure 2.1 above shows the percentage distributions of incidence rate for the most common cancers and the most common female cancers in the Western Africa region (regardless of patient gender and age) for the year 2020. It also shows the percentage distributions of common cancer incidence among Ghanaian women. The population of these countries were classified as Western African: Benin, Burkina Faso, Cape Verde, Côte d'Ivoire, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, The Republic of the Gambia, and Togo (Ferlay *et al.*, 2020). The rate of breast cancer deaths in the Western Africa region (27.1%) is higher than the global mortality rate (15.5%) because of the cancer type and higher case fatality rates (Sung *et al.*, 2021; Ferlay *et al.*, 2020).

The estimated mean age of women diagnosed with breast cancer in Africa is below 50 years (Brinton *et al.*, 2014). Late-stage presentation in most African countries is a leading factor for decreased survival. Strategic policies for early breast cancer diagnosis should be regarded as a major priority by governments in their cancer control programs in sub-Saharan Africa (Jedy-Agba *et al.*, 2016). Regular breast screening is also very important in catching the disease earlier for a better treatment outcome. Discovering breast cancer earlier (detection and diagnosis) and getting state-of-the-art care (treatment) are the two most critical strategies for preventing deaths resulting from the disease. Monthly breast self-examinations and periodic breast examinations by health professionals are the first steps in detecting any symptoms (like a lump in the breast). The use of mammography and breast ultrasound are the two major clinical breast diagnostic imaging examinations recommended during screening (Oeffinger *et al.*, 2015). Additional imaging tests may be requested after one has been diagnosed with breast cancer. This may include the use of chest X-ray, CT scan, Magnetic Resonance Imaging (MRI) scan, Positron Emission Tomography (PET) scan and bone scan. These imaging tests may be carried out to examine the inside of patients

to identify if the cancer has spread to the surrounding organs such as the lungs, liver, brain, spinal cord and bones (NCCN, 2023; Bonnie *et al.*, 2023).

Breast cancer survival rates estimate the percentage of patients with the same type and stage of the disease that are still alive after a period (usually after 5 years of diagnosis). Survival rates may help health professionals and patients alike to understand the success of the intended breast cancer treatment (American Cancer Society, 2023). They are based on previous outcomes of large numbers of breast cancer patients with specific types and may not predict individual treatment outcome. A relative survival rate compares breast cancer patients with the same type and stage of breast cancer to non-cancer women in the overall population. A 90 percent 5-year relative survival rate for a specific breast cancer means patients with that breast cancer are on average, about 90% as likely as healthy women who do not have breast cancer to live for at least 5 years after being diagnosed. The American National Cancer Institute (NCI) hosts a huge database on cancer Surveillance, Epidemiology, and End Results (SEER) in providing survival rate statistics for different types of cancer (Young *et al.*, 2001).

For breast cancer 5-year relative survival rates, SEER represents them based on how far the cancer has spread (localised stage, regional stage, and distant stage) as defined below (Young *et al.*, 2001).

- **Localised:** There is no clinical evidence of cancer spread outside of the breast tissue. The 5-year relative survival rate is 99 %.
- **Regional:** There is clinical evidence of cancer spread outside the breast to nearby tissues or lymph nodes. The 5-year relative survival rate is 86 %.
- **Distant:** There is clinical evidence of cancer spreading to distant organs such as the lungs, liver, brain or bones. The 5-year relative survival rate is 30 %.

To be able to describe how much cancer is in the breast and the body, staging is conducted to determine how serious the cancer is and the best way to manage it. Breast cancer staging helps the radiation oncologists to ascertain if it has spread and how far it has. This process may also help with the patient's survival rate analysis before any treatment is chosen or prescribed. Stage 0 (carcinoma *in situ*) is the earliest stage (no spread) of breast cancer and then ranges from stage I (less cancer has spread) through to stage IV (cancer has spread more) (NCCN, 2023). The staging system most often used in breast cancer is the TNM system of staging cancers established by the American Joint Committee on Cancer (AJCC) (American Joint Committee on Cancer, 2017). In the TNM system of staging, the alphabet T represents the extent (size) of the breast tumour, N represents the spread to nearby lymph nodes and M, the spread (metastasis) to distant sites/organs in the body.

To determine if the breast cancer has spread and its extent of spread to the axillary (underarm) lymph nodes, one or more nodes are surgically removed for laboratory analysis (Jagsi *et al.*, 2020). The lymph nodes under the arm are the axillary lymph nodes, the ones inside the chest (breastbone) are the internal mammary lymph nodes and the ones around the collar bone are the supraclavicular (above collar bone) and infraclavicular (below collar bone) lymph nodes as illustrated in Figure 2.2. Breast cancer may spread through the blood or lymphatic system and then proceed to other parts of the body. Breast cancer that are located in these lymph nodes may have a higher chance of spreading through the lymphatic system and spread (metastasise) to other parts of the body (Henry *et al.*, 2020).

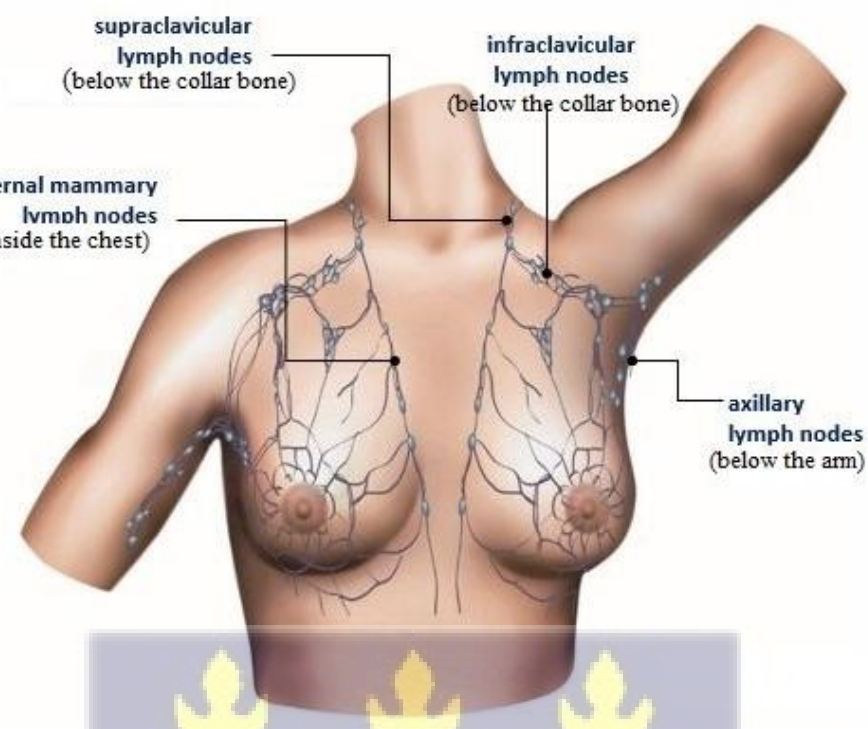


Figure 2.2: The three types of lymph nodes where breast cancer can spread to are located under the arm, inside the chest, above and below the collar bone (BCNA, 2023).

Most breast cancer patients will have some form of surgery as part of their treatment. The two main types of breast cancer surgery are breast conserving surgery (BCS) and mastectomy. BSC is done to remove cancer in the breast as well as the portions of the surrounding tissues which are sometimes referred to as lumpectomy. When the entire breast is surgically removed including all the breast tissue and sometimes other normal tissues, this is known as mastectomy. Patients with early-stage breast cancer may benefit from BCS or lumpectomy (partial mastectomy) depending on many other factors. Late-stage patients on the other hand may undergo radical (modified) mastectomy for a better relative survival rate, slow the cancer spread and for pain management (Henry *et al.*, 2020) as shown in Figure 2.3. Breast cancer is classified as low risk (of recurrence) when the tumour size is smaller than 1 cm in diameter and has not spread to the lymph nodes. A

high risk (of recurrence) breast cancer is when the tumour size is bigger than 5 cm in diameter and has spread to more than 4 lymph nodes (American Cancer Society, 2023).

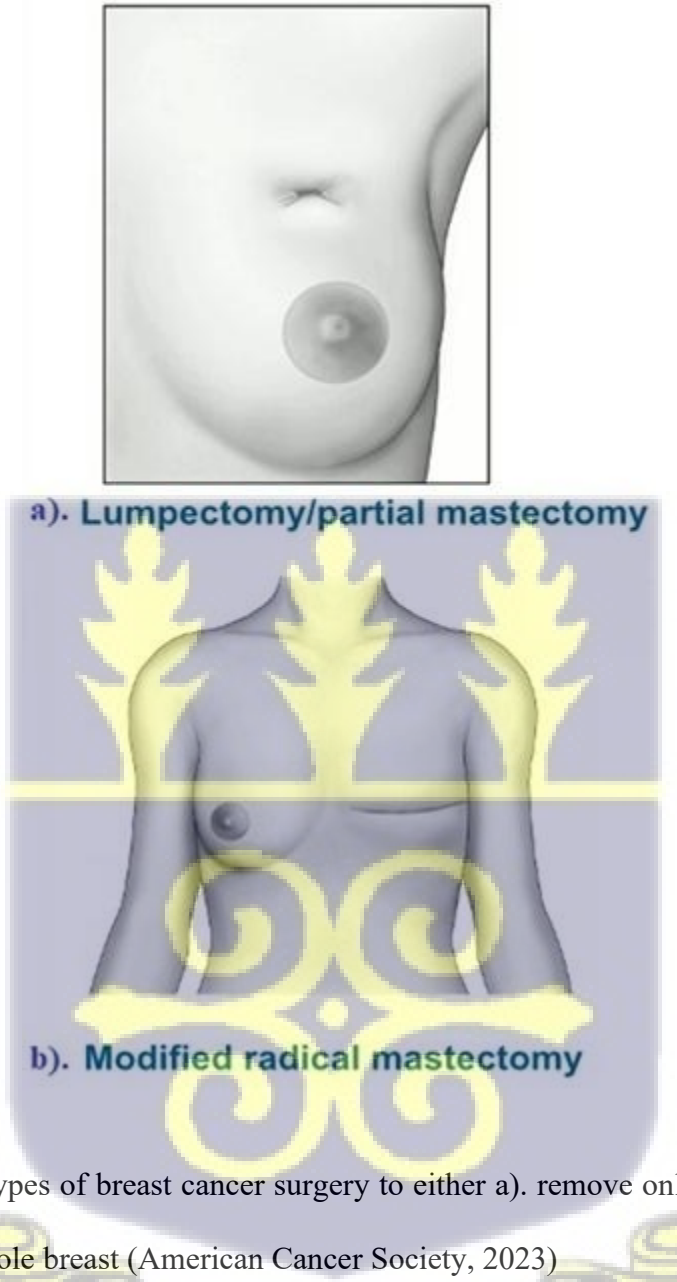


Figure 2.3: The two types of breast cancer surgery to either a). remove only the tumour or to b). totally remove the whole breast (American Cancer Society, 2023)

2.2 BREAST CANCER SURVEY

Surveys have been widely used to understand various aspects of breast cancer among women worldwide. Breast cancer surveys have focused on breast screening and awareness, risk factors

and prevention, quality of life and patient experiences, treatment outcomes, access and disparities, survivorship and follow-ups. These surveys have explored factors influencing treatment choices, patient satisfaction, assessed the impact of treatment on quality of life, examined patient-reported outcomes and investigated treatment disparities. Many of these surveys have employed various methods and mixed approaches to come out with findings that have informed breast cancer control programmes, national policies, international guidelines and future research directions (Van der Laan *et al.*, 2010). Surveys may use cross-sectional and longitudinal methods to collect patient data. The cross-sectional method collects patient data from many different respondents at a single point in time (administered at one time) while the longitudinal method collects data over multiple times, allowing for changes over time from the same respondents. The longitudinal method of data collection usually focuses on smaller groups of respondents within a particular area of expertise (Johnson *et al.*, 2010). Another method known as the mixed-longitudinal approach combines survey data (quantitative) with qualitative interviews or may focus on larger groups to provide a more comprehensive understanding of the collected data (Johnson *et al.*, 2010).

However, questionnaires are widely used in breast cancer surveys in radiotherapy to collect patient-reported outcomes, assess quality of life, and evaluate treatment techniques. These questionnaires may help researchers to evaluate treatment effectiveness, monitor outcomes, identify areas for improvement, develop personalised treatment plans and enhance overall breast cancer care. The European Organisation for Research and Treatment of Cancer (EORTC) (Van der Laan *et al.*, 2010) employed questionnaires in assessing the quality of life in breast cancer patients (Michels *et al.*, 2013). The Radiation Therapy Oncology Group (RTOG) (Scott *et al.*, 1994) and International Breast Cancer Study Group (IBCSG) (Bernhard *et al.*, 1998) used quality of life questionnaires to assess quality of life in cancer patients undergoing radiation therapy. The

Breast Cancer Symptom Scale (BCSS) used patient-focused questionnaires to measure the symptom burden in breast cancer patients (Horigan *et al.*, 2009). The Breast Cancer Treatment Outcome Scale (BCTOS) designed questionnaires to measure treatment outcomes, including symptoms and side effects (Feißt *et al.*, 2019). Questionnaires were employed by the Functional Assessment of Cancer Therapy-Breast (FACT-B) (Matthies *et al.*, 2019) and the Patient-Reported Outcomes Measurement Information System (PROMIS) (Sikorskii *et al.*, 2018) to evaluate physical, emotional and social well-being in breast cancer patients.

Breast cancer surveys may be local, National, Regional or International involving single or multiple facilities, researchers and working groups spanning from months to decades of data collection and analysis. The National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) (National Cancer Institute, 2023) Program for example collects National data on breast cancer incidence, treatment, and survival rates among the USA population. The European Breast Cancer Survey, conducted by the European Cancer Observatory (European Cancer Observatory, 2013) collects data among European women to understand breast cancer in Europe (Sterliarova-Foucher *et al.*, 2015). The American Cancer Society (ACS) (American Cancer Society, 2023) has a breast cancer working group focused on breast cancer research, education and patient support system. The World Health Organization (WHO) (World Health Organization, 2023) has a working group, Breast Cancer Control Program which helps develop guidelines and strategies for breast cancer control globally. The Breast Cancer and Radiation Therapy (BCRT) working group focuses on radiation therapy research and best practices.

2.3 BREAST CANCER TREATMENT

The type of breast cancer treatment depends on the stage and may consist of chemotherapy, surgery and radiation therapy (also known as radiotherapy) or any combination to effectively manage or treat the disease. Radiation therapy (RT) is needed to reduce the risk of local disease recurrence, cancer-related death and prevent metastasis after surgery (Osei *et al.*, 2020). External beam radiation therapy, the most used radiation therapy type, is required as part of the breast treatment to increase therapeutic outcome (EBCTCG, 2005). The overall quality of treatment may differ across multiple locations depending on resources available (surgery, chemotherapy, hormonal therapy and radiation therapy). Sub-Saharan Africa accounts for a rather higher mortality rate (51.9%) from breast cancer incidence among women (Ferlay *et al.*, 2020). This may be due to the inaccessibility or absence of high-quality breast cancer treatment and very late cancer presentation to the cancer facilities. The introduction of CT scanners into EBRT planning process began the era of various treatment planning simulation techniques. While parallel opposed tangential treatment planning remains the gold standard, modern radiation oncology has embraced innovative approaches like arc therapy and tomotherapy (Teoh *et al.*, 2011). Concurrently, image guidance and respiratory motion management have emerged as crucial complements to advanced treatment techniques. Techniques such as respiratory gating and deep inspiration breath hold (DIBH) have demonstrated efficacy in minimising cardiac exposure during left-sided breast cancer irradiation, ultimately reducing long-term cardiac complications and mortality rates for patients (Dodul *et al.*, 2016).

Comparatively, breast cancer curative treatment employs relatively lower doses for tumour control (Henry *et al.*, 2020). Conventionally, dose fractionations used in breast tumour control are 2 Gy daily fraction over 5 weeks, or 2.66 Gy daily fraction over a 3-week course. Sometime these

treatments are sequentially boosted by a total local dose of 10 Gy within 5 days to the surgical bed in certain groups of patients. To effectively manage the disease after surgery, the radiation therapy may be combined with chemotherapy to improve survival rate (Henry *et al.*, 2020). Critical concerns in radiation therapy include contour irregularities, variations in dose planning, and risks of long-term toxicity and secondary carcinogenesis due to excessive organ exposure (Darby *et al.*, 2013). Advanced treatment planning and delivery techniques, such as VMAT enables dynamic intensity-modulated radiotherapy through multileaf collimator leaf sequencing and simultaneous gantry rotations, ensuring optimal tumour coverage and minimised doses to critical organs (Teoh *et al.*, 2011). Simultaneous integrated boost (SIB) provides dose differential irradiation with VMAT technology, which is faster, efficient, and better conformed. A survey on EBRT breast cancer treatment conducted in Ghana as part of this study identified certain inter-facility and intra-facility variations in breast treatment planning protocols (Acquah *et al.*, 2022). The study recommended and emphasized the importance of individual cancer facilities to establish and use their own standardised facility-based breast treatment planning protocols.

One of the main challenges confronting the delivery of the same high quality breast cancer care to all patients is the lack of consistency in radiation treatment planning among different facilities and even individuals within the same facility. International organisations, professional bodies and researchers have made huge investments and committed resources into conducting and publishing task group reports, recommendations and guidelines (EBCTCG, 2005; Thompson *et al.*, 2018; Van der Laan *et al.*, 2010; Cuzick *et al.*, 1994) for best practices on almost every aspect of radiation therapy in ensuring consistency in workflow. Clinical research and trials are usually conducted by some of these working groups (Parulekar *et al.*, 2019; Mamounas *et al.*, 2014; Chen *et al.*, 2011) collectively to provide well-defined breast cancer treatment criteria through consensus, whereby

establishing regional or national standardised guidelines. These have helped improve clinical practice by establishing breast quality assurance (QA) procedures.

2.3.1 Radiation Therapy

Radiation therapy is a type of cancer treatment where cancerous cells in the body are destroyed by exposing them to high ionising radiation, such as x-rays, gamma rays, high-energy electrons or heavy particles. It involves using carefully selected doses of ionising radiation to damage the DNA of cancer cells (Vlasov *et al.*, 2023). When the ionising radiation passes through the body, it causes changes and transfers its energy to the body. This transferred energy can either directly kill the cancer cells or indirectly change them genetically, which can lead to cellular death primarily by apoptosis (Baskar *et al.*, 2012). Ionising radiation can cause tumours to shrink and, in some cases, even to die completely. Radiation therapy has been used since the early 1890s to treat or control almost all types of cancers (Vlasov *et al.*, 2023). Radiation therapy is most effective when the cancer is localised, easily accessible, and located away from healthy critical organs in the body. It is mainly used for curative intent (to treat the cancer) or for palliative intent (to relief pains caused by the cancer). Radiation therapy can be used before surgery to shrink the size of the cancer, or after surgery to destroy the remaining cancer cells and reduce the probability of cancer recurrence (Baskar *et al.*, 2012).

There are two types of radiation therapy utilisation, external (known as teletherapy), and internal (known as brachytherapy). In external radiation, it is generated and delivered from a distant source, from outside the body and directed at the patient's cancer site. For brachytherapy, the radiation is delivered from inside the body (temporarily or permanently) to the cancer by small encapsulated radioactive sources (Baskar *et al.*, 2012). The most common type of radiation therapy is the teletherapy (external beam therapy), whereby radiation is emitted from a machine located at a

distance from the body, such as a cobalt-60 unit (Co-60) or a medical linear accelerator. Radiation therapy is recommended as the best treatment of cancer due to its superior outcome compared to other modalities. This superiority is because of better survival rates, local disease control and very low organ toxicity rates (Barton *et al.*, 2014). Approximately more than half of all cancer patients receive radiation therapy at a certain point in their treatment course due to its important role in cancer management (Baskar *et al.*, 2012; Barton *et al.*, 2014; Barton *et al.*, 2006).

Before external beam radiation therapy commences, the breast target (tumour) volumes and organs at risk are defined by the radiation oncologist according to the principles of target definition in radiotherapy (ICRU 50, 1993). The most obvious target volumes are the Clinical Target Volume (CTV) and the Planning Tumour Volume (PTV). In postoperative breast cancer radiation therapy, the Gross Tumour Volume (GTV) would have been already removed by the surgeon during breast conserving or total breast removal surgery. GTV is hence no longer required and therefore not defined by the radiation oncologist. GTV is defined as the volume that can be seen by the eye or by palpation either on the patients or with the help of imaging. CTV is defined as the volume when margins for possible microscopic disease extensions are added to the gross tumour volume. PTV also is defined as the volume that accounts for all the internal tumour movement, geometric daily set-up uncertainties and mechanical accuracy of the treatment machine (ICRU 50, 1993; ICRU 83, 2010). Finally, the Organs at Risk (OARs) are the defined or delineated healthy organs by the radiation oncologist. For breast cancer external beam radiation therapy, the main OARs defined are the ipsilateral lung volume, contralateral lung volume, contralateral breast volume and the heart volume. Other organs that may be defined in addition to the main OARs are the spinal cord volume and oesophagus volume (NCCN, 2023).

2.3.2 External Beam Radiation Therapy

External beam radiation therapy (EBRT) is the most common type of radiation therapy for breast cancer treatment (Karunakaran *et al.*, 2016). EBRT is a localised treatment that is precisely delivered from a treatment machine aimed at the cancer as shown in Figure 2.4. It is a highly effective and well-established treatment modality for the treatment of many types of cancer including breast cancer.

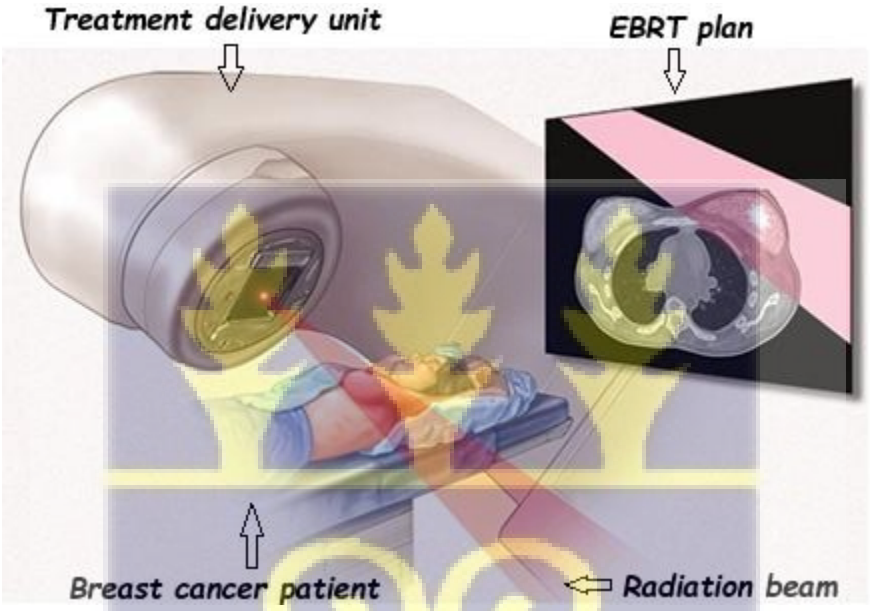


Figure 2.4: External beam radiation therapy (EBRT) for breast cancer treatment.

During the irradiation, the patient lies on a treatment couch while the delivery machine moves around the body, directing precise doses of radiation at the cancer from several desired angles while sparing the normal tissues (Vlasov *et al.*, 2023). Radiation beams used in external radiation therapy may come from photons, electrons and protons. Most external beam radiation therapy machines use photon beams that can reach deep seated tumours in the body. Photon beams cannot be totally stopped but their intensities reduce after they have reached their target thereby depositing small doses into the normal organs in the body.

External photon beam radiation therapy is executed with more than one radiation beam to achieve an optimal dose distribution inside the target and lower dose to surrounding organs. The International Commission on Radiation Units and Measurements (ICRU) report 50 recommends a target dose distribution within +7% and –5% of the photon dose delivered to a well-defined prescription point within the target (ICRU 50, 1993). Electron beams on the other hand cannot travel very far through the body; therefore, its application is limited to cancers of the skin or near the surface of the body (superficial). Like photon beams, proton beams can also reach tumors deep in the body, however, they stop once they have reached their targets (NCI, 2023). Results from randomised trials and individual patient data analysis support the use of EBRT in treating both early and locally advanced breast cancer patients as it increases the overall survival rate (EBCTCG, 2005). BCS followed by EBRT has also been shown to reduce disease recurrence by half and mortality rate by one-sixth as stated in the meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) on over 10,000 breast cancer patients in 17 randomised trials (Ragaz *et al.*, 2005; EBCTCG, 2005). There have been many other randomised clinical trials over the years that have led to the concept of breast cancer hypofractioned treatment schedules. These high doses per fraction over shorter periods have the same biological equivalent doses to the conventional fractionation schedules (Whelan *et al.*, 2010). More recently, accelerated partial breast cancer irradiation has been employed to further reduce the overall treatment time and schedules in selected breast cancer patients (Formenti *et al.*, 2005).

The use of external beam radiation therapy for breast cancer treatment started with the use of superficial kilovoltage (kV) radiation to the high megavoltage (MV) photons. The change to high energy particles started from the invention of cobalt treatment machines followed by high energy linear accelerators in the 1950s (Karunakaran *et al.*, 2016). After that, breast planning and

treatment have gone through changes in technical aspects beginning from clinical breast markup planning, lookup table manual dose calculations, two-dimensional planning techniques (2-D) to the more advanced computer-based 3-D planning currently being utilised. The inclusion of CT scanners in breast cancer radiation therapy, also brought a lot more significant changes to treatment plan simulation, patient immobilisation, and tumour localisation (Teoh *et al.*, 2011). Incorporating modern treatment equipment, treatment planning techniques and imaging have brought into breast cancer radiation therapy practice newer radiation therapy planning and delivery technologies.

2.3.3 Modern Breast Treatment Planning Techniques and Technology

From the era of skin marking-based treatment planning to the computer software-based treatment planning, very notable techniques have been established in breast radiation therapy. The advent of CT-based radiation therapy breast simulation advanced the modernity of its treatment. CT's heterogeneity correction brought a significant change in patient-based planning compared with earlier 2-D standard planning techniques. Breast cancer radiation therapy has evolved from the conventional 2-D technique to the modern 3-D CRT and more precise yet resource intensive techniques and technology like the proton beam therapy, IMRT, VMAT, tomotherapy/helical and its hybrid variances intended to improve survival rates with reduced complications. Static opposing tangential beam arrangements were regarded as the standard approach in planning and treating intact breast and chest-wall but resulted in high dose heterogeneity mostly outside the PTV (Ercan *et al.*, 2010; Barnett *et al.*, 2009). Recent techniques and technology aimed at optimising dose homogeneity have demonstrated superior target coverage and normal tissue sparing (Barnett *et al.*, 2009; Lauche *et al.*, 2016). These modern treatment planning optimisation techniques and technology enable possible reduction in radiation-related adverse effects, with improved overall local disease control and increased overall survival rate (Donovan *et al.*, 2007; Keller *et al.*, 2012).

The position of the PTV with reference to the OARs and breast separation (BS) informs the best planning technique to be used in achieving a quality breast plan (Figure 2.5).

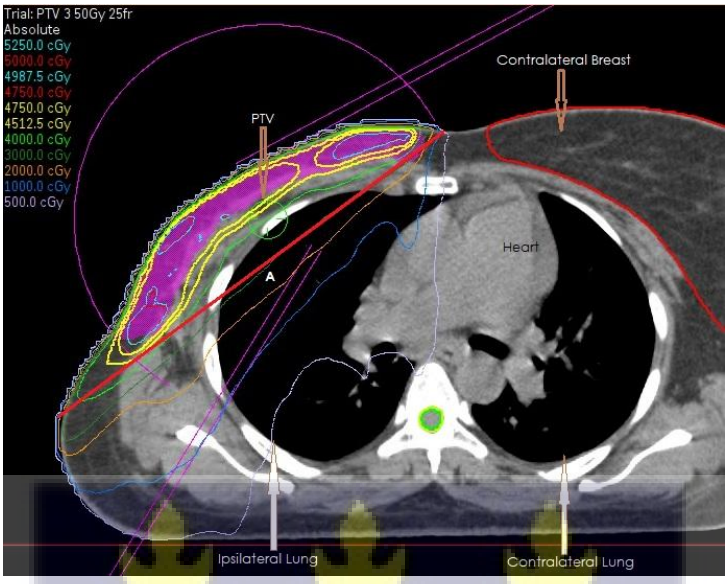


Figure 2.5: Anatomic structures and parameters used in breast treatment planning; Chest-wall planning target volume (PTV) and various delineated organs at risk (OARs), A is the breast separation (BS) measurement parameter.

2.3.3.1 Three-Dimensional Conformal Radiotherapy (3-D CRT) Breast Technique

Three-dimensional conformal radiation therapy breast planning involves using a CT scan and TPS to design breast plans for radiation therapy treatment. The aim of 3-D CRT breast planning is to generate and deliver a 3-D conformal dose of prescribed radiation to the intact breast or chest-wall volumes while sparing the surrounding OARs as much as possible. Accurate doses of radiation can be significantly delivered directly to the breast cancer when detailed patient information is used in the planning process. 3-D CRT techniques mainly use lateral and medial tangential beams arrangements to limit areas of high doses in the underlying ipsilateral lung and heart volumes for left-sided breast cases. However, this results in poor dose conformity, dose homogeneity, and hot

spots outside the target volume (Hall *et al.*, 2003). The 3-D CRT breast technique is the most adopted technique for intact breast and chest-wall external beam radiation therapy planning and treatment. It can be designed either with or without wedges or employ the use of an open beam forward planning field-in-field method. 3-D conformal radiation therapy is a common type of external beam radiation therapy. It may use images from MRI and PET together with CT scans to precisely plan the breast treatment area, a process called planning simulation.

2.3.3.1.1 Tangential Wedge Breast Technique

Intact breast and chest-wall target volumes usually have irregular shapes and it is generally difficult to achieve homogeneous isodose distribution throughout the target. To achieve dose homogeneity, wedges are usually used to decrease the dose in the dorsal part of the breast or chest-wall while increasing the dose in the ventral part. This occasionally makes it possible to overcome, to an extent, dose inhomogeneity across the intact breast and chest-wall targets. The use of the tangential wedge field techniques (physical wedges, motorized wedges and dynamic wedges) is still widely employed in many radiation therapy facilities worldwide. Although the tangential wedge technique gives good local control, generally, it does not provide good results in terms of dose homogeneity and becomes a significant issue when hypofractionated schemes are adopted (Zeverin *et al.*, 2018). When planning with tangential fields, dose distribution obtained from the open beams is complicated because of the complex breast volume. Therefore, wedge filters are carefully introduced and collimated unto the open beams to improve the dose distribution. Conventional hard wedge systems alleviate dose inhomogeneities caused by severe breast surface irregularities and tissue heterogeneities in radiation therapy. Typically, two tangential wedged fields utilising 6 MV photon beams are employed for breast cancer treatment.

2.3.3.1.2 Field-in-Field Breast Technique

The introduction of segmented field techniques has significantly enhanced isodose distribution in radiation therapy. Leveraging multileaf collimators and advanced computerised treatment planning systems, the field-in-field (FIF) technique has emerged as a preferred method for tangential whole-breast radiotherapy. Numerous studies have validated the efficacy of FIF in achieving optimal dose distribution, making it a widely accepted approach in radiation oncology (Acquah *et al.*, 2017; Tanaka *et al.*, 2015; Borghero *et al.*, 2007). Compared to physical wedges, FIF minimise the impact of breathing movements on radiation delivery (Tanaka *et al.*, 2014). The field-in-field technique utilises 3-D forward planning, combining two tangential open fields and multiple subfields for optimal dose distribution and homogeneity. This process involves the initial isodose optimisation on open fields to identify overdose areas. Then, the creation of 3-4 subfields per gantry angle as a lung-block field and MLC-shaped fields to match lung contours to reduce lateral hot spots. Additional subfields with MLCs are manually fitted to hot areas (105-115% isodose lines) using a beam weighting as follow; open beams (80%) and subfields (20%). This wedge-free approach ensures precise dose delivery and minimised hot spots.

2.3.3.2 Intensity-Modulated Radiotherapy (IMRT) Breast Technique

Intensity-modulated radiation therapy is the primary treatment option for most patients receiving radiation therapy exclusively to the breast. As an advanced form of 3-D CRT, IMRT precisely tailors the radiation beam by modulating beam intensity in the breast volume. This cutting-edge technique enables optimal treatment precision, ensuring accurate dose delivery and minimising exposure to surrounding tissue. IMRT uses many small beams to precisely target the breast tumour where the fluence of these beams can be adjusted to deliver higher doses to specific areas, ensuring effective treatment while minimising damage to surrounding tissues. It improves dose uniformity

with less immediate and long-term side effects than 3-D CRT irradiations. IMRT's higher monitor units and longer delivery times (3-4 times vs. VMAT) may increase leakage and scatter radiation, potentially impacting tumour cell repair and repopulation (Wang *et al.*, 2003).

2.3.3.3 Volumetric Modulated Arc Therapy (VMAT) Breast Technique

VMAT is a type of radiation therapy in which a three-dimensional dose is delivered with a single rotation of a delivery machine such as linear accelerator. VMAT emerged in 2007, revolutionising radiation oncology with its innovative approach that enables simultaneous adjustment of three key parameters during treatment delivery. These parameters are the gantry rotation speed, treatment shape through MLC leaf movement and variable dose rate. There are currently two main forms of arc-based therapies delivery: volumetric VMAT and tomotherapy. Compared to other techniques, in which the treatment unit must rotate around the patient several times delivering static beams, stopping periodically throughout the process. VMAT is faster and more efficient, improving dose conformity within the breast target but at the risk of increased low doses to the contralateral lung (CL) and contralateral breast (CB) volumes (Hall *et al.*, 2003). An additional advantage of VMAT is its ability for differential dose distributions allowing simultaneous integrated boost delivery (Teoh *et al.*, 2011). Two partial arcs are normally used for intact breast and chest-wall VMAT irradiation.

2.3.3.4 Tomotherapy and Helical Tomotherapy Breast Technique

Tomotherapy (slice therapy) is the second form of arc-based radiation therapy where delivery machines are considered as hybrid CT-Linac technology. This radiation therapy technique employs a fan-beam CT distribution with the x-ray source rotating continuously while the patient translates through the machine, delivering precise and targeted radiation. Tomotherapy techniques

can be further divided into helical tomotherapy (HT); where the radiation is delivered in a continuous spiral and axial tomotherapy; where the radiation is delivered slice by slice (Mackie *et al.*, 1993; Welsh *et al.*, 2002; Mackie *et al.*, 2006; Beavis *et al.*, 2004). Helical tomotherapy is considered as a rotational-IMRT for precise tumour targeting, dose escalation, and normal tissue sparing.

HT in breast cancer treatment offers improved radiation uniformity, precision, and reduced high-dose organ exposure. Yet, it increases low-dose organ exposure, posing a rare secondary cancer risk. Helical tomotherapy is ideal for complex breast cancer cases with irregular shapes, challenging locations, or obesity. Personalised patient selection maximises HT's benefits for breast cancer irradiations. Post-mastectomy radiotherapy benefits from helical tomotherapy due to its enhanced skin coverage by the tangential beams which deliver significant doses to the skin. However, HT also increases low-dose exposure to a larger volume of healthy tissue, potentially elevating the risk of secondary cancers. This is particularly concerning for younger patients, who are more susceptible to long-term radiation effects (Beavis *et al.*, 2004).

2.3.3.5 Hybrid Breast Planning Technique

In the hybrid breast planning, a mixture of 3-D CRT and IMRT or VMAT techniques was used to spare OARs without compromising the target dose coverage. Most of the hybrid plan studies have used static 3-D CRT fields as the base plan in combination with other advance planning techniques (Balaji *et al.*, 2020; Balaji *et al.*, 2018; Mayo *et al.*, 2005). Other hybrid techniques involve the combination of IMRT and VMAT techniques that simultaneously optimise the desired intensity modulation with VMAT angular sampling (Blom *et al.*, 2015; Raturi *et al.*, 2021). Hybrid breast planning combines techniques that would further improve the treatment of breast as well as chest-wall and reduce the disadvantages of existing planning techniques. Detailed research is required

among different hybrid techniques to explore their benefits as they may produce higher monitor units, scatter radiation and hot areas outside the target (Karaca *et al.*, 2022).

2.3.3.6 Proton Beam Breast Treatment Technology

Proton beam therapy (PBT) has emerged as a cutting-edge treatment option for breast cancer patients. Leveraging its distinct physical properties, it minimises unnecessary radiation exposure to healthy tissues and enhances target coverage, particularly for internal mammary nodes (IMNs) located near critical organs (heart and lungs). PBT offers a cutting-edge solution for enhancing long-term breast cancer treatment results, however, its implementation is offset by two significant factors. These are the high cost stemming from the intricate and large-scale machinery required for proton acceleration; and the distinct technical hurdles that demand specialised expertise and infrastructure. Whole breast PBT with or without regional nodal irradiation (RNI) lacks extensive clinical outcome data. However, dosimetric studies suggest PBT's potential advantage in reducing heart exposure, minimising doses to the heart and lowering lung radiation (Lin *et al.*, 2015; Fogliata *et al.*, 2002).

Whole breast with regional nodal irradiation using proton beam therapy has been documented in a limited number of cases (Cuaron *et al.*, 2015). Nevertheless, due to the small sample size and brief follow-up period, toxicity assessments remain inconclusive, long-term cosmetic outcomes are uncertain and optimal delivery techniques have yet to be determined.

2.3.4 Treatment Planning Systems

Treatment planning systems (TPS) are at the heart of radiation therapy practice and vital to achieving improvement in patient outcomes. TPS are used in external beam radiation therapy to generate radiation treatment beam shapes and dose distributions with the intent to maximise disease control and minimise normal tissue complications (Evans *et al.*, 2005). Earlier treatment

planning systems relied on 2-D orthogonal simulation techniques for tumour localisation and for treatment beam arrangement where 2-D images were used to represent 3-D patient information for tumor localisation. Modern radiotherapy planning systems use 3-D tissue-specific information from a CT scan to accurately calculate dose. Modern TPS are an integral part of the successful treatment of cancer with radiation. They provide a set of computerised tools that allow the radiation oncologist, medical physicist, and treatment planner to create and visualise radiotherapy, given the imaging data available. Successive improvements in treatment planning software and hardware have been most notable in the graphics, calculation speed and dose optimisation aspects of current systems (Evans *et al.*, 2005). Once image datasets are loaded and the tumours are identified, the system's software develops a suitable plan using various beams to determine how the treatment unit will deliver radiation to the patient. The software computes the expected radiation dose distribution in the patient's tissue regardless of the tissue heterogeneity involved (e.g., bone or lung vs. muscle). TPS also help with the placement of beams from directions to avoid critical structures that are more sensitive to radiation. This process may also include collimation, complex movement of MLC sequencing to shape the beam around these critical structures during dose delivery (Taschetta-Millane *et al.*, 2023).

As imaging technology and dose calculation algorithms have advanced, so have treatment planning system capabilities. Currently, 3-D TPS can superimpose radiotherapy treatment beams on 3-D image sets with any geometry or orientation using the beam's eye view feature to visualize the radiation beam in conjunction with the relevant patient anatomy. Furthermore, secondary images from multiple imaging modalities can be rigidly registered to the primary treatment planning CT (image fusion), where additional anatomical and functional information can be examined with respect to the treatment plan (Hegi *et al.*, 2018; Taschetta-Millane *et al.*, 2023). Current TPS are

also able to integrate 4-D image data into the treatment planning process to analyse the extent of tumour motion. This 4-D treatment planning system functionality is especially beneficial for lung and breast cancer patients undergoing radiation therapy. The combination of these advanced treatment planning system tools allows for accurate and efficient treatment planning for lung tumors and other cancers (Hegi *et al.*, 2018). Modern systems also include advanced tools for treatment plan optimisation and dose analysis. Treatment planners can easily adjust beam angles and weighting factors for conventional forward planning, whereas optimisation parameters and associated weightings can easily be adjusted for inverse planning. In addition, doses analysis tools, such as the dose volume histogram (DVH), provide a more thorough investigation of the dose delivered to the radiotherapy target and the surrounding organs at risk. Advanced TPS are now able to represent patient anatomy, tumour targets and dose distributions in three dimensional models (transverse, sagittal and coronal) (Evans *et al.*, 2005).

2.3.4.1 TPS Software and Calculation Algorithms

The main objective of external beam radiation therapy is to deliver the maximum prescribed dose to the tumour and minimise dose to the surrounding healthy tissues and OARs. In practice, there is always a trade-off between delivering the desired maximum prescribed dose to the tumour and maintaining lower dose to OARs surrounding the tumour. Before the radiation treatment is delivered to the patient, a comprehensive treatment planning process is performed. This process includes dose prescription and fractionation, patient positioning and immobilisation, patient imaging, tumour and OAR delineation, dose calculation, and treatment plan verification and plan QA. The treatment planning process is performed with a software package and its hardware components using different dose calculation algorithms. Patient image datasets containing various image related parameters such as patient identification, patient information and technical

information about the CT equipment used as well as the type of examination are kept on the TPS. This information is stored as standard DICOM format for accurate interpretation by the TPS to ensure connectivity and interoperability between various systems. The extension of the DICOM format used in radiotherapy is known as the DICOM-RT (Evans *et al.*, 2005; Law *et al.*, 2009). DICOM-RT formats commonly used in radiotherapy TPS are:

- **RT Plan:** This DICOM type contains information related to the treatment plan such as beam's gantry angles, collimator angles and field configuration, dose prescription and fractionation used, and patient setup.
- **RT Dose:** This DICOM type contains dose data generated by TPS such as 3-D dose distribution data, isodose curves and dose volume histograms.
- **RT Structure Set:** This DICOM type contains information related to the patient's anatomy such as the external contour, tumour volumes and OAR volumes.
- **RT Images:** This DICOM type is not an ordinary DICOM image but includes image information, and image presentation (orientation and plane). It is used in the design of patient geometry, such as the digitally reconstructed radiographs (DRRs).

The TPS also have dose calculation algorithms used for treatment planning and are generally classified as factor-based algorithms or model-based algorithms. The factor-based calculation algorithms also known as correction-based algorithms are based on absorbed dose measurements in water phantoms using rectangular fields as functions of field sizes, depths, isocentre distances and off-axis positions. Factors are then applied to account for the difference between these measurements in a water phantom and patient data by extrapolating dose for specified treatment fields. These applied factors may include those for missing tissue on the patient's surface and the approximation of tissue heterogeneities. Factor-based algorithms are very fast to compute and do

not distinguish between photon and electron radiation transport in patients and in the Linac (Sontag *et al.*, 1977). The model-based algorithms were introduced to account for the limitation in the factor-based algorithms to effectively account for absorbed dose variations due to tissue heterogeneities and field geometry variations. They are based on convolution or superposition methods of absorbed dose computation and are widely used in commercial TPSs, such as pencil-beam convolution (PBC), analytical anisotropic algorithm (AAA) and collapsed cone convolution (CCC) (Ulmer *et al.*, 2005; Sievinen *et al.*, 2005). Monte Carlo (MC) simulations, which is also model-based, can provide an alternative method to conventional TPS algorithms to determine the dose distribution, particularly in areas located far from the treatment field. MC simulation is the most accurate method for dose calculation in radiotherapy because of its most complete and detailed description of radiation interaction with matter (Jabbari *et al.*, 2011).

2.3.4.2 TPS Commissioning and Quality Assurance

Commissioning of radiotherapy equipment takes place after acceptance of the equipment and its components by the medical physicists together with the equipment vendor to assure that the hardware and software meet predefined expectations. The treatment planning system commissioning involves a more detailed characterisation of its dosimetric and non-dosimetric performance. The American Association of Physicists in Medicine (AAPM) technical group report number 53 (TG-53) provides high level guidance on what aspects of a TPS system need to be commissioned (Fraass *et al.*, 1998). The dosimetric aspect of the TPS commissioning mostly includes algorithm and dose calculation verifications, end-to-end-testing, evaluation of limiting cases and its ability to recreate input data. The non-dosimetric TPS commissioning on the other hand includes assessing the accuracy of image interpretation, model of beam energy spectrum and profiles and accurate localisation and computation of contoured volumes (Smilowitz *et al.*, 2015).

To understand in details of how the treatment planning software functions, it is very important to establish a QA procedure for the TPS. The QA of the TPS should involve testing the accuracy of patient's anatomical structures, beam description and dose calculation algorithms. A well-established QA procedure goes a long way in preventing treatment planning errors. The QA of a 3-D TPS used for IMRT and VMAT planning techniques should not only consist of verifying the algorithms in the system but combine testing simultaneously with the planning and delivery of such advanced techniques (IAEA TRS 430, 2004). The QA procedure does not end once the TPS has been commissioned and is very important to be maintained. The QA program must be flexible enough to adapt to changes. Written procedures must be established to cover future software upgrades, changes to associated devices, methods of data transfer and modifications to beam data. Periodic checks of the integrity of the TPS's hardware, software and data transfer should be continued.

2.3.5 *Linear Accelerator (LINAC)*

The discovery of x-rays by Roentgen in 1895, ushered in the technology of x-ray production in the treatment of diseases especially cancers. Since the inception of radiotherapy in the early 1950s, the use of high photon and electron energies and intensities have revolutionary external beam radiotherapy. The invention of the cobalt-60 teletherapy treatment machine provided tremendous drive in the quest for higher photon energy, placing the cobalt-60 machine at forefront of radiotherapy for decades. The development of medical linear accelerators (LINACS), however, soon became the most widely used radiation source in modern radiotherapy due to their compact and efficient design and versatility. In general, LINACS are pulsed accelerators which accelerate electrons to various kinetic energies using electromagnetic high radiofrequency (RF) fields. The electron beam is generated by the source and then delivered to the users in pulses of a duration

between a few microseconds and a few milliseconds at a given repetition frequency (Khan *et al.*, 2014; Lennox *et al.*, 2001). The main components of a modern LINAC consist of the source of the electron injection, the radiofrequency system, the electron beam transport system and the LINAC treatment head (as shown in Figure 2.6).

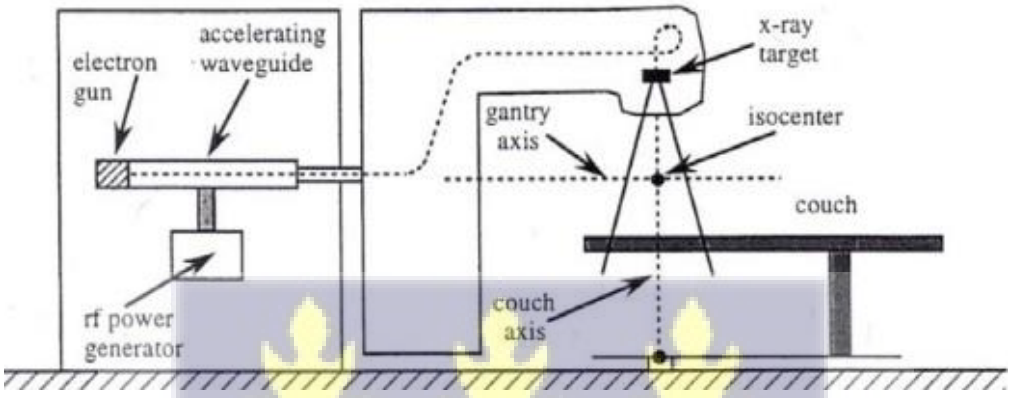


Figure 2.6: Linear accelerator design configuration for Elekta Infinity treatment machine showing the main components and its isocentre location (Podgorsak *et al.*, 2005).

- **Electron Source:** The electron injection system of the accelerator is also referred to as the electron gun. The electron gun consists of a heated filament cathode which emits electrons when a high voltage is applied, focusing the electron beams and accelerating them to an anode through an accelerating waveguide. The electrostatic fields used to accelerate the electrons in the electron gun are directly supplied from a pulsed modulator.
- **Radiofrequency System:** The RF system in the Linac is used for additional acceleration of the electrons in the accelerating waveguide to the desired kinetic energy. The electromagnetic wave used to accelerate electrons is produced by the RF system, which consists of two major components: an RF power source and a pulsed modulator. The accelerating waveguide consists of an evacuated copper tube. The tube interior is divided by

copper disks with various apertures and distances. Electrons are injected into the accelerating waveguide with an approximated initial energy of 50 keV, they interact with the field of the electromagnetic wave and gain energy from the sinusoidally varying electric field. The high-energy electrons exit the accelerating waveguide in the form of a pencil beam with a diameter of approximately 3 mm (Khan *et al.*, 2014).

• **Beam Transport System:** The beam transport system of the Linac helps transport the electron beam from the accelerating waveguide to the x-ray target (in photon beam mode) or to the Linac exit window (in electron beam mode). The transport system mainly consists of flight tubes and a couple of bending magnets. Additionally, steering and focusing coils are used to keep the electron beam centred and to reduce its divergence. The bending magnets are used to change the direction of the electron beam in LINACS operating at energies above 6 MeV, where the waveguide is long and parallel to the gantry rotation axis. In low energy LINACS, the waveguide is short, and the target is embedded in the accelerating waveguide in the same direction as the LINAC head central axis (CAX). Consequently, no beam transport between the accelerating waveguide and target is required (Podgorsak *et al.*, 2005).

• **LINAC Head:** The Linac head (as shown in Figure 2.7) contains the beam collimation and monitoring system and is responsible for the production of clinical beams. It consists of several components to shape (beam shaping using filters and collimators), localise (field sizes), monitor the treatment beam (dosimetry) and modulate its intensity (dose rate). The important components of the modern LINACs include the:

- Retractable x-ray targets.
- Primary collimator.

- Flattening filter (in photon beam mode) and electron scattering foils (in electron mode).
- Dual transmission ionising chamber.
- Secondary collimator (X-jaws, Y-jaws and MLCs).

Figure 2.7: The Elekta Linear accelerator (LINAC) used in this study with various components; A is the LINAC head, B is the EPID detector panel, C is the treatment table, D is the CBCT system and E is the XVI detector penal.

2.3.5.1 Linac Electronic Portal Imaging Device (EPID)

EPIDs are used in image guided radiotherapy (IGRT) for patient positioning verification and are rigidly linked to modern LINACs (labelled B in Figure 2.7). They are also used for dosimetric verifications due to their high-quality spatial resolution as well as its large detection areas (McCurdy *et al.*, 2009; Mijnheer *et al.*, 2017). Currently, several approaches have been developed to use EPID in patient-specific pretreatment dosimetric verification (McCowan *et al.*, 2017; Van

Elmpt *et al.*, 2008). Advancement in external beam radiotherapy has increased the accuracy requirements for dose delivery to patients. Quality assurance procedures before treatment delivery can potentially ensure a high level of accuracy necessary for treatments designed to achieve adequate tumour control and reduction of normal tissue complications. Electronic devices that are commercially available can be categorised according to their technical design. The first commercially available EPIDs were the liquid-filled ionisation chambers and camera-based detectors. More recently, the amorphous-silicon (a-Si) EPID has become the most commonly available portal imager. The Elekta Infinity LINAC used for this study is equipped with a standard iViewGT flat mega voltage portal imaging device. The EPID imaging detection system has powerful image processing and display using industry standard IT hardware and software (Elekta, 2023; Acquah *et al.*, 2014).

2.3.5.1.1 EPID-based Pretreatment Verification Software (EPIbeam)

The EPIbeam on-line software uses the EPID to check external beam radiation therapy plans in pretreatment conditions. It automatically compares the delivered radiation dose with the treatment planning dose computed by the TPS (RP=Radiotherapy Plan) as presented in Figure 2.8.

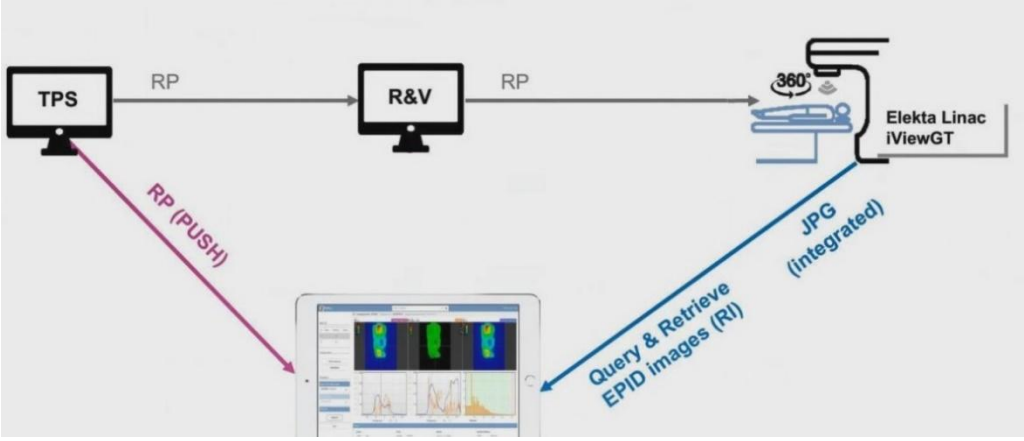


Figure 2.8: Integration of Elekta LINAC with TPS and Record and Verifying (R&V) system as the main components of the EPIbeam pretreatment QA setup.

This QA ensures the correct dose distribution is delivered, the correct MLC patterns and LINAC parameters are functioning, and the integrity of patient data transfer is accurate. The Elekta LINAC's 6 MV photon energy beam data must be installed on the Pinnacle TPS as a prerequisite for the EPIbeam commissioning. An iView GT DOSIsoft license will then be generated and installed on the iView GT workstation (DOSIsoft., 2024).

2.3.5.2 LINAC Commissioning and Quality Assurance

The installation of the LINAC is followed by acceptance testing to ensure that the treatment machine meets the specifications and user-vendor purchase agreement. This is to assure the safety of patients and staff using the machine and to provide machine baseline data for future quality assurance reviews. After satisfactory acceptance testing, the commissioning process of the LINAC for clinical use commences. During the commissioning process, comprehensive measurements of dosimetric parameters are collected to validate the TPS in determining the optimal radiation modalities and treatment techniques to be utilised for patient treatment planning. It also involves

the entry of beam data into the planning system and then testing its accuracy. The dosimetric dataset may include percentage depth dose (PDD) measurements, beam profile measurements, isodose distribution, and output factor measurements for various field sizes. It is very vital to compare these measured LINAC commissioned dosimetric beam data parameters with a published or master data of the same LINAC model or matched treatment machine, if available. Clinical use of a Linac without the proper commissioning process may potentially cause harm to patients (Palta *et al.*, 2024). A comprehensive LINAC commissioning procedure should cover specific mechanical tests, safety check, imaging tests and radiation dosimetric tests. The absolute beam dosimetry calibration of the LINAC may be performed using either the American Association of Physicists in Medicine's Task Group report number 51 (AAPM TG-51) or International Atomic Energy Agency's Technical Report Series 398 (IAEA TRS-398) protocols (Almond *et al.*, 1999; Andreo *et al.*, 2000).

The success of external beam radiotherapy depends on the accuracy with which the prescribed dose in the TPS is delivered to the tumour volume by the LINAC. AAPM TG-40 recommends that the dose delivered to the patient be within ±5% of the prescribed dose (Kutcher G. C., 1994) and ICRU 50 and 83 recommends -5%, +7% (ICRU 50, 1993; ICRU 83, 2010). Quality assurance describes programmes for checking the performance of the linear accelerator and for measuring the characteristics of the output from the LINAC. The LINAC QA must specify the method of testing and test equipment, the parameters to be tested and the frequency of testing. It also states the responsibilities of different staff, the baseline values and tolerances for these values, action levels and documentation guidelines (Acquah *et al.*, 2014).

2.4 RADIATION TREATMENT PLANNING PROCESS

Radiation treatment planning represents a major part of the overall treatment process. Treatment planning consists of many steps including patient diagnostic, tumour staging, image acquisition for treatment planning, the localisation of tumour and organs at risk volumes, optimal beam placement, and treatment simulation and optimisation (as seen in Figure 2.9). The treatment planning itself involves arranging radiation beams such that they cover the target volumes while minimising their reach to the adjacent normal organs. Prior to the use of any form of images, radiation treatment planning was generally carried out by manually manipulating standard isodose charts unto patient body contours that were generated by direct tracing or lead-wire representation (Parker *et al.*, 2003). Simultaneous development of CT scanners along with the advent of superior computers, lead to the development of CT-based computerised radiation treatment planning (Teoh *et al.*, 2011). CT- based radiation treatment planning provides the ability to localise the tumour and the surrounding OARs and in addition, the dose distribution within the patient is accounted for using the body's tissue densities (Battista *et al.*, 1981).

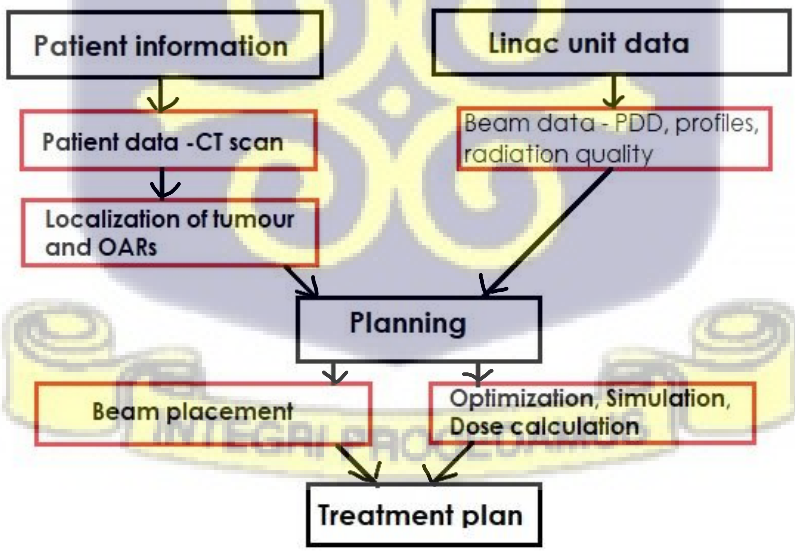


Figure 2.9: Overview of radiation therapy treatment planning process.

There are two types of radiation treatment planning processes, the forward planning and inverse planning methods. In the forward planning method, treatment plans are typically generated by trial-and-error processes until an optimal plan is achieved. This type of planning is generally very time-consuming, tedious and manually skilled based which does not necessarily produce high-quality treatment plans. With increased advancement in modern computerisation, better strategies for obtaining treatment plans were introduced leaning toward the inverse treatment planning method (computer-based treatment planning) (Evans *et al.*, 2005). During this planning method, objective functions are defined to measure the quality of a radiation treatment plan. Dose-based models and radiobiological models are the two main objective functions often used in inverse-planning. Dose-based places emphasis on the physical dose distribution to the tumour target and to normal tissues using evaluation tools like DVH. The biological model argues that optimisation should be based on the biological effects resulting from the dose distributions. The treatment objective is usually to maximise the tumour control probability (TCP) while maintaining the normal tissue complication probability (NTCP) to within acceptable levels. Unfortunately, this type of objective function is not commonly used clinically and hence it is currently not well suited in planning optimisation (Wu *et al.*, 2001).

Although radiation treatment delivery can be performed in minutes using advanced treatment techniques like VMAT, the treatment planning process is time consuming. The two main challenges in treatment planning are the speed of planning process and accuracy of the dose calculation. For many complex cancer cases, several hours are required by the TPS to calculate the desired dose distribution. Fast dose calculation algorithms do not account for the effects of heterogeneities in patients and may often lead to dose inaccuracies. In addition, a vast radiation treatment planning output variation is observed among different planners. Normally, treatment

planners may require years of planning experience to gain adequate knowledge in terms of achieving the best possible dose distribution in treatment plans. Many radiation treatments plans approved by radiation oncologists are far from optimal. However, treatment planning variations may occur even among members of the same facility and do not significantly correlate with experience. The introduction of online network treatment planning and automation presented promising technologies that can potentially create plans much faster and with greater consistency and help eliminate variability among treatment plans (Hussein *et al.*, 2018).

Radiation treatment planning objectives may include but are not limited to dose homogeneity, dose conformity, dose avoidance, and plan simplicity. Dose homogeneity requires the tumour target volume to be irradiated within specified dose levels and to have uniform dose distributions on the target (reducing cold spots). A cold spot in radiation treatment planning is defined as a portion of target volume that receives doses below the required level (usually below the 95% of prescribed dose). On the other hand, the term hot spot in radiation treatment planning refers to a portion of an organ that receives more than the desired dose level (usually above 105% of the prescribed dose). Dose conformity requires that maximum doses are delivered to the tumour target volume to achieve tumour control while minimum doses are delivered to the OARs to avoid damage and complications. The conformity index becomes a very useful dosimetric evaluation tool in assessing the dose conformity to the target volume. Dose avoidance simply requires dose limits to the OARs according to their dose constraint levels. Finally, plan simplicity requires that a radiation treatment plan should be as simple as possible, reduce treatment time as well as delivery error. A treatment plan should not be too complex to be delivered by the treatment machine.

2.5 AUTOMATION IN RADIATION TREATMENT PLANNING

Complex radiotherapy planning techniques such as VMAT, is a resource-intensive process requiring a high level of human intervention to ensure high plan quality. This, in many cases, leads to variability in the quality of treatment plans and overall planning efficiency, depending on the planner's experience and planning time availability. Within the last decades, there has been significant progress in the research and development (R&D) of advanced treatment planning approaches with automation support, with most TPS commercial vendors now offering some form of automation (McIntosh *et al.*, 2017). At the core of these developments is the key role of optimised, high quality and efficient treatment planning. VMAT radiation treatment planning techniques must be inversely planned. This means that a computerised treatment plan is generated by defining a set of planning objectives and dose constraints for tumour coverage and organs at risk sparing and the TPS's software uses these to generate a plan to deliver the prescribed dose. Even though the inverse planning method is highly computerised, it still requires human interventions, and a high level of treatment planner skills is required to ensure a high-quality plan is produced. To eliminate manual repetitive tasks and to maximise treatment planning efficiency, efforts to streamline and standardise the radiation treatment planning process are ongoing (Hussein *et al.*, 2018). The three main methods of treatment planning automation employed in clinical practice are the knowledge-based planning (KBP) (Zhang *et al.*, 2010; Shiraishi *et al.*, 2016) the protocol-based automatic iterative optimisation (PB-AIO) (Wilkens *et al.*, 2007; Yan *et al.*, 2003) and the multi-criteria or multi-objective optimisation (MCO) (Bokrantz *et al.*, 2015; Schlaefer *et al.*, 2013; Craft *et al.*, 2007).

Knowledge-based planning approach directly utilises prior knowledge and experience of previous plans to either predict an achievable dose in a new patient of a similar population or to derive a

better starting point for further trial-and-error optimisation (Yang *et al.*, 2004). There are two distinct approaches to the KBP methods, the atlas-based approach and the model-based approach. The atlas-based approach utilises the knowledge base to select the closest matching patient plan (s) to give a better starting point for the inverse optimisation (McIntosh *et al.*, 2016). The model-based approach employs many clinically accepted treatment plans and contours to characterise the relationships between anatomical and geometric features for a given anatomical site to build a predictive model for that site. The major limitation of the model-based dose prediction approach is that the plan quality for new patients strongly depends on the quality of plans generated in the past. Model-based approaches are either be based on DVH-guidance approach or voxel-based dose prediction approach (Yang *et al.*, 2015; Campbell *et al.*, 2017). The DVH-guidance approach relies on many clinically accepted treatment plans and contours to build a predictive DVH model for specific treatment sites. This knowledge can then be used to predict an achievable plan DVH which is based on the relationships between anatomical and geometric features of the given anatomical site. DVHs do not provide any patient spatial information and hence tend to limit the quality of treatment plans developed with the DVH-guidance approach. The voxel-based approach was introduced to overcome the inefficiencies of the DVH-based approach. Rather than predicting DVHs, the idea is to use knowledge from prior plans to build a model that can predict doses to individual voxels within the patient's image (Campbell *et al.*, 2017).

The protocol-based automatic iterative optimisation planning considers the best trade-off between target coverage and normal tissue sparing, taking into consideration the clinical objectives and priorities regarding organ sparing. This protocol requires iterative adjustment of optimisation criteria (trade-offs) to challenge the optimizer in achieving a progressively better plan until no improvement in plan quality is possible. The fundamental principle of protocol-based iterative

optimisation is to begin with a user-defined site-specific template with desired facility's clinical objectives and constraint priorities. The TPS optimizer then generates a plan that meets all the objectives, at which point the high priority constraints are locked down as hard constraints. An automatic optimisation then begins which iteratively pushes the DVH of all the structures to the point where the hard constraints are breached. The optimizer then reverts to the point before the breach occurs and stops the optimisation. At this point, the plan cannot be improved further and considered as the optimal radiation treatment plan (Wilkens *et al.*, 2007).

The multi-criteria or multi-objective optimisation approach seeks to overcome the issue of finding the optimal trade-offs between tumour target coverage and sparing of all organs at risk. Key to multi-criteria optimisation is the concept of what is known as the "pareto" optimal solution. A pareto optimal plan is a plan whose set planning objectives cannot be improved without degrading at least one of the other set objectives. There are two main approaches to multi-criteria optimisation, "a posteriori" MCO approach and "a priori" MCO approach (Monz *et al.*, 2008; Bokrantz *et al.*, 2015). The 'a posteriori' approach involves the optimiser automatically generating multiple plans where each of these plans has achieved its pareto optimal solution. Therefore, in this approach, the multiple trials of pareto optimal plans which are automatically generated are interactively (a posteriori) navigated by the planner to choose a clinically optimal plan (Teichert *et al.*, 2011). The main setback with 'a posterior' MCO is the infinite number of pareto optimal plans that can be generated, requiring higher computing power. Also, especially with the large number of clinical objectives, selection of an optimal plan may be difficult and may vary since its operator-dependent (Monz *et al.*, 2008; Serna *et al.*, 2009). However, in the 'a priori' MCO approach, for each patient, only one pareto optimal plan is fully automatically generated. This

single optimal plan has clinically desired trade-offs between all objectives, in line with the facility's clinical protocol (Breedveld *et al.*, 2007; Breedveld *et al.*, 2012).

2.5.1 Treatment Planning Objectives and Constraints

To fully understand radiation treatment planning optimisation, plan objectives and constraints must be defined. An objective is a desired treatment planning goal which the TPS calculation software may not be able to achieve when trying to determine the optimal plan. A constraint informs the TPS software that it must satisfy the treatment goal regardless of how objectives are changed. Constraints tend to decrease the speed of planning optimisation because they restrict the solutions available to the optimisation algorithm. The calculation algorithm must try to satisfy the objectives without violating the constraints. When constraints are used in planning, the objective value may rise during optimisation until the constraints are met. Once the constraints are met, the optimisation will then attempt to reduce the objective values. If the values in the optimisation phase continue to rise during optimisation, the constraints cannot be met (Philips Healthcare, 2023).

2.5.1.1 Target Objectives and Constraints

At least one of the objectives must be a target objective for the plan to be optimised. If a target constraint is used, it must be used in conjunction with a target objective. Target objectives and constraints are those whose goals are to deposit dose within the specified region of interest (ROI). Minimum dose, minimum DVH, minimum EUD (equivalent uniform dose), and target EUD are target objectives/constraints, uniform dose is a target objective, whiles uniformity is a target constraint, because the planner wants at least a certain amount of dose delivered to the ROI. When objectives and constraints are defined, it should always start with the target(s); the plan is typically not acceptable if the target objectives and constraints are not satisfied. A min dose and max dose objective for the target can be specified, although a single uniform dose objective will work well

and accomplish the same goals in most situations. An effective combination for target structures is a uniform dose or min dose objective combined with a uniformity constraint. Specifying min dose, max dose, or uniform dose objectives to the target may not always result in an acceptable dose distribution. To force the dose distribution to better conform to the target, one can create a "ring" ROI around the target ROI and specify a max dose objective within that volume. To create a ring around a target ROI, first create an expanded target ROI with an expansion of usually 0.5 to 1.5 cm. Then, specify the expanded ROI as the source ROI and the target ROI as the limiting ROIs. A destination ROI, which will be the ring ROI is then specified as well. A max dose objective is specified to the ring ROI between 100 and 95% of the prescribed target dose (first using the 100%). If it was overly aggressive, the dose would be too constricted around the target, and if it was not aggressive enough, the dose would not conform as much as it could. The illustration in Figure 2.10 shows a dose around the target volume that is not conformal when the objective is to give a uniform dose. Dose is much more conformal when a 1.0-cm ring ROI is used to constrain the dose as shown.

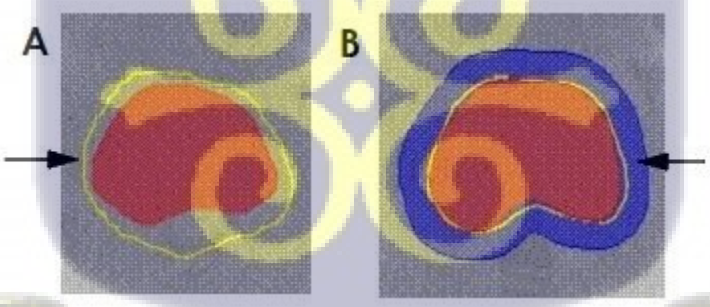


Figure 2.10: Forcing better conformed dose distribution (95% isodose yellow line) by utilising rings and maximum dose specification. A). the dose around the target is not conformal and B). the dose around the target is very conformal.

Figure 2.10 shows the forcing of better conformed dose distribution to the target (red colour) using ring ROI (blue colour) around the target ROI and specifying a Max Dose objective within that volume. On the left (A), the dose around the target is not conformal (yellow isodose line) while on the right (B), the dose is much more conformal (yellow isodose line) with the creation of a ring around the target. Avoid specifying target objectives or constraints to ROIs that extend outside the external patient contour. If a planner specifies a minimum dose to an ROI that extends near or outside the patient's skin surface, the optimisation algorithm will try to achieve a high dose to the air, resulting in a high dose at the surface (Philips Healthcare, 2023).

2.5.1.2 Critical Structure Objectives and Constraints

Non-target objectives and constraints are those whose goals are to avoid depositing dose within the specified ROI. Maximum dose, maximum DVH, and maximum EUD are non-target constraints and objectives because the planner wants a certain amount of dose not to be delivered to the ROI. The planner specifies the maximum dose to be delivered because less dose is desirable whiles more dose is not. When objectives for critical structures are created, the most straightforward approach is to create objectives that pull the dose down as low as possible. It is important to note that once the DVHs meet the goal of a max dose or max DVH objective, there is no incentive for the optimisation algorithm to do better. Therefore, max dose and max DVH values should be set aggressively. Another strategy is to create a set of max dose and max DVH objectives that define a DVH for a critical structure that meets delivery tolerances. Then, add a lightly weighted max dose or max DVH objective to the same structure for a dose that is 10 to 30% less than the clinically acceptable tolerance levels. This lower dose objective provides an incentive for the optimisation algorithm to continue removing dose from that structure even though the other objectives have been met. For example, a planner may specify a max dose objective of 45 Gy to the spinal cord

with a weight of 100, and a max dose objective of 30 Gy with a weight of 1 (Philips Healthcare, 2023).

2.5.1.3 Dose-Shaping Objectives and Constraints

In some cases, one may find that specifying target and critical structure objectives and constraints does not fully define the desirable dose distribution. In these cases, it can be beneficial to create other ROIs to help "shape" the dose distribution. A "surrounding tissue" ROI, which consists of an external patient contour with other target and critical structure ROIs removed from it, can be used to reduce high dose regions outside the target volumes and make the dose to the target volumes more conformal. Use the ROI expansion/contraction tool to create a surrounding tissue ROI by defining the patient contour as the source, adding all other ROIs to the limiting structure list, and then expanding with a zero margin in all directions. Assign an objective to the patient contour that has a maximum dose of the background radiation level. The Figure 2.11 shows a surrounding tissue ROI with the target ROI and critical structures removed (Philips Healthcare, 2023).

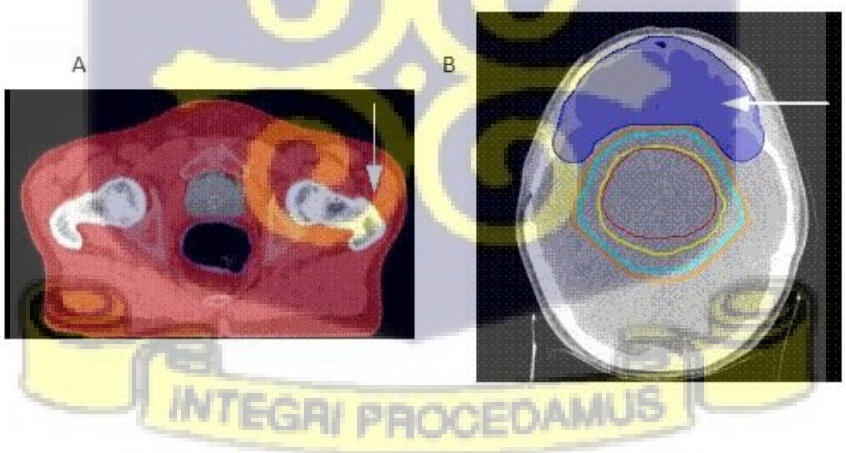


Figure 2.11: Creating a dose shaping ROI to direct doses to specific areas during optimisation in Pinnacle TPS. A). dose shaping ROI around the target volume and B) dose shaping ROI anterior to target volume.

Figure 2.11 illustrates the creating of a "dose-shaping" ROI that can help the optimisation algorithm overachieve goals and direct dose to specific areas. On the left side (A), normal tissues surrounding the target volume removed (red colour) and on the right side (B), the dose-shaping structure (light blue colour) is designed to limit the dose anterior to the target volume. Dose-shaping ROIs do not have to correspond to specific structures but can simply define an area in which you would like to shape the dose by specifying a suitable objective. The dose conformity around the target can also be increased by specifying "surrounding tissue" or "dose-shaping" objectives or constraints, as described in the dose-shaping objectives and constraints section (Philips Healthcare, 2023).

2.6 RADIATION TREATMENT PLANNING OPTIMISATION

External beam radiation therapy planning optimisation is a crucial process of the entire planning phase that contributes to the potential success of the treatment (Philips Healthcare, 2023). Planning optimisation ensures that the tumour target volumes have a high probability of being included in the optimised volumes receiving the highest absorbed prescribed doses, while the normal healthy surrounding organs are excluded from significantly high doses as much as possible. There are three main factors to be considered and require inputs in the optimisation approach in radiation treatment planning. The first factor or concern is the specification of the radiation delivery machine. The second and most crucial factor is the radiation dose distribution in the tumour volumes of a given treatment plan. The third factor or input is the requirement for the desired radiation dose levels of anatomical structures that are of interest. Other types of inputs and factors can also be specified depending on the particular radiation treatment planning problems. However, a desirable radiation

treatment planning technique (manual or automated) should be able to generate high quality treatment plans with minimum additional inputs and human skills (Nelms *et al.*, 2012).

When developing a radiation therapy plan for a specific cancer case, the radiation oncologist generally presents the medical physicist/planner/dosimetrist with a number of dosimetric goals of varying importance mostly based on facility's protocol. Although the main aim is to deliver as much of the prescribed radiation dose to the tumour target while at the same time the sparing organs at risk, a major challenge remains how to make the inevitable trade-offs between these two conflicting goals. Treatment planning optimisation is that process that provides the planner tools that allow for an efficient assessment of the interplay and trade-offs between conflicting goals. Conventionally, radiation treatment planning is based on optimisation models containing a single objective function to be optimised subject to a set of hard constraints on the treatment plan. Primary goal dose is defined as the dose goal or volume that the plan must meet as defined by the facility's clinical practices. For dose goals that require a volume, the volume should be set for the dose goal. Secondary goal dose is the dose goal that the plan must meet if the primary goal dose cannot be met as defined by the facility's clinical practices. Secondary goal dose is that goal that is less stringent but can still be acceptable (Philips Healthcare, 2023).

The treatment planning pathway for intact breast cancer case is shown in Figure 2.12. The steps as shown in the figure are as follows: (A) a CT scan with intact breast PTV (presented by the red colour) and OARs delineated; where the dark blue colour is the ipsilateral lung volume OAR, the pink colour is the contralateral lung volume OAR, the orange colour is the heart volume OAR, and the violet colour is the contralateral breast volume OAR. Step B - create a series of helpers (ROI) to help the optimizer.

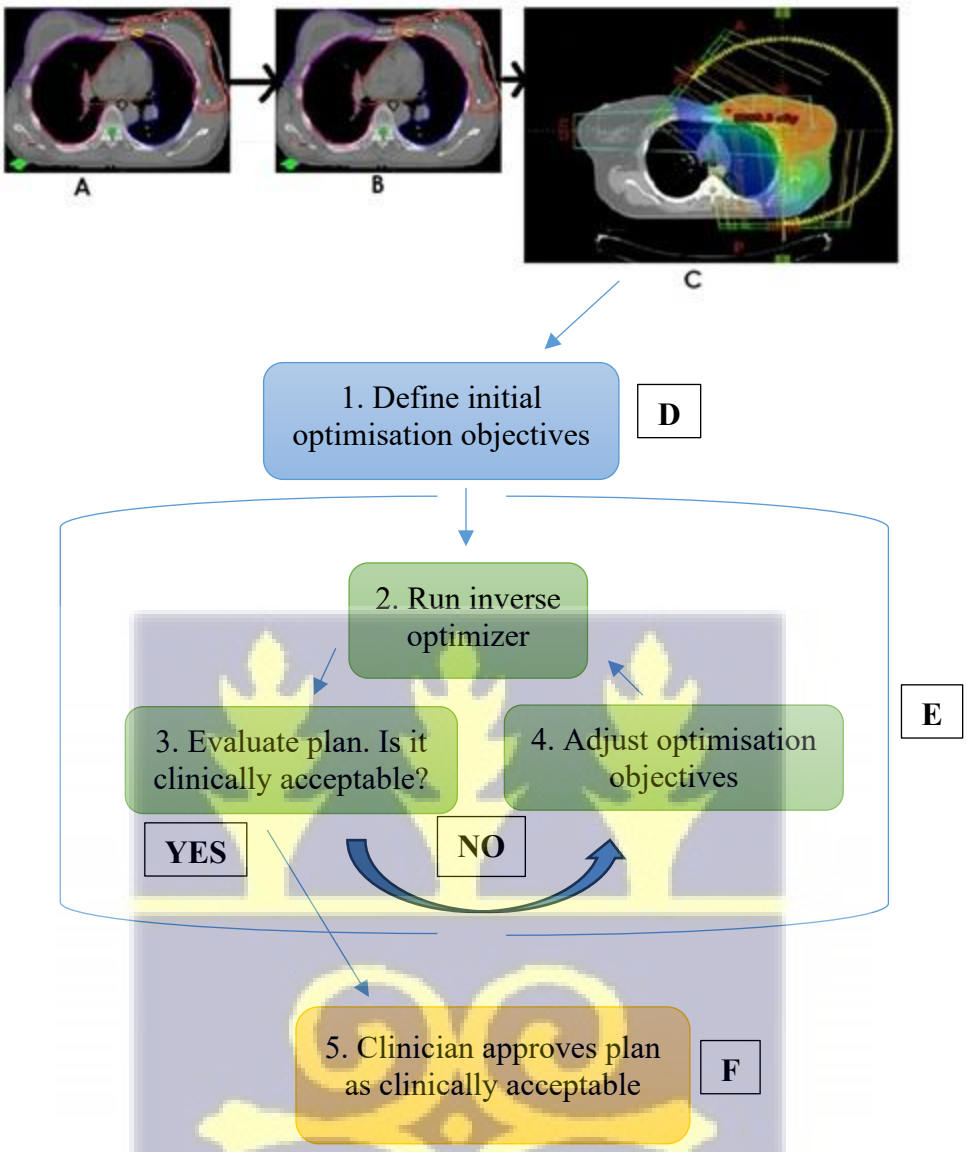


Figure 2.12: A typical VMAT inverse planning treatment planning pathway for intact breast.

An example is the part of an ipsilateral lung OAR overlapping with the intact breast PTV, PTV optimisation volume, and various ring structures to control dose spillage (1 and 2 cm margins around the PTV). In step C is the VMAT beam set-up geometry using 2 partial arcs. Step D- define the initial facility optimisation objectives. In step E, 2 - run the inverse optimizer until it reaches a solution and calculates the plan's dose distribution, while 3 - evaluate the resulting radiation

treatment optimal plan, if it is clinically acceptable proceed to 5, otherwise go to 4 to adjust the optimisation objectives. The step E, which involves 2, 3, and 4, is the iterative process of optimisation required by the planner to arrive at a clinically acceptable treatment plan to be approved by the radiation oncologist in 5. The stage 2 (Inverse plan optimizer) in step E above, represents the actual optimisation technique used in the Pinnacle TPS for treatment VMAT planning dose calculation. The flow chart as summarised in Figure 2.13 shows the Direct Machine Parameter Optimisation (DMPO) technique used in the VMAT dose computation.

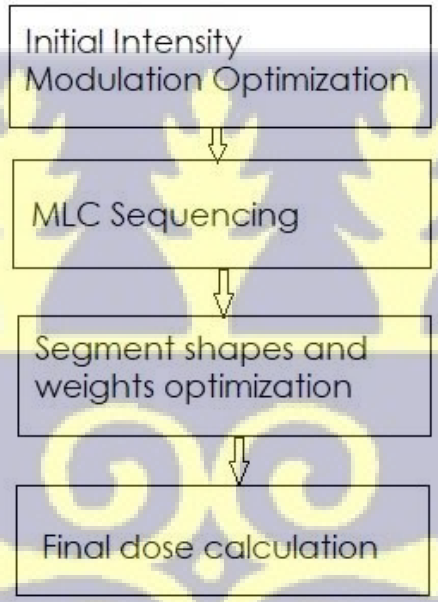


Figure 2.13: Flow chat summarising the DMPO optimisation technique sued in the Pinnacle TSP for VMAT breast cancer treatment planning.

DMPO optimisation used in VMAT results in radiation treatment plans that are delivered more efficiently than IMRT plans. As a prerequisite, before the optimizer is started in VMAT, the planner must add at least one dynamic arc and define its parameters (arc length; start and stop angles). The plan prescription is then defined and the target and OAR objectives set. The DMPO

VMAT optimisation consists of two phases: an initialisation phase and the refinement phase. The initialisation phase of the optimisation is only performed once, then followed by the refinement phase that can be repeated multiple times by the planner. Once the plan clicks the "Start Optimisation" in Pinnacle, the initialisation phase commences. This phase calculates the fluence of the arc, estimates the MLC shapes in every arc segment, calculates dose for each control point using the adaptive convolution algorithm and then performs segment weight optimisation (Philips Healthcare, 2023).

The term "control point" in treatment planning optimisation is a general concept for specifying a point during treatment where the beam changes. The aspects of a control point that might change during treatment include gantry, collimation, MLC leaf position, jaw position, and MU/sec. The output of the initialisation phase is an initial estimate of the MLC shape and weight for each control point in the given arc. The main purpose of the refinement phase is to improve the treatment plan quality by refining the already generated MLC segment shapes and weights. This phase consists of several iterations where each iteration considers a different portion of the estimated segments. This mainly consists of the fluence map optimisation, segment refinement and segment weight optimisation. During radiation therapy planning optimisation in the TPS, the following ROI types are used under the following conditions as defined below to achieve a specific goal (Philips Healthcare, 2023).

- **Min DVH (%):** At the volume (%) that a goal is specified, the dose that is delivered to the ROI must be greater than or equal to the dose value that was specified as the goal. This applies only to a percentage volume of the region of interest, and the constraint or objective is satisfied if the % volume of the ROI which exceeds the specified target dose is greater than the specific % volume.

- **Max DVH (%):** At the volume (%) that a goal is specified, the dose that is delivered to the ROI must be less than or equal to the dose value that was specified as the goal. This applies only to a percentage volume of the region of interest, and the constraint or objective is satisfied if the % volume of the ROI which exceeds the specified target dose is less than the specific % volume.
- **Min DVH (cm^3):** At the volume (cm^3) that a goal is specified, the dose that is delivered to the ROI must be greater than or equal to the dose value that was specified as the goal. This applies only to a volume in cm^3 of the region of interest and the constraint or objective is satisfied if the volume (cm^3) of the ROI which exceeds the specified target dose is greater than the specific volume (cm^3).
- **Max DVH (cm^3):** At the volume (cm^3) that a goal is specified, the dose that is delivered to the ROI must be less than or equal to the dose value that was specified as the goal. This applies only to a volume in cm^3 of the region of interest and the constraint or objective is satisfied if the volume (cm^3) of the ROI which exceeds the specified target dose is less than the specific volume (cm^3).
- **Min Dose:** The minimum dose that is delivered to the ROI must be greater than or equal to the dose value that was specified as the goal. This applies to the whole region of interest volume and represented at the 100% volume level of the DVH.
- **Max Dose:** The maximum dose that is delivered to the ROI must be less than or equal to the dose value that was specified as the goal. This applies to the whole region of interest volume and represented at the 0% volume level of the DVH.

- **Mean Dose:** The mean dose that is delivered to the ROI must be less than or equal to the dose value that was specified at the goal. Mean dose goals are intended for OAR optimisations rather than the tumour target volumes.
- **Uniform Dose:** This applies to the whole region of interest and can only be used as an objective. This objective comes closer to being satisfied as the dose throughout the ROI's volume becomes more uniform.
- **Uniformity:** This applies to the whole region of interest and can only be used to set a constraint. This constraint is met when the variation of dose within the ROI is less than the specified % variation. The objective value for uniformity constraint is the percent uniformity that the TPS meets.

2.7 RADIATION TREATMENT PLANNING EVALUATION

Radiation plan evaluation is a key component in the radiation planning and treatment process. Radiation oncologists mostly rely on the conventional method of slice-by-slice visual verification of prescribed isodose lines conforming to the PTV and the use of the DVH and DVH-derived metrics. Plan evaluation is used to assess the quality of the treatment plan as produced by the TPS. Evaluation of treatment plans can be done using a number of quantitative and qualitative methods. This includes the use of dose metrics in assessing plan quality. Dose metric evaluation of calculated dose distribution is based on the dose volume histograms, which represent the 3-D dose information into a 2-D metrics (that is dose and volume). The use of DVH only in plan evaluation does not provide the spatial dose distribution information and may require slice-by-slice evaluation in addition. There is no globally accepted single method of evaluating treatment plans, but most radiotherapy facilities use treatment plan dosimetric evaluation methods to assess the quality of a

plan. Another metric evaluation method is the use of biological models to assess the quality of a treatment plan. The radiobiological evaluation uses the tumour control probability and the normal tissue complication probability to evaluate the tumour coverage and risk of toxicity to normal organs. Aspects of treatment planning evaluation which are mostly ignored by many radiotherapy facilities are the treatment plan robustness and plan complexity. When all these different aspects that affect the quality of treatment planning and treatment process are evaluated, then the overall quality of clinically acceptable treatment plans may be better understood (Hernandez *et al.*, 2020).

2.7.1 Evaluation of Dosimetric Parameters

The tumour target dose coverage is usually evaluated by comparing DVH and the DVH-derived metrics with the facility's planning goals. Regions inside the target areas are also checked for any cold spots and those outside the target areas are checked for hotspots. DVH-based dosimetric analyses inherently assume that organ function is uniformly distributed within an organ. Organs at risks evaluations are commonly done using the Quantitative Analyses of Normal Tissues Effects in the Clinic (QUANTEC) clinical tolerances based on DVH metrics study by Emami and its updated publication by Bentzen (Emami *et al.*, 1991; Bentzen *et al.*, 2010). Other protocols developed by the Radiation Oncology Group (RTOG) of the American College of Radiology (ACR) are also used by cancer facilities in evaluating the OARs for breast cancer radiation treatment plans (RTOG 1005, 2014; Vinici *et al.*, 2022; Chitapanarux *et al.*, 2023). During radiation treatment planning, the planner needs information to predict the risk of a normal tissue complication vis-a-vis the target 3-D dose distribution. This information goes a long way to help optimise the therapeutic ratio of the treatment plan. The goal of QUANTEC and RTOG is to summarise the available 3-D dose-volume-outcome data from patient studies. However, understanding the exact trade-off between an expected decrease in organ toxicity resulting from

an improved dose distribution, or the possible increase in toxicity otherwise, is not fully established. The setbacks of using the QUANTEC constraint tables lie on the fact the tolerance values rely on a single DVH endpoint and are based on arbitrary toxicity acceptability levels. A single dose metric derived from a DVH might not represent the actual relationship between radiation dose and organ response; hence other dose metrics should be explored in evaluating acceptable limits (Hernandez *et al.*, 2020).

The dosimetric quality of dose distribution in the target volume can also be objectively quantified by using the DVH-derived dose metric calculations. The metrics include the homogeneity index (HI), conformity index (CI), uniformity index (UI), quality index (QI) and other indices that even ensure low doses to organs at risk. Homogeneity indices for example are usually based on ratios of three points on the DVH of the target volume (maximum dose, minimum dose and prescribed dose). The HI formula as given by Yoon M. (Yoon *et al.*, 2007) is stated as:

$$HI = \frac{(D_2 - D_{98})}{D_{PD}} \qquad 2.7.1$$

where;

D_2, and D_{98} represent the doses received by 2% (maximum dose), and 98% (minimum dose) volumes of the PTV_opt, respectively. D_{PD} is the prescribed dose of 50 Gy.

Conformity index involves ratio of the target volume treated at a given isodose (usually the 95% isodose) to the target volume as stated below (ICRU 83, 2010).

$$CI = \frac{V_{RI}}{TV} \qquad 2.7.2$$

where;

V_{RI} is the volume of PTV_opt covered by the reference isodose line (95% isodose line using the ICRU-83), and TV is the target.

Uniformity index is defined as the ratio of the dose received by 5% of the target volume to that received by 95% of the target volume as stated below (ICRU 83, 2010).

$$UI = \frac{D_5}{D_{95}} \qquad 2.7.3$$

where;

D_5, and D_{95} represent the doses received by 5%, and 95% volumes of the PTV_opt, respectively.

Quality index was implemented as a quality measure aimed at minimising hot spots and are calculated using the formula below as introduced by Adnani N. (Adnani *et al.*, 2020)

$$QI = \frac{V_{105}}{V_{95}} \qquad 2.7.4$$

where;

V_{95} and V_{105} represent the PTV volume that received 95% and 105% of PD, respectively.

The aim of introducing QI is to investigate what effects, if any, minimising dose to the volume that receives 105% (V_{105}) of the prescribed dose in breast cancer irradiation will have on cosmetic outcomes.

The ROI statistics are also very vital in evaluating the doses to the target volume and the organs at risk. The absolute minimum dose, maximum dose and mean doses calculated by the TPS were also used in evaluating the dosimetric parameters of the breast treatment plan. The Pinnacle TPS provides a variety of tools for evaluating and comparing radiation treatment plans. These include tools for dose distribution information, point dose information, dose volume histograms, ROI dose statistics, dose comparison, biological response comparison, generation of dose profiles, and

evaluation of plans with QA phantoms (Philips Healthcare, 2023).

2.7.2 Evaluation of Radiobiological Parameters

Radiotherapy relies on the delivery of therapeutic doses of radiation to the tumour volume whilst minimising the dose to surrounding normal tissues. To maintain a high 'tumour control probability (TCP)', it must deliver as much dose as possible to the target to kill all the viable cancer cells. In doing so, it also damages surrounding normal tissues and this dose must be minimised to give a low 'normal tissue complication probability (NTCP)' (Gay *et al.*, 2007) as shown in Figure 2.14.

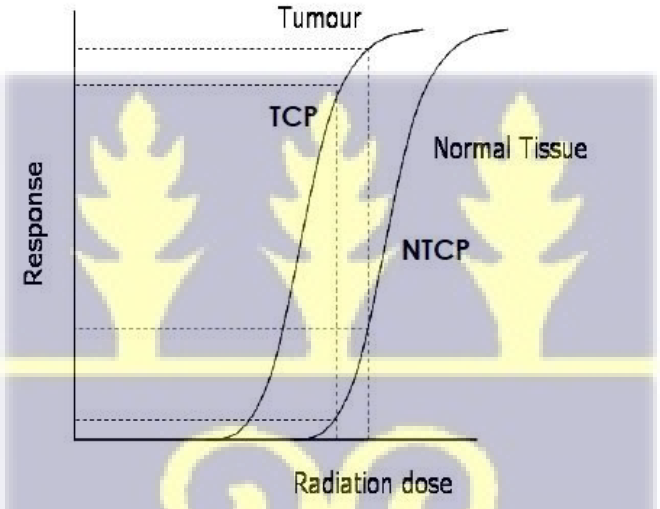


Figure 2.14: Model threshold-sigmoid dose-response curves for tumour control probability and normal tissues complication probability.

NTCP and TCP provide additional information for evaluating treatment plans based on the doses to critical structures and tumour. The NTCP and TCP response values can be obtained for any structure (ROI) for which a DVH has been computed. Beyond the NTCP threshold, a small change in dose has a much greater effect on the normal tissue than on the tumour itself. The biological response model used for the radiobiological evaluation in the Pinnacle TPS was the Kallman S-

model (Kallman *et al.*, 1991), the NTCP response calculations with the Lyman-Kutcher-Burman model (Lyman *et al.*, 1985; Kutcher *et al.*, 1989; Kutcher *et al.*, 1991; Burman *et al.*, 1991).

2.7.2.1 Tumour Control Probability (TCP) Calculation

TCP model generally relies on the assumption that tumour control requires the killing of all clonogenic cells. Tumour control probability for a given tumour is represented by a sigmoid curve in which an increase in dose results in greater tumour cell kill. So, the Poisson statistics predict that the probability of this happening is given by:

$$TCP = e^{[-N * Cs\,(D)]} \qquad 2.7.5$$

where N is the initial number of clonogenic cells, and Cs(D) is the survival fraction of clonogenic cells after a dose D is given. The cell survival fraction can be assumed to be described by linear and quadratic contributions (linear-quadratic model), given by:

$$Cs(D) = e^{(-\alpha D - \beta D^2)} \qquad 2.7.6$$

where α and β represent the intrinsic radiosensitivity of the irradiation cells, α is the linear radiosensitivity coefficient for the tumour (in Gy^{-1}) and β is the quadratic radiosensitivity coefficient for the tumour (in Gy^{-2}). Cells with a higher α and β are more sensitive to radiation while the ratio of the two parameters, α/β, represents the measure of the fractionation sensitivity of the cells. Cells that are less sensitive to the sparing effect of fractionation have a higher α/β and vice versa (Thames *et al.*, 1982).

2.7.2.2 Normal Tissue Complication Probability (NTCP) Calculation

NTCP calculation was performed using Lyman-Kutcher-Burman (LKB) model (Burman *et al.*, 1991; Kutcher *et al.*, 1989; Lyman *et al.*, 1985). This model calculates the complication probability of normal tissues in a non-uniform irradiation using dose-response histograms. Moreover, this model can be used to estimate the probability of complication for uniformly irradiated organs as well. The normal tissue complication probability is also represented by a sigmoid curve. The basic assumption is the Poisson statistics for describing cell survival and the categorisation of the normal organs at risk as serial and parallel organs. The Lyman model expresses the NTCP model for uniform irradiation of organs with a dose D given by:

$$NTCP = 1/\sqrt{(2\pi)} * \int_{-\infty}^{u} e^{-t^2/2}\, dt \qquad 2.7.7$$

where $u = \frac{(D - TD_{50})}{(m * TD_{50})}$

where TD_{50} is the whole organ dose D for which the normal tissue complication probability is 50%, and *m* is a dimensionless parameter.

The LKB model was developed by Kutcher and Burman (Kutcher, 1989) using the Lyman model to develop a volume reduction algorithm for an inhomogeneously irradiated organ.

2.7.3 Evaluation of Plan Robustness and Complexity

2.7.3.1 Plan Robustness Analysis

Robustness evaluation is a very critical step in radiation therapy planning. The main aim of external beam radiation therapy is to deliver sufficient dose to tumour volume while preserving surrounding

healthy organs. This aim is achieved by using irradiation techniques that will conform radiation doses to the target volume as much as possible. However, the actual radiation dose delivery can be affected by many sources of uncertainty. The introduction and use of robust treatment planning and plan evaluation methods have been developed to ensure that dose delivery meets plan objectives despite the many associated uncertainties. In photon beam external radiation therapy, robust treatment planning is typically implemented by the addition of safe margins around the CTV and OARs in defining the PTV (Van Herk *et al.*, 2000) and planning risk volume (PRV) (Stroom *et al.*, 2006; McKenzie *et al.*, 2002). In advanced treatment modalities such as IMRT and VMAT, these margins may not be adequate to account for the failure of static-dose cloud approximation, which assumes that changes in patients (shifts) do not affect dose distributions during treatment delivery (Fredriksson *et al.*, 2012). Moreover, whether the target receives the prescribed dose or not also depends on the dose distribution rather than only on geometric margins added to the CTV. It should also be noted that planned dose distributions are neither perfectly conformed to the PTV nor equally conformed on all sides of the PTV (Gordon *et al.*, 2008). Additionally, the margin may depend on the steepness of the dose fall-off near the target because a sharp dose fall-off may require a bigger margin than a naturally gradual dose fall-off. As a result of this assumption, many robust planning and plan robustness evaluation methods have been proposed by many researchers (Unkelbach *et al.*, 2018; Yock *et al.*, 2019; Sterpin *et al.*, 2021; McGowan *et al.*, 2015; Fredriksson *et al.*, 2012).

Robust optimisation must explore different approaches, thereby addressing uncertainties explicitly without solely relying on margins. Thus, instead of optimising a single scenario, for example errors due to set-up uncertainties, planned dose distributions should be optimised for a number of scenarios. Each scenario represents a possible treatment fraction and should include all possible

uncertainties (both systematic and random errors) in calculating a final planned dose distribution. The final plan can then be optimised considering all the possible scenarios at once. During robust planning, the worst-case scenario (minimax approach) or a combination of different scenarios should be included. Each case scenario must be assigned a certain probability (probabilistic approach) during optimisation (Hernandez *et al.*, 2020). A treatment plan that is considered both 'optimal' (clinically acceptable nominal dose distribution), and 'robust' will yield a final dose distribution that is suitable for all, or majority number of error scenarios considered. Robust optimisation in commercial treatment planning systems was first implemented in 2014 for proton therapy (Liu *et al.*, 2014). In most TPS, there are available scenario option lists to choose from for proton beam robustness analysis. It has become the golden standard in proton beam radiation therapy and is now gaining interest in photon radiation therapy (Korevaar *et al.*, 2019).

Robustness analysis is a plan evaluation tool that allows planners to define different scenarios to evaluate how different set ups or ranges of error will affect the plan's final dose distribution. Plan robustness evaluation hence offers the planner how the nominal planned dose distribution may change as compared to the final robust plan obtained with different error scenarios. This robustness evaluation method may offer the possibility of quantifying all uncertainties in the derived DVHs and other dose metrics. To make robustness analysis clinically useful, it is extremely important to define a benchmark for robustness analysis tools and agree on what constitutes a safe degree of deviation from the nominal plan dose parameters (DVH calculations, dose axis display, and volume axis display). Robustness evaluation tools in clinical applications are in their early stages and their current availability in commercial TPS for photon beam plans is not well established. It is of great importance to reach a consensus on which methods are most appropriate for both robust optimisation and evaluation. Retrospectively analysing plan robustness for patients already treated

with photons backed by patients follow up data (including survival rates) on toxicity and tumour control can be an interesting starting point. These data could be very vital in establishing appropriate photon beam references for robustness parameters for typical IMRT and VMAT plans in different treatment site (Korevaar *et al.*, 2019).

2.7.3.2 Plan Complexity Analysis

Modern modulated radiation therapy techniques like IMRT and VMAT involve modulation of many machine parameters, placing significant demands on treatment units and TPS. This increase in machine parameter modulation is usually referred to as treatment plan complexity. The definition of the term "complexity" of a radiation therapy plan among researchers varies and it is understood as an estimation of the degree of dose uncertainty because of its calculation and delivery. Radiation treatment plan complexity may be defined as the frequency and amplitude of fluctuations in beam intensity distributions (Antoine *et al.*, 2019). Most volumetric modulated arc therapy beam complexity is due to this fluctuation in fluence. The more complex a plan is, the larger the uncertainties in dose calculation and treatment delivery compared to non-modulated or less modulated treatment plans (Miften *et al.*, 2018). A more complex plan is generally characterised by many MUs, typically involve smaller, narrow, off-axis with more irregular beam shaped apertures and larger tongue-and-groove effects. The degree of plan complexity can significantly affect treatment dose delivery, mainly due to the positioning accuracy of the MLC, performance of treatment machine and dose calculation accuracy of the TPS (Jurado-Bruggeman *et al.*, 2017). Very complex treatment plans during delivery influence the sensitivity of delivered dose to small deviations in machine parameters even when within tolerances. They are also sensitive to variations in patient geometry like organ motion and respiratory motion (Hubley *et al.*, 2017). Plan complexity can be inherently explained as an assessment of plan robustness to all these

uncertainties. A high degree of plan complexity may therefore compromise the overall accuracy and quality of treatment and should be avoided if possible. However, a certain degree of radiation treatment plan complexity is necessary because it is often required to achieve an optimal prescribed dose distribution.

Many researchers (Mohan *et al.*, 2000; Gordon *et al.*, 2013; Crowe *et al.*, 2014; Jurado-Bruggeman *et al.*, 2017; Hernandez *et al.*, 2018; Chun *et al.*, 2019) have developed and adapted several complexity metrics for advance radiation therapy. The first proposed metrics used were based on fluence map-based metric, like the Fluence Map Complexity (FMC) and the Modulation Index (MI) (Santos *et al.*, 2020). Modulation Complexity Score (MSC), which is an aperture-based metric, was later introduced to directly evaluate the size, shape and location of beam apertures (Chun *et al.*, 2019). Others have proposed complexity metrics to include the use of degree of freedom (DOF) and fixed-physical properties (FPPs)–based calculations to quantify plan complexity. A degree of freedom corresponds to all achievable beam values during its delivery, like dose rate, gantry speed, collimation speed, MU per control point while the FPPs correspond to parameters like the MLC limits, leaf speed, leaf transmission and leaf edge shape (Antoine *et al.*, 2019). The AAPM (Ezzell *et al.*, 2009) recommends the need to quantify plan modulation and to adapt plan complexity tolerance limits to a certain degree (Miften *et al.*, 2018).

Plan quality in radiation treatment plans does not only depend on the calculated dose distribution (dosimetric analysis), but also on the accuracy of the dose calculation and dose delivery. Therefore, the overall plan quality in radiation therapy must incorporate an assessment of a plan's complexity. Additionally, commercially available TPSs should clearly describe the plan complexity metrics that they use in plan optimisation and subsequently provide tools for scoring and reporting these

values to facilitate the assessment of plan complexity in radiation therapy clinical settings (Antoine *et al.*, 2019).

2.8 PLAN QUALITY IN RADIATION THERAPY

Plan quality in radiation therapy planning and treatment workflow is very important in cancer treatment and management. The parameters that are used in defining the quality of a treatment plan must at least be agreed on and understood by the facility and its personnel. Plan quality is generally defined as the clinical suitability of a treatment plan that can be delivered in a clinical setting as expected (Hernandez *et al.*, 2020).

2.8.1 Treatment Plan Quality

Plan quality is mainly assessed by evaluating the planned dose distributions calculated by the TPS. The quality of treatment plans is mainly affected by planner's skills, experience and the manual (trial-and-error) aspects of radiation therapy planning processes. These may introduce variations among planners and facilities resulting in varying plan quality and possible patient outcomes. However, the idea of what a quality plan is encompasses many different aspects of the treatment plan. Currently, there is no global consensus on how exactly to define, measure, and report radiation treatment plan quality (Hernandez *et al.*, 2020). The understanding of what constitutes a quality treatment plan continues to evolve with new techniques, dose delivery strategies, and evidence-based treatment planning research and clinical trials. The development of robust radiation treatment plan evaluation tools is needed in defining plan quality both quantitatively and qualitatively. Plan quality measures and indicate the degree by which a calculated plan dose distribution fulfils the desired dose objectives specified by facility's treatment goals. It is worthy to note, however, that the dose distribution displayed by the TPS during evaluation may not

necessarily be the actual plan dose been delivered to the patient. These disparities may be due to the TPS's calculation algorithm limitation, and uncertainties in the actual delivery of the treatment plan. Errors in dose delivery may include those associated with the treatment machine daily output, daily patient set-up, interfractional and intrafractional motions, and changes in the patient's anatomy (Hernandez *et al.*, 2020).

In summary, the quality of radiation dose delivered to the patient does not only depend on the calculated dose distribution but also on the robustness and complexity of the treatment plan. Therefore, all aspects need to be considered when evaluating the overall plan quality. Overall plan quality should as much as possible be linked to clinical outcomes. To achieve this, collection of facility data on dose metrics, robustness and complexity as well as clinical information from patients is very important. A better assessment of these concepts together with the utilisation of useful tools in the treatment planning system will be helpful in increasing the overall treatment quality in radiation therapy.

2.8.2 Quantifying Treatment Plan Quality

Quality of treatment plans can be analysed and compared using the concept of plan quality metric (PQM) scoring. The use of radiation treatment PQM scoring serves as a relative scoring system designed to remove any ambiguity as well as provide direct comparative results for each dosimetric parameter and overall plan quality. Significant variations in the quality of treatment plans do exist between facilities and even planners within the same facility (Giglioli *et al.*, 2020). A comprehensive PQM that incorporates plan or dosimetric parameter scores may facilitate objective plan comparison and reduce perceived subjectivity (Hernandez *et al.*, 2020; Nelms *et al.*, 2012). The use of plan scoring methods has been employed in numerous studies (Rayn *et al.*, 2023; Blanck *et al.*, 2016; Nelms *et al.*, 2012) and have helped detect institutional differences in treatment plan

quality. Scoring treatment planning dosimetric parameters enables planners to rank and prioritise plan metrics that contribute to improved overall plan quality.

2.9 QUALITY ASSURANCE PHANTOMS AND QUALITY CONTROL

The introduction of advanced radiation planning and treatment techniques such as IMRT and VMAT involves computer controlled dynamic MLC movement and results in differences in dose gradients. Due to its complexity, specific quality assurance (Machine QA, pretreatment QA and patient-specific QA) is an essential requirement to meet (Basran *et al.*, 2008; Klein *et al.*, 2009; Miften *et al.*, 2018). QA in radiation therapy are all the procedures that ensure consistency of radiation prescription, and the safe delivery of that prescribed radiation therapy. Machine QA relates to the treatment unit's capacity to deliver accurate VMAT beams such as MLC test QA. Pretreatment QA relates to the delivered dose distribution validation using a detector such as Octavius 4-D phantom (PTW, PTW Dosimetry, 2014). Patient-specific QA is related to the *in-vivo* measurement of the delivered dose using diodes or EPID systems. The dose distribution in VMAT plans is characterised by steep and numerous dose gradients which are related to the complex dynamic MLC pattern. As plan complexity increases, dose inaccuracy and error in dose delivery increases as well and may lead to potential clinical implications, hence the need for a comprehensive specific QA.

Given the complexities of modern advanced radiation therapy techniques, stricter processes are necessary to meet the increasing requirements for radiation quality and safety. The main aim of quality control procedures during VMAT is to check the consistency between the planned and delivered treatments. Validations of the equipment and software used should be tested as a form of QC procedure. QC is the process through which the actual quality performance is measured,

compared with existing standards, and the actions necessary to keep the standards. QCs are to check that quality requirements are met and to adjust or correct performance if the requirements are found to be out of tolerance (Leer *et al.*, 1998). The general QA/QC equipment and associated software used during the study are described in sections below.

2.9.1 Water and Water-Equivalent Phantom

Phantoms mimic the human body and are used in radiation therapy to simulate as close as possible the interaction of radiation for dosimetry measurements. They are used in the determination of absorbed dose at various depths and positions within a human body. This helps to measure or calculate doses in tumour volumes and in normal healthy tissues in the human body. The use of water as tissue equivalent material was first employed in radiation measurement due to its density been similar to that of the human body. About 70% of the human body is composed of water molecules though in reality the human body is a heterogeneous medium. The radiological properties of water are like human tissue and closely resemble the radiation absorption and scatter properties of human tissues and muscles (Prasad *et al.*, 1997). However, other types of phantoms (known as anthropomorphic phantoms) are developed with special materials to exactly mimic the real human body structures (Yavav *et al.*, 2021). The use of water as a reference phantom material is internationally accepted as it is easily definable and its density can be maintained with a fair degree of accuracy in any shape or size. In addition, water is also easily accessible, inexpensive, and widely available. However, in routine clinical practice, plastic water phantoms are often used instead of water due to its practicability. Plastic or water-equivalent or solid water phantoms are expected to perform very similar to that of water though correction factors may be applied during their use in absorbed dose determination (Andreo *et al.*, 2000). Some examples of water equivalent phantoms are Poly Methyl Methacrylate (PMMA) (Ozturk *et al.*, 2023), Polystyrene (Ashby *et al.*,

2013), Solid water (WT1), Acrylonitrile-butadiene-styrene (ABS), plastic water, virtual water, RW1, and RW3 slab phantom (Kurudirek *et al.*, 2013). The PTW water equivalent phantom (RW3 slab) (PTW, PTW Dosimetry, 2014) has a physical density of 1.029 g/cm^3, which is almost equivalent to the physical density of water (1.000 g/ cm^3) used in the PTW BEAMSCAN phantom (BEAMSCAN, 2017) as shown in figure 2.15. ICRU Report 44 (ICRU 44, 1989) recommends a list of phantom-water equivalence quantification with uncertainties not less than 1% in absorb dose calculations.

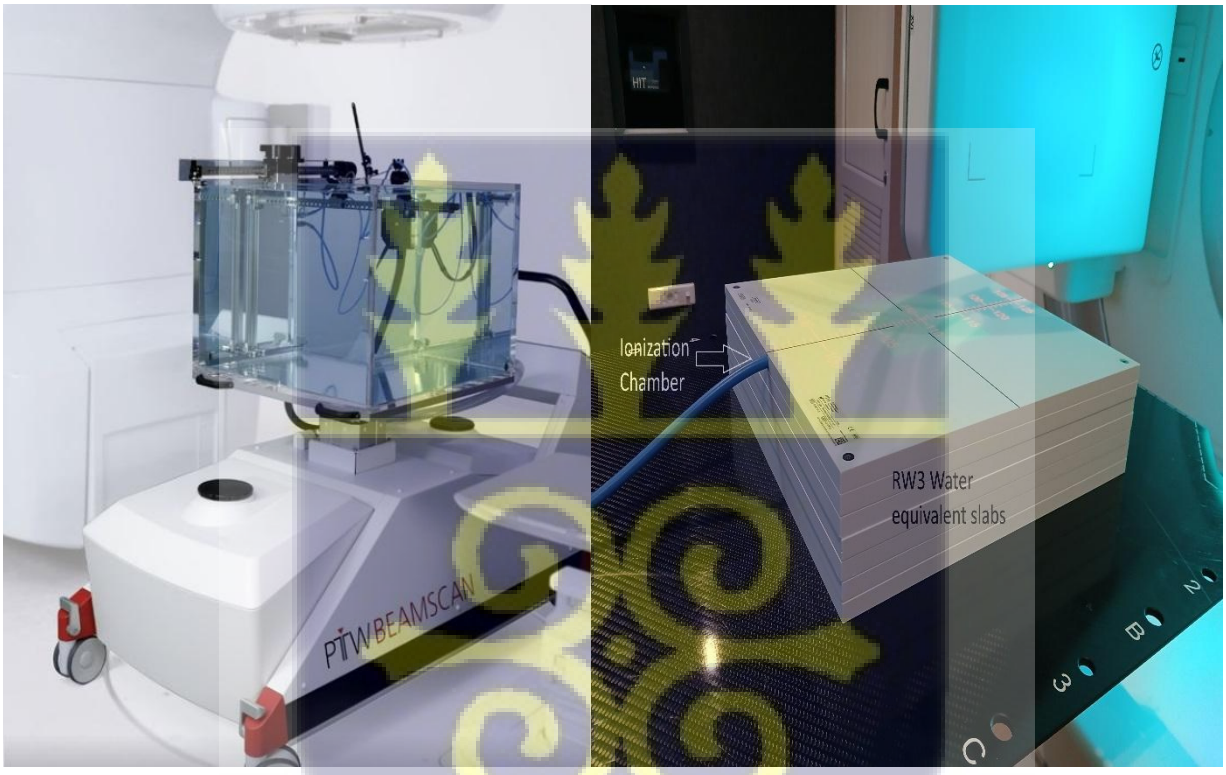


Figure 2.15: **left** is PTW BEAMSCAN water phantom and **right** is PTW water equivalent water phantom (RW3 Slabs with an ionisation chamber inserted) used during dosimetry measurements.

2.9.2 Dosimetry Equipment

Radiation dosimetry essentially involves the measurements, calculations, assessment and optimisation of ionising radiation doses deposited in a medium, usually in the human tissue. Dosimetry is extensively used in dose quantification and monitoring in radiation therapy. In order to plan and deliver radiation treatment plans, the radiation been produced by the treatment unit must be characterised with PDD curves, dose profiles and point dose measurements. Absolute radiation dose determination under reference conditions as well as relative dose measurements under non-reference conditions are very important in achieving accurate dose distribution in radiation therapy. Acceptance testing, commissioning and quality assurance of treatment units require various dosimetric measurements with the use of dosimetry equipment. To obtain accurate measurements, detailed knowledge of the dosimetry equipment's characteristics needs to be understood (Andreo *et al.*, 2000). Some key properties include the dosimetry equipment's accuracy and precision, signal response to radiation dose, dose and dose rate dependence, energy response, and calibration factor stability (Das *et al.*, 2008). The most common dosimetry equipment used in radiation therapy is the detectors like ionisation chambers, and diodes. Others are the electrometers, beam scanning systems, dosimetric phantoms, thermometers, and barometers.

2.9.3 Pretreatment QA Phantom

Advanced external beam radiation therapy techniques have facilitated complex treatments that achieve better dose conformity with the tumour volume while minimising radiation doses to surrounding organs at risk. The accuracy in the delivery of planned radiation dose becomes very vital with these advanced complex treatment techniques. To achieve delivery of same planned doses, emphasis is placed on the need for pretreatment phantom measurements to validate

treatment plans (Yu *et al.*, 2011). Pretreatment QA is a crucial part of radiation therapy, especially for IMRT and VMAT techniques. It ensures the accurate delivery of planned dose under actual treatment conditions of the delivery machine. Once treatment plans for patients are completed on the TPS, a verification plan is created. Essentially, a verification plan is a copy of the clinical plan with the same gantry angles, dynamic MLC pattern, and monitor units. Verification plans are calculated on scanned phantoms or virtual QA phantoms in the TPS which were used during verification measurements.

For a conventional 3-D CRT treatment plan, a typical QA method will measure 2-D dose distribution and/or a point dose using an ionisation chamber or a radiochromic film in a water-equivalent phantom. For a more advanced treatment plan, where complex beam parameters are involved, special phantoms are usually required to measure 3-D dose distribution and /or fluence. Commercially available pretreatment phantoms may be a two-dimensional array device or three-dimensional detector array device. The 2-D QA phantoms include the IBA MatriXX 2-D array (Letourneau *et al.*, 2004), and the Sun Nuclear MapCHECK (Jursinic, 2010) which can only be used to validate planar dose distributions. The 3-D QA phantoms are used to overcome this problem and include the Sun Nuclear ArcCHECK 3-D diode array (Li, 2012), the ScandiDos Delta^4 diode array phantom (Bedford *et al.*, 2009), the PTW Octavius 4-D phantom (Urso *et al.*, 2018), and the EPID-based QA systems (Kruszyna-Mochalska *et al.*, 2018; Slosarek *et al.*, 2010).

2.10 Absorbed Dose Prescribing, Recording and Reporting in Radiation Therapy

The International Commission on Radiation Units and Measurements (ICRU) has been providing guidance for over 90 years in the fields of radiation science, radiation medicine, and radiation protection. ICRU's aim is to develop and promulgate internationally accepted recommendations on radiation-related quantities and units, terminology, measurement procedures, and reference

data. It seeks to collect and evaluate data relevant to radiation measurement and dosimetry and to recommend acceptable values and techniques for efficient use in ionising radiation in diagnosis and therapy (ICRU, 2024). The ICRU's recommendations undergo continuous and periodic reviews to keep abreast with the rapid changes in technology in the field of radiation. ICRU has published several reports recommending dosimetry protocols for photon beams (Reports 17, 23, 24, and 64) and other particles (electron beams - Report 29 and 71, neutron beams - Report 45, proton beams - Report 59 and light ion beams - Report 93) (ICRU, 2024).

Aside from developing accurate dosimetry protocols, the Commission has been championing the publishing of reports on radiation oncology regarding the communication and understanding of patient radiation treatment data exchange among the multidisciplinary team. These reports are known collectively as "ICRU Reports on prescribing, recording and reporting in radiation therapy". ICRU Report 50 (ICRU 50, 1993), Report 62 (ICRU 62, 1999), Report 83 (ICRU 83, 2010) to include IMRT and Report 91 (ICRU 91, 2014) for stereotactic beams are recommendations for photon beam radiation therapy. Recommendations on the use of other types of radiations are also published in their Report 71 (ICRU 71, 2004), Report 78 (ICRU 78, 2007), and Report 93 (ICRU 93, 2016) for electron beam, proton beam and light ions respectively. ICRU reports also covered interstitial brachytherapy (Report 58) and cervical cancer brachytherapy with Report 38 and Report 89. In all these ICRU reports, tumour volumes (GTV, CTV, PTV) and organs at risk for various cancer sites were introduced and well-defined, which are being used globally in radiation therapy practice. Currently, ICRU is working on a report that will establish a common language for reporting fractionation schedules, dose prescription, and treatment techniques for optimal cancer patient management. This report will offer a platform to compare clinical results achieved in different facilities throughout the world using different radiation types and protocols

(ICRU, 2024). The Commission feels that it is the responsibility of facilities or National bodies to introduce their own detailed clinical protocols, however, ICRU urges close adherence as much as possible to the internationally recommended basic concepts.

2.10.1 ICRU Report 83, Prescribing, Recording and Reporting Intensity Modulated Photon Beam Therapy

Developments in imaging technology have fueled the drive to implement new methods of delivering 3 - dimensional radiation therapy, such as IMRT and its variant VMAT with very high accuracy. In comparison with the 3-D CRT technique, it is possible with these advanced techniques to escalate the absorbed dose in the target volume while reducing doses to normal tissues, resulting in improved tumour control and less toxicities. The demands on TPS to ensure accurate dose delivery necessitate the employment of complex iterative optimisation processes. ICRU 83 provides information necessary to standardise guidelines and to harmonise the prescribing, recording, and reporting of IMRT with those modalities. Applicable recommendations in other ICRU Reports concerning other radiation therapy techniques are adopted and extended where required in ICRU 83. This Report describes the physical, technical, treatment-planning, and clinical aspects of modulated radiation therapy. ICRU 83 provides a very useful reference for advanced treatment techniques with basic background and requirements for implementing IMRT and its other variants. This Report recommends that a CTV should always be associated with the GTV for malignant tumours while only a CTV is delineated in postoperative irradiation such as in breast cancer treatment. Organs at risk should always be delineated because organs that are not delineated can receive significant radiation absorbed doses from advanced radiation therapy techniques. Contouring these OARs is the first step in controlling radiation dose to normal tissues, which might cause complications. ICRU 83 recommends dose-volume-based specification of

absorbed dose which is accomplished by employing the concept of DVHs. The minimum ($D_{95\%}$) and maximum absorbed doses are not recommended for reporting, but are replaced by the near-minimum, $D_{98\%}$, and near-maximum, $D_{2\%}$, values (ICRU 83, 2010) as shown in Figure 2.16. It also recommends that the median absorbed dose, $D_{50\%}$, should be reported, as it corresponds best with the previously defined dose at the ICRU reference point. Finally, the previous ICRU recommendation (ICRU 50, 1993) of 5% absorbed-dose accuracy is replaced by a statistical measure in ICRU 83.

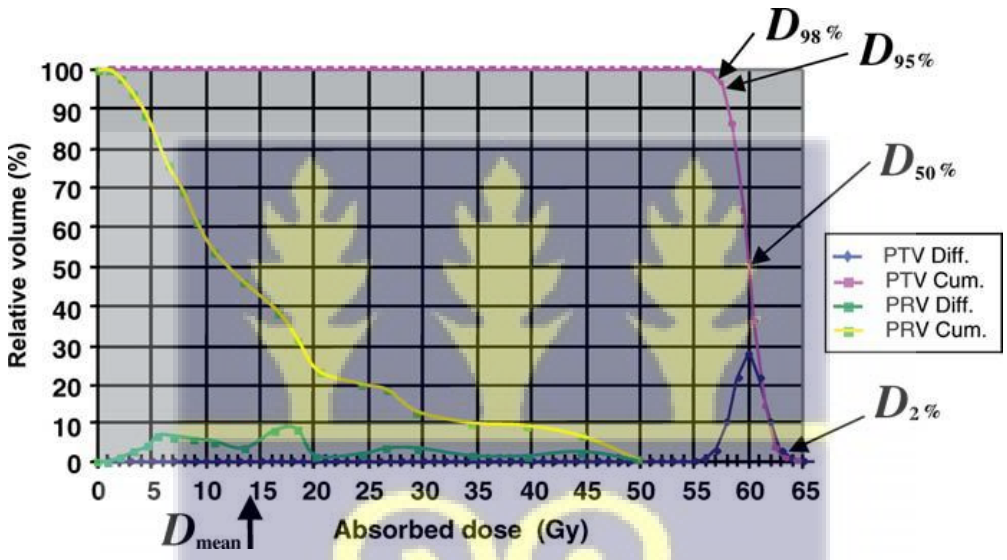


Figure 2.16: Differential DVHs and their corresponding cumulative DVHs indicating the dose–volume metrics, D(near-min) = $D_{98\%}$, $D_{95\%}$, $D_{50\%}$ (median), and D(near-max) = $D_{2\%}$ for the PTV. (ICRU 83, 2010)

Often for IMRT and VMAT planning techniques, the median absorbed dose (D_{median}) is closer to the mean absorbed dose (D_{mean}) for a target volume. Figure 2.17 is a graph from a study conducted by Das (Das *et al.*, 2008) to assess the variability in IMRT planning dosimetry and reporting among cancer patients planned and treated with different TPS. The median absorbed dose was shown to be computed accurately by many of the commercially available TPS used in the study (Das *et al.*,

2008). D_{median} value is also very easy to determine from a tumour target's cumulative DVH. $D_{50\%}$ is a good absorbed dose measure of a dose distribution in a relatively homogeneously irradiated tumour target.

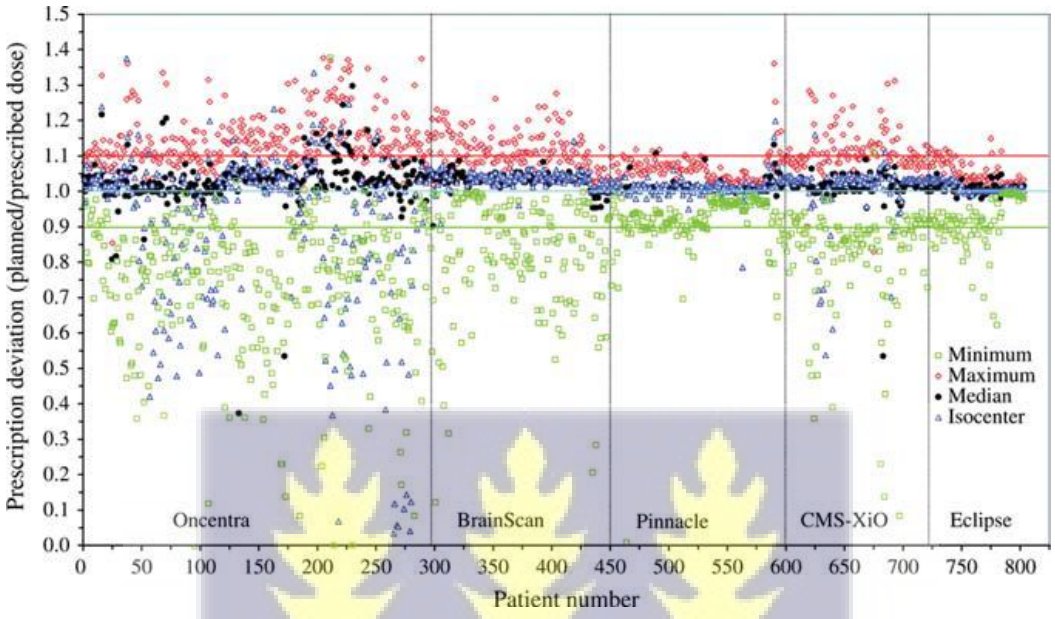


Figure 2.17: Dosimetric deviations between prescribed and planned absorbed doses among 803 patients from five cancer facilities with different TPS (Das *et al*., 2008).

ICRU 83 recommends that in low gradient regions, 85% of target-volume absorbed dose samples should be within 5%. For high gradients, the use of distance-to-agreement (DTA) is recommended instead of absorbed dose. In high gradient regions, the dose distribution should have 85% of absorbed dose samples within 5 mm of the intended position. Therefore, a rigorous QA should be performed to ensure that the planned doses and treatment doses delivered are within the tolerances required for IMRT and VMAT. QA in advanced techniques are demanding and should involve all aspects of the clinical workflow, and the goals of the treatment. The appropriate patient-specific QA is necessary to ensure that the patient receives the prescribed dose as accurately as possible without toxicity. Finally, ICRU 83 recommends facilities to record and retain the dosimetric

parameters of patients for at least the life of the patient plus a minimum of 5 years or in accordance with local regulation (ICRU 83, 2010).

2.10.2 Prescribing and Reporting Levels of Absorbed Dose in Intensity-Modulated Radiation Therapy

ICRU Reports identified three levels (level 1, 2, and 3) of prescribing and reporting absorbed dose and dose volume in radiation therapy (ICRU 50, 1993; ICRU 62, 1999; ICRU 71, 2004 and ICRU 78, 2007). As a recommendation, all information required for level 1 prescribing and reporting should be included in level 2, and that for level 1 and level 2 should also be included when reporting at level 3.

- **Level 1 Prescribing and Reporting Recommendations:** Level 1 is considered the minimum standard for prescribing and reporting required in cancer facilities below which radiation therapy should not be performed. Operating at level 1 is sufficient for simple treatments and implies that knowledge of absorbed doses on the central beam axis (point doses) is known and that simple 2-D absorbed-dose distributions at the central axis are available. Level 1 reporting of absorbed dose at a point is inadequate for radiation planning and treatment techniques like three-dimensional conformal therapy, intensity modulated radiation therapy and volumetric modulated arc therapy.
- **Level 2 Prescribing and Reporting Recommendations:** Level 2 involves the designing of radiation treatments using computational dosimetry and three-dimensional imaging, usually CT images. All regions of interest are defined for level 2 recommendation and 3-D absorbed dose distributions are available which also includes tissue heterogeneity corrections. Dose Volume Histograms for tumour targets and organ at risk volumes are also computed for reporting. Modern TPS have sufficient evaluation tools for level 2 reporting and should be the standard in IMRT and

VMAT. A comprehensive QA programme must also be implemented to ensure that the complex prescribed dose planned is accurately delivered by the treatment machine.

• **Level 3 Prescribing and Reporting Recommendations:** Level 3 prescribing and reporting is an optional research and developmental approach which includes the development of new techniques and/or strategies for which reporting criteria are not yet established. These developmental techniques and strategies under level 3 reporting describe approaches and concepts that are still under development. They have not yet reached a stage at which they are sufficiently established to recommend their routine use in clinical practice. However, their continuous investigations are encouraged, and such concepts include the use of concepts such as tumour control probability, normal tissue complication probability, or equivalent uniform dose (ICRU 78, 2007). Dose homogeneity and dose conformity are also independent specifications of reporting the quality of absorbed dose distribution in target volumes.

Radiotherapy facilities in the developed world focus on developing new treatment planning strategies, techniques and technology aimed at providing maximum tumour coverage with minimal radiation doses to surrounding healthy structures (Thompson *et al.*, 2018). This is mainly achieved through conducting various clinical research/trials into advanced intact breast and chest-wall radiation treatment planning simulations (Zeverin *et al.*, 2018) using computerised treatment planning systems. Unfortunately, on the Africa continent, there is insufficient extensive clinical research and trials on breast cancer radiotherapy treatment and management (Odedina *et al.*, 2020). In the absence of such local research (national or facility-based), radiotherapy facilities then tend to adopt international guidelines that are formulated on the basis of foreign resources (equipment, technology and patient-type data) that may be limited or even lacking on the continent.

CHAPTER THREE

MATERIALS AND METHODS

This chapter outlines the equipment, materials and methodologies that were employed in the research study. The approach and methods that were applied to achieve the study's' objectives have been discussed in this chapter. The research was conducted in four (4) phases and the methodology for each phase has been well explained in this chapter.

3.1 MATERIALS

The materials and equipment used in the study include the following:

- MinFound ScintCare Blue 755 Computed Tomography (CT) scanner (MinFound Medical Systems Co., Ltd, Zhejiang Province, P.R. China)
- Pinnacle^3 Treatment Planning System (Version 16.2.1; Philips Medical Systems, Fitchburg, WI, USA)
- Elekta medical linear accelerator (Infinity Linac, Elekta Inc., Sunnyvale, CA, USA)
- Octavius 4-D 1500 phantom (PTW-Freiburg, Germany)
- BEAMSCAN water phantom with Beamscan software (v4.5) (PTW-Freiburg, Germany)
- Semiflex 3-D Ionisation chambers (0.125 cm^3 / 0.07cc, PTW-Freiburg, Germany)
- Electrometer UNIDOS E (PTW-Freiburg, Germany)
- Water-equivalent Slab phantom (RW3) (PTW-Freiburg, Germany)
- ART-Plan auto-contouring software (Version 1.11.3; TheraPanacea, Paris, France)
- MosaiQ record and verification system (Version 2.81, Elekta Inc., Sunnyvale, CA, USA)

- Onchronos hospital information system (Onchronos RT version, Webtech, Metz, France)
- Verisoft software (Version 8.0, PTW-Freiburg, Germany)
- MEPHYSTO mc^2 software (Version 3.4, PTW-Freiburg, Germany)
- Google web-based survey questionnaires (Google LLC., Mountain view, California, USA)
- Microsoft Excel 2016 MSO (Version 16.0.4390, Microsoft Corporation, Redmond, Washington, USA)
- EPIbeam web-based software (ThinkQA Version 1.0.6.35, Elekta)

3.1.1 CT Simulator Used

A dedicated CT simulator manufactured by MinFound; the ScintCare Blue 755 CT scanner (MinFound Medical Systems Co., Ltd, Zhejiang Province, P.R. China) was used to scan both breast cancer patients and the Octavius 4-D phantom for the study. The CT scanner was manufactured in August 2020 and installed at the cancer facility in December 2020. It is a 64-slice scanner integrated with a fully digital ScintiStar detector with multiple dose control technologies to enable high-resolution dose-efficient scans. It produces high-resolution images with a low radiation dose and an excellent signal-to-noise ratio. The CT scanner employs Nano dose iteration (NDI) algorithm (an innovative iterative technique) for image reconstruction. This technique takes full advantage of deep learning in anatomical structure in image space with the aim to generate sharp images in high resolution at the lowest possible dose. The software of the CT scanner also has a lung reverse scanning technique that helps eliminate respiratory motion artifact (Minfound medical, 2023) especially very useful for breast scans. It is also fitted with a flat couch top and can accommodate an inclined breast board immobilizing device. All selected retrospective intact breast

and chest-wall irradiated patients and the Octavius 4-D phantom used in the study were simulated on this CT scanner.

3.1.2 Pinnacle Treatment Planning System

The Pinnacle treatment planning system (Version 16.2.1; Philips Medical Systems, Fitchburg, WI, USA) provided a comprehensive set of tools for planning and evaluating treatment plans. The TPS software included options for plan simulation for external beam treatment planning with photons, electrons, stereotactic radiosurgery and proton, as well as brachytherapy planning. The Pinnacle TPS software operated within the DICOM (Digital Imaging and Communications in Medicine) standards and the manufacturer's conformance statement for DICOM as developed by the American College of Radiology (ACR) and the National Electrical Manufacturers Association (NEMA) (Philips Healthcare, 2023). These made the transfer, storage, archiving, retrieval, processing, display and analysis of patient data possible.

3.1.2.1 Photon-Specific Dose Calculation

In the Pinnacle TPS, all doses were presented in terms of cobalt-equivalent effective doses and not the physical doses. The two doses were related through the relative biological effectiveness (RBE) factor, which was equal to 1 for photon beam, hence making the two doses numerically equivalent. While it is difficult to manually compute the doses/monitor units in a complex patient geometry, the TPS software enabled analysis on how final dose calculations were affected by individual patient anatomy. The dose calculation software considered changes in dose and MUs throughout the patient's body curvature. The software modifies the primary scatter using the patient density, and finally the secondary scatter using tissue heterogeneities (Philips Healthcare, 2023). The following dose computation algorithms or engines were available for dose calculations:

- **Fast Convolve Computation:** It performs a convolution superposition calculation with fewer ray directions used for the scatter calculation. It is less accurate near the surface and in the penumbra region, with the maximum error typically being less than 5%. It was not recommended for clinical use and was not used for the study.
- **Adaptive Convolve Computation:** It performs adaptive sampling during convolution dose calculation. This algorithm reduces computational time by sampling every fourth point in the dose grid and interpolating dose in flat areas. It is recommended for clinical use especially for shorter optimisation time and was used in this study.
- **Collapsed Cone Convolution Computation:** It performs a full computation superposition calculation. It interpolates accurately for every point in the calculation grid and was recommended as the clinical computational algorithm of choice for dose/MU calculations. CCC increases the optimisation time especially for VMAT plans.

3.1.2.2 Inverse Planning VMAT Technique

Inverse planning volumetric modulated arc therapy is a treatment planning technique in Pinnacle that uses beams with varying intensities to conform the high dose region to the target volume while sparing normal tissue structures. This enabled dose escalation and improved local tumour control as well as reduced normal tissue complications. Beam intensities were modulated using MLCs. The term "inverse" is used because the planning process begins with the desired solution in terms of dose distribution and the TPS software develops the desired treatment plan. The basic workflow for creating an inverse planning VMAT treatment plan for breast cancer was as follows:

- Importing patient image data

- Creating regions of interest (ROIs) for both target and critical structures.
- Adding points of interest (POI), beams and isocentre.
- Setting up a dose calculation grid and isodoses
- Adding the prescription(s)
- Setting up dose volume histograms (DVHs) for all the ROIs
- Adding treatment planning objectives and constraints.
- Selecting the optimisation parameters for the beams and optimising the plan
- Computing the final dose distribution and reviewing plan
- Exporting plans for all necessary quality assurance procedures and treatment.

3.1.2.3 Treatment Planning Automation

Auto-planning or plan automation allows for a rapid creation of high-quality treatment plans based on clinical goals using SmartArc optimisation in Pinnacle. This is a commercially available automation solution in Pinnacle TPS. The user can generate a treatment technique template which has the target prescription and goals for OAR sparing according to the facility's protocol. The Pinnacle software will automatically generate dummy optimisation structures based on the PTV and OARs defined by the user. The generated optimisation structures together with other defined settings will aid the software to automatically generate starting optimisation criteria for onward iterative optimisation cycles and fine tuning to achieve a solution based on the predefined clinical protocol set by the user (Hansen *et al.*, 2016). In Pinnacle TPS, the following tools can help to automate the treatment planning tasks (Philips Healthcare, 2023):

- **Auto-Segmentation:** Auto-Segmentation is a tool that automatically produces contours for normal tissues in CT image sets. It comes pre-loaded with factory atlases, which include the abdomen, head and neck, male pelvis, and the thorax atlases.
- **Auto-Planning Techniques:** The Auto-Planning techniques are templates for a standard IMRT and VMAT trial that includes ROIs, POIs, beams, prescriptions, and clinical goals. This can be applied to rapidly create a standard SmartArc plan trail and then optimised for desired results.
- **Auto-Planning:** Auto-Planning tools allow to automate the SmartArc optimisation trial process. Targets and organs at risk goals can be set and then allow the Auto-Planning engine to complete the VMAT planning process.
- **Protocols:** Protocols are stored settings of objectives, constraints, and optimisation and conversion parameters. Protocols for common classes of treatment specific to the facility can be created and stored.
- **Scripting:** The scripting allows for recording and playing back scripts of software operations. Scripts can be written using computer programming language for all the processes in the planning procedures. It can be used for everything from repeating very simple operations, such as setting the window and level for a different body site, to complex beam setup operations. Scripting was used in the automated planning of all the VMAT breast treatment plans in this study with Python programing language.

3.1.2.4 Plan Evaluation Tools

The Pinnacle planning system provided a variety of tools for evaluating and comparing treatment plans. Once the doses were computed, the dose distributions were displayed with patient data. They can be displayed both in 2-D as colour wash and as isodose lines and in 3-D as solid or

transparent surfaces. Point dose information can also be obtained for any point in the patient volume. The dose distributions for various ROIs were also evaluated with DVHs, it provided plots of normalised or absolute doses versus normalised or absolute volumes. However, DHVs do not provide any spatial information about the dose distribution within a given volume. The TPS software was used to generate biological response comparisons as well. It was used to view and analysed the radiobiological response probability based on biological responses for ROI selected. The default TPS's biological response probabilities were evaluated using the Kallman S-model (Kallman *et al.*, 1992) while the normal tissue complication probability and tumour control probability response values were based on the Lyman-Kutcher-Burman model (Lyman *et al.*, 1985; Kutcher *et al.*, 1989).

3.1.3 Elekta Infinity Linear Accelerator

The Elekta Infinity (Elekta Inc., Sunnyvale, CA, USA) is a high-end, high-performance medical linear accelerator. It offers clinical freedom to optimally treat a diverse range of patients with simple-to-complex radiotherapy needs. The full field, high-definition beam shaping device of Agility MLC provided superior target conformance. The Agility head utilises a 160 x 5 mm leaves (80 pairs of MLC of 5 mm width at isocentre) across full 40 cm x 40 cm field size. It has a 15% larger dynamic field size and fast leaf speed up to 6.5 cm/s that enable effective coverage and treatment of complex targets (Elekta, 2023). It delivers dynamic treatments with more than twice the leaf speed of other LINACs making it very convenient for VMAT treatment delivery. Infinity offered rapid beam shaping and ultra-low transmission, reducing dose to critical structures and healthy tissue. The combination of ultra-low MLC leakage and high dose rate mode reduces non-therapeutic body dose up to 70% (Elekta, 2023). It used Rubicon optical technology for real-time

MLC leaf positioning and monitoring that gave reliable high-performance precision. The Elekta Infinity LINAC, equipped with Agility, facilitates the delivery of sophisticated image guidance treatments. The high performance of Agility and VMAT did not only offer reduced treatment time, but it also reduced the uncertainties due to intrafractional motion. Patients also benefitted from the more precise adaptation to target volumes and thus increased sparing of organs at risk (Elekta, 2023). During treatment, processes of verification take place using an in-built imaging device on the Elekta Infinity LINAC to take images of the treatment site. These images were used to verify both the patient's position and the accuracy of the treatment beam. Cone beam computed tomography technology integrated within the Infinity LINAC provided volumetric imaging at the time of treatment setup to aid patient position accuracy. It also has iViewGT imaging that provides 2-D megavoltage planar images within a fraction of a second, making on-line patient position correction possible. This was also used to validate the planned and delivered doses of the different treatment plans using its electronic portal imaging device.

3.1.4 PTW Dosimetry Equipment

PTW is a global market leader for dosimetry solutions in radiation therapy, diagnostic radiology, and radiation monitoring. For radiation therapy, PTW provides dosimetry equipment for machine-related QA, patient-related QA and for different radiation therapy treatment modalities (PTW, 2017). The dosimetry equipment employed in this study were the BEAMSCAN water phantom, Octavius phantom, ionisation detectors, patient QA solutions, electrometer, and its associated QA software.

3.1.4.1 Octavius 4-D 1500 Phantom

Octavius 4-D 1500 phantom is a one system for patient and Linac quality assurance. Its innovative modular design, coupled with the best detector technology, makes it an ideal system for routine patient and machine QA of major radiotherapy techniques. It was used for 3-D dose verification in phantom and patient geometry with its rotating phantom offering a true 3-D and true isotropic geometry. It comes with a cutting-edge detector technology based on gold standard ionisation chambers. The Octavius phantom was used in the verification of all intact breast and chest-wall radiation therapy plans. The phantom does not require data input from the Linac for dose measurement and 3-D dose reconstruction. A simple set of percentage depth doses measured in water was required for its commissioning. Unlike other commercially available systems, Octavius 4-D is completely independent of environmental settings and guarantees maximum reliability in patient QA procedures. It ensured perpendicular irradiation of the PTW array detector through synchronous phantom rotation with the Linac gantry. Besides standard VMAT or IMRT deliveries Octavius 4-D covers a wide range of clinical applications including special applications like verification of treatment plans with non-coplanar beams, verification of large fields, verification of extremely off-axis lying target volumes or verification of treatments with multiple energies. Octavius 4-D's user interface software Verisoft, provides powerful 3-D dose comparison and evaluation tools necessary to verify IMRT, VMAT or SRS/SBRT treatment plans. It computes 3-D gamma analysis, DVH analysis in patient anatomy, profiles, dose-difference distributions and dose distribution overlays. Unlike other QA devices, DVH 4-D calculates patient dose-volume histograms that are truly independent of the TPS but entirely based on Octavius 4-D 1500 measurement data and the patient's anatomy, using density values from the patient's CT scan (Patent No. D913.200.08/01, 2017).

3.1.4.2 BEAMSCAN Water Phantom

BEAMSCAN water phantom comes with software that makes it easy to collect, analyse, process and format beam data. It was used in the verification of the Linac acceptance and commissioning data, TPS beam data commissioning verification, and Octavius phantom commissioning. It is an all-in-one 3-D water scanning system with wireless (iPod and Wi-Fi connection) auto setup and operation. Its driving mechanism consists of a stainless-steel worm gear drive with three stepper motors. It can scan both in continuous and step-by-step mode with a scanning speed of up to 20 mm/s, and 0.1 mm minimum step size. It has a total dimension of 1548 mm (Length) x 783 mm (Width) x 1298 mm (min. height) /1798 mm (max. height) with a total weight of approximately 240 kg (empty), and approximately 440 kg (filled). The 3-D water tank is made from a PMMA material of 15 mm wall thickness and has a scanning range of 500 mm (X horizontal) x 500 mm (Y horizontal) x 415 mm (vertical). It has a built-in electrometer with two channels for field and reference detector connections (vented waterproof cylindrical ionisation chambers) (PTW, 2019).

3.1.4.3 Ionisation Chambers

Ionisation chamber detectors suitable for photon dosimetry were used in the study. Detectors for radiation therapy were available for relative dosimetry, reference dosimetry, and small field dosimetry. The detectors for relative and reference dosimetry used in the study were the:

- **MicroDiamond Synthetic Diamond Detector:** The microDiamond is the first commercially available single crystal diamond detector (SCDD) suitable for clinical dosimetry. As a synthetic diamond detector, which is reproducibly manufactured in a new innovative production process, it combines the advantages of natural diamond detectors and silicon diode detectors almost perfectly. Due to its special design and material properties, microDiamond shows almost no deviations in absorbed dose to

water even in the smallest field sizes, making it a perfect choice for accurate small field dosimetry. It has a very small sensitive volume (0.004 mm^3) which is a perfect choice for small field dosimetry.

- **Semiflex 3-D:** The semiflex 3-D detector is a vented, waterproof, fully guarded thimble ionisation chamber ideal for relative and reference dosimetry measurements in water, air or solid-state phantoms. It comes with exceptional dosimetric characteristics suitable for reference dosimetry following standard dosimetry protocols like the IAEA TRS-398, AAPM TG-51, and DIN 6800-2. It has a small size of 0.07 cm^3, a high spatial resolution perfect for measurements in small and flattening filter free (FFF) fields down to a field size of 2.5 cm x 2.5 cm. Semiflex 3-D meets and exceeds the performance requirements of a reference-class ionisation chamber as laid out in AAPM TG-51 and IEC 60731 (These have minimal polarity effect, very low post-irradiation leakage, extremely low volume effect, reliable k_Q and k_S values). Semiflex 3-D detectors are used for Linac acceptance testing, TPS beam data commissioning, clinical reference dosimetry and point dose measurements (PTW, 2017).
- **Semiflex Ionisation Chamber 0.125 cm^3:** This ionisation chamber type 31010 is a standard radiation therapy chamber for scanning systems and for reference dosimetry. It has a sensitive volume of 0.125 cm^3 which is vented and waterproofed. The chamber is the ideal compromise between small size for reasonable spatial resolution and large sensitive volume for precise dose measurements. The sensitive volume gives enough signal to use the chamber for high precision reference dose measurements. The sensitive volume is approximately spherical resulting in a flat angular response and a uniform spatial resolution along all three axes of a water phantom (PTW, 2017).

3.1.4.4 UNIDOS E Electrometer

The UNIDOS E electrometer is a microprocessor-controlled universal dosemeter for the measurements of dose in radiotherapy and diagnostic radiology. It corresponds as a field class therapy dosemeter to the standard IEC 60731 and as a diagnostics dosemeter to the standard IEC 61674. It displays reading in radiological units (in Gy) or electrical units (in nC) for the measurement of dose/charge and dose rate/current with ionisation chambers and solid detectors. UNIDOS E has a chamber menu for the storage of up to 35 ionisation detectors and high voltage adjustable in 50 V intervals from 0 to ± 400 V (PTW, 2017).

3.1.4.5 VeriSoft Software

VeriSoft software was used in performing volumetric 3-D gamma index analysis that ranged from a plane to a volume with great accuracy. It calculated the gamma value for each voxel in the entire phantom volume and provided the results within less than a minute. VeriSoft supports the control of all available PTW Octavius solutions necessary to verify IMRT, VMAT or SRS/SBRT treatment plans. It provides powerful 3-D dose distribution comparison and evaluation tools needed to answer the question "Does the patient plan agree with my acceptance criteria?" with full confidence. In addition to all standard comparison tools, VeriSoft gives a full range of advanced tools for comparison in axial, sagittal and coronal planes.

It does not only improve passing rates, particularly in regions of steep dose gradients, but also significantly increases evaluation efficiency. Failed points, measured isodoses, contours of the CTV, PTV and organs at risk can be overlaid onto the patient's CT image, making it easier to immediately detect dose errors and identify the possible causes for failures. This can be used to optimise treatment plans based on additional, independently acquired dose data. Verisoft enabled calculating not only the 2-D but also 3-D gamma index for each of the three planes (axial, sagittal,

coronal), which may reduce the number of failed points in high dose gradients. If local dose is chosen as gamma evaluation criterion, overdosage in low dose regions can be detected which may be overseen when using the maximum dose level as reference value. Verisoft allows evaluation of verification data depending on user-defined criteria for different types of treatment (e.g., breast, prostate, head & neck, etc.), treatment techniques (VMAT, IMRT, SBRT, etc.) or photon energy (PTW, 2017).

3.1.4.6 Gamma Index

Gamma index established by Low et al. has become the standard technique used to compare two dose distributions in radiotherapy (Low *et al.*, 1998). It integrates both percent dose difference (DD) and distance-to-agreement (DTA) concepts to calculate an index for each point in the evaluated distribution. DTA is the distance between a measured dose point and the nearest point in the calculated dose distribution that shows the same dose value. It compares the dose difference between the calculated and measured dose values directly within the low and high dose gradient regions. In these regions, the DTA concept is used to evaluate the acceptability of the dose calculation. A gamma value less than 1 indicates that the evaluated point has passed the DD/DTA criteria. The gamma index is represented by the total percentage of points that have passed a given DD/DTA criteria (Hussein *et al.*, 2013). Although the DD/DTA criteria of 3%, 3 mm are widely used as standard QA evaluation criteria for gamma index (Nelms *et al.*, 2007), studies suggest that these criteria are not sensitive enough to provide optimal results in VMAT comparison, and tighter tolerances such as 2%, 2 mm should be adopted (Nelms *et al.*, 2013; Crowe *et al.*, 2016). In this study, gamma index criteria of 3%, 3 mm was used for Octavius measurement analysis and gamma index criteria of 2%, 2 mm was used for the EPIbeam measurement analysis with 90% and 95% passing criteria, respectively.

3.1.4.7 PTW Water-Equivalent Slab Phantom (RW3)

The PTW RW3 slab phantom (PTW-Freiburg, Germany) is water-equivalent for the energies ranging from Co-60 to 25 MV photons. This water-equivalent solid phantom is used for absolute dose or monitor unit calibration and quality assurance measurements. The slabs come in plate thicknesses of 1 mm, 2 mm and 5 mm with a complete phantom size of 30 cm x 30 cm x 30 cm. This makes it possible to vary the measurement depths up to 30 cm in increments of 1 mm as well as providing backscatter when the slabs are placed below the measuring point. It also provides adapter plates for a number of ionisation chamber types for measurements. The PTW RW3 phantoms were used to perform both dose measurements in the TPS (solid phantom) and dose output measurements on the Linac (PTW, 2017).

3.1.4.8 BEAMSCAN Software

BEAMSCAN is a PTW scanning software with advanced functions and tools that help obtain accurate beam data much faster. It instantly analysed scans based on preset quality criteria or dosimetry protocols and compared multiple scans with reference scans within seconds and helped spot any critical deviations immediately. It has an automatic water level check and reminder for efficient evaporation control during long data collection periods. It saved measurement time and improved scan quality with artificial intelligence-based (AI-based) data processing. There is a variety of mathematical functions and filters that aid in visualisation and data analysis. Commissioning data verification and Octavius commissioning measurement with PDDs, beam profiles (in-line, cross-line, diagonal) and point dose were performed using BEAMSCAN software apart from the regular PDDs and beam measurements (PTW, 2017).

3.1.5 EPIbeam On-line Software

EPIbeam is a web-based software used to validate external beam radiotherapy beams along with the electronic portal imaging device (EPID) in pretreatment conditions. It compares the planned doses calculated from the TPS to the delivered doses measured from the Linac using the MV EPID. This is a patient-based quality assurance carried out prior to the first fraction to ensure the correct dose delivery. This dose validation method does not involve the use of phantoms which sometimes introduce error due to their setup. EPIbeam is dedicated to EPID-based pretreatment quality control check for photon beams especially for rotational and fixed-gantry intensity modulated radiotherapy techniques. EPIbeam relies on the comparison of actual images and reference images expressed in terms of absolute dose. The RT plan which is defined in the TPS is used to acquire the actual (test) portal image at the Linac in open EPID condition. The reference (predicted) portal image on the other hand, is the same RT plan used to compute a theoretical portal image in open EDIP condition as described in Figure 3.1. Specific algorithms are then respectively applied to express both the actual and reference images in terms of absolute dose (DOSIsoft, 2019). Each portal image and its reference dose are taken at the treatment machine after importing the DICOM RT Plan from the planning system. The EPIbeam software automatically performs the association of image data and DICOM RT file together with the stored measurements for computation (DOSIsoft, 2019).

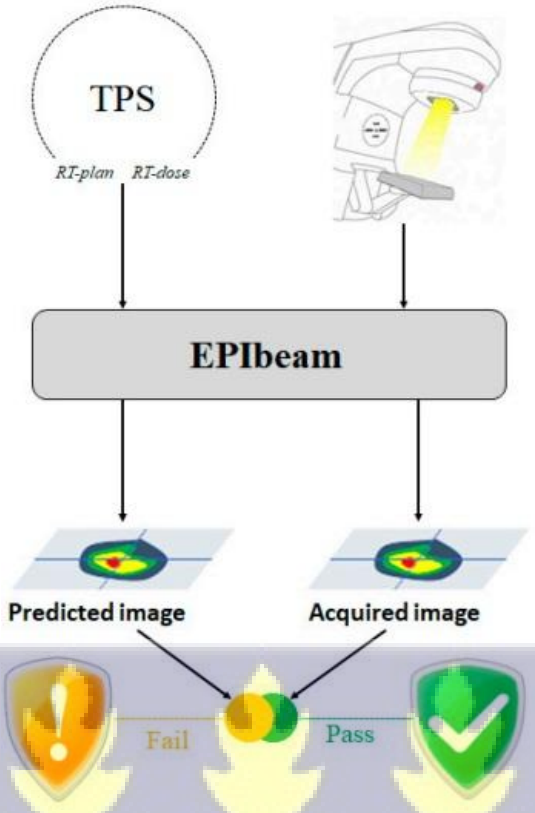


Figure 3. 1: Calibration of the EPID-based QA measurement set-up

3.1.6 Online Survey Design

Google online survey forms were used to create customised questionnaires for the breast cancer external beam treatment survey. The questionnaires provided various answer selection options, from multiple choice question types, drag-and-drop to customise values. All the inputs and responses were collected and data analysed in the google spreadsheets. It was easy to share questionnaires with target groups or with a broad audience by embedding the forms on a website or sharing the links using emails and social media. The forms were created, accessed, and edited on-the-go on computers or mobile phones. Target audiences also responded to the survey using any mobile device, tablet, or computer. The charts with response data update can be seen in real-time or the raw data can be opened with google sheets for detailed analysis and graphical presentation.

3.1.7 Date Analysis

The data obtained from all the phases of the study were stored and statistically analysed using Microsoft Excel 2016 MSO version 16.0. To validate the significant effect during the third phase of the study, all mean values were compared using the paired sample t-test at 5% significance level to indicate any significant difference (p-value < 0.05) between the two datasets. Using the paired sample t-test, the null hypothesis was that the mean of the difference between the paired observations in the two samples was zero. A null hypothesis is a statistical inference by which an experimental factor is tested against a hypothesis of no effect or no relationship based on a given observation. If the calculated p-value was less than 0.05, the conclusion is that, statistically, the mean difference between the paired observations was different from 0, hence statistically significant and test hypothesis were false and should be rejected. On the other hand, if the p-value was greater than 0.05, then there exists a probability that the null hypothesis set were true and that no effect was observed. To validate the significant effect during phase four of the study, the mean and standard deviation values were reported for any relevant statistically significant using the one-way ANOVA (Analysis of Variance) with Tukey-Kramer Post-hoc Test. The significance difference value of 5% significance level was considered to be statistically significant (p-value < 0.05) between the three planning cohorts with respect to planning repeatability and reproducibility.

The Microsoft excel spreadsheet's data analysis tool was used to run all statistical tests. During the data analysis, the t-test: 'Two sample assuming equal variances' option was selected, and the P (T≤ t) two-tail was the most important p-value result recorded for phase 3. During the data analysis in phase 4 of the study, the Anova: single factor option was selected. This was a one-way ANOVA test to analyse if the single independent factor (the proposed optimisation criteria) had a measurable effect on the plan quality (PTV dose distributions and OARs sparing). A p-value ≤

0.05 was considered statistically significant. A Tukey-Kramer Post-hoc test was then conducted to determine if the relationship between any two sets of plans (REF, PLAN1 and PLAN2) is statistically significant. It should be noted that any p-value of 0.000 will be stated as $p < 0.001$. The one-way ANOVA data analysed in the Microsoft excel spreadsheet were used to perform the Tukey-Kramer Post-hoc test using the formula below:

$$TSD = q\sqrt{\frac{MS_w}{nk}} \qquad 3.1.1$$

where;

TSD is the Tukey Significant Difference,

q is a constant (derived from the Studentised Range Q table),

MS_w is the mean square within the groups (variance across all groups),

nk is the sample size for a given group.

The Microsoft excel software was also used to design the facility's "*PlanAccept*" for breast treatment planning. The "*PlanAccept*" was an evaluation tool developed with defined facility clinical goals to help in achieving an optimal breast plan. The primary goals and secondary goals were defined for all ROI parameters. For dose goals which required percentage volume, the volume for the said dose goal was set. A dose goal that could not meet the primary dose goal (ideal) was referred to as the secondary dose goal (acceptable) which was mostly less stringent but was acceptable. The spreadsheet displayed results of the goals as follows:

- MET – When the primary goal for the dose is met (green),
- OK – When the primary goal for the dose is not met but the secondary goal is met (yellow),
- FAILED – When neither the primary goal nor secondary goal for the dose is met (red).

The "*PlanAccept*" can be used to evaluate plan quality during the treatment planning process and prior to plan approval. To validate this, the designed "*PlanAccept*" was used to evaluate a breast plan by inputting test dose and volume values into the sheet.

The percentage changes (difference) for the two cohorts of plans in terms of their dosimetric values and radiobiological values were calculated using the formula below:

$$C = \frac{(X2-X1)}{|X1|} x100 \qquad 3.1.2$$

where;

C is the relative change,

X1 is the initial value (PAC-based automated cohort plans),

and X2 is the new or final value (POC-based manual cohort plans).

3.1.8 Sample Size

In phase two of the study, a censor sample size of all breast conserving surgery (referred to as intact breast in the study) and post-mastectomy (referred to as chest-wall in the study) patients planned and treated with automated VMAT technique at the cancer center during study period were considered as the sample size.

In the third phase, the sample size calculation for testing hypothesis especially for clinical trials and clinical interventional studies was used. This calculation was useful for this kind of research design where one wanted to observe the effect of an intervention. The estimation of sample size for phase 3 was calculated with the Charan and Biswas' formula below (Charan *et al.*, 2013).

$$N = \frac{2SD^2\,(Z_{\alpha/2}+Z_{\beta})^2}{d^2} \qquad 3.1.3$$

where;

N is the total sample size,

SD is the assumed standard deviation from previous studies or pilot study,

$Z_{\alpha/2}$ is the standard normal variate at type 1 error of 5%,

Z_{β} is the standard normal variate for statistical power at 80%,

d is the effect size or difference between mean values.

Using 5% error margin ($p < 0.05$) since p-value ≤ 0.05 was considered statistically significant in the study, the $Z_{\alpha/2}$ value for the desired significant criterion is $Z_{0.05/2} = Z_{0.025} = 1.960$ as shown in table 3.1 on the Z-table. The desired Z_{β} value at 80% statistical power is $Z_{0.20} = 0.842$ as shown in table 3.2.

So now the formula will be

$$N = \frac{2SD^2\,(1.960+0.842)^2}{d^2} \qquad 3.1.4$$

The minimum effect size (d) from phase 2 was 2.64 Gy. From the previous dosimetric estimation in phase 2, the mean dose to the contralateral breast be reduced by approximately 2.64 Gy to be considered clinically significant. The standard deviation (SD) found in the previous study was 2.87 Gy. These contralateral breast values when used in the sample size estimation resulted in the biggest sample size out of all the calculated N values for the PTV and other OARs metrics. Both $Z_{\alpha/2}$ and Z_{β} are derived from the standard normal probability distribution table (tables 3.1 and 3.2)

along the x-axis that demarcates the matching probabilities for the specified significance standard normal variate and statistical power, respectively (Charan *et al.*, 2013).

Table 3.1: Standard normal variate $Z_{\alpha/2}$ corresponding to selected significance criteria on standard normal probability distribution.

Significance Criterion	$Z_{\propto/2}$ Value
0.01 (99)	2.326
0.02 (98)	2.326
0.05 (95)	1.960
0.10 (90)	1.645

Table 3.2: Standard normal variate Z_{β} corresponding to the selected statistical powers on standard normal probability distribution.

Statistical Power	Z_{β} Value
0.80	0.842
0.85	1.036
0.90	1.282
0.95	1.645

$$N = \frac{2(2.87)^2\ (1.960 + 0.842)^2}{2.64^2}$$

$$N = 18.56$$

From the same breast cancer treatment database and according to the sample size estimation, 20 left-sided cancer patients were randomly selected using the Microsoft Excel spreadsheet's random sample without duplicates (RAND, INDEX and RANK) functions for the third phase of the study. These patients were selected to include ten (10) patients planned and treated for left-sided intact breast and ten (10) left-sided chest-wall irradiated cases. In probability theory, the 20 random sample is the data subset selected from the larger 61 left-sided breast planning dataset or the study population. Each of the 20 random patients was chosen entirely by chance with an equal probability of being selected. This represents the non-biased representation of the 20 selected patients from the total population.

3.1.9 Research Ethics

All human investigations must be conducted according to the principles expressed in the Declaration of Helsinki (Lie *et al.*, 2004). The study protocol was reviewed and approved by the ethics committee of the Basic and Applied Sciences, University of Ghana, (ECBAS 009/21-22) to retrospectively collect and analyse patient data. Informed consent for the study was not necessary since no direct involvement with any patient was required. However, permission was sought from the radiotherapy department of Centre International de Cancerologie de Lomé to access its treatment plan database. Copies of the ethical clearance approval and Institutional approval for this clinical research are presented in the appendix section.

3.2 METHODS

"The study was conducted in four phases, each detailed below.

3.2.1 Subjective Experimental Method for Phase 1 (Breast Survey)

Ghana has three radiotherapy facilities, catering to a population of approximately 32 million (Gaisie *et al*., 2014). These three facilities were the target of the questionnaire: the national radiation oncology and nuclear medicine center (NRONMC), oncology directorate of the Komfo Anokye teaching hospital (OD-KATH) and the Sweden Ghana medical center (SGMC). To achieve the purpose of the survey, questionnaires were developed and rigorously refined in collaboration with the survey team. The European Organisation for Research and Treatment of Cancer-Radiation Oncology Group (EORTC-ROG) survey framework (Van der Laan *et al*., 2010) served as a guided reference.

The study employed two web-based surveys hosted on Google Forms. An initial survey was hosted from August 21, 2020, to December 31, 2020. It had 54 questions on general EBRT for breast cancer irradiation. The follow-up survey was from February 15, 2021, to March 31, 2021, with 14 targeted questions covering dose fractionation schemes, treatment target definitions and organs-at-risk delineation. The general questionnaire targeted radiation oncologists (ROs), medical physicists (MPs), and radiation therapy technologists (RTTs). It explored general aspects of breast cancer management in Ghana and gathered broad, facility-level insights from the three radiotherapy centres. The questionnaire covered a range of topics related to breast cancer treatment, including patient numbers, total number of cases treated yearly, and annual number of intact breast and chest-wall patients treated. It also included treatment planning details, utilisation of 2-D and 3-D treatment planning techniques, treatment planning techniques employed and plan acceptance criteria. Radiation therapy aspects regarding target definition, OARs, position

verification, radiation types, energies, dose fractionation, bolus usage, imaging protocols, innovative strategies and future potential adoption of advanced technologies were covered in questionnaire one. To ensure a comprehensive understanding and verify consistency, multiple responses were solicited from each facility. The follow-up questionnaire, specifically designed for radiation oncologists, was administered to gather more detailed information on dose fractionation regimens, breast clinical target volume to planning target volume margins. This supplementary questionnaire aimed to clarify certain ambiguous responses from the initial survey and to provide deeper insights into radiation oncology practices.

The questionnaires primarily consisted of closed-ended questions, requiring minimal explanatory text. The response formats included Multiple-Choice Questions (MCQs), checkboxes (select multiple options), dropdown menus, and quantitative questions (numeric responses). Google web-based questionnaires were distributed through various channels including official professional WhatsApp groups, direct emails, personal phone messages, and colleague referrals (reshared by recipients). To maximise participation, reminders and follow-ups were sent regularly. Additional clarification was sought through discussions with the key correspondents from the three radiation therapy facilities. The survey yielded responses from radiation therapy professionals across all three facilities. The responses were collected online and data analysed using Microsoft Excel spreadsheet. Since the survey did not involve patient data or direct patient participation, ethical clearance and informed consent were not required. However, permission was obtained from the targeted radiation oncology professionals in the three RT facilities (Acquah *et al.*, 2022).

3.2.2 Experimental Method for Phase 2 (Establishing plan acceptability criteria)

Treatment plans for intact breast and chest-wall cancer patients treated with VMAT at the study site were retrospectively evaluated for a 2-year period. Patients with conserved breast and

lumpectomy treated with standard 50 Gy radiation in 2 Gy fractions were included in this study. Data collected from each patient's plan were their ages, breast separation and laterality, PTV for optimisation (PTV_opt) and normal body/external, ipsilateral lung volume, heart volume for left-sided cases, contralateral lung volume and contralateral breast volume. For each VMAT treatment plan, the following target and OAR volume dosimetric parameters were collected; and intact breast/chest-wall optimisation volumes (Brst_opt/Chst_opt), minimum dose, maximum dose, mean dose and the standard deviation were calculated. The dose-volume histograms for all contoured structures were also analysed using various percentages of the prescribed dose and given volumes. For all PTV used for optimisation, their $V_{90\%}$, $V_{92\%}$, $V_{95\%}$, $V_{100\%}$, $V_{105\%}$, $V_{107\%}$, $V_{108\%}$ and $V_{110\%}$ (volume receiving a certain percentage of the prescribed dose) were derived from PTV DVHs and recorded. Additional attention was focused on volumes receiving 95% (47.5 Gy) of prescribed dose (V_{95}) and 105% (52.5 Gy) of prescribed dose (V_{105}). The PTV dose indices calculated were the homogeneity index, uniformity index, conformity index (Acquah *et al.*, 2023).

3.2.2.1 Patient Characterisation

A total of 94 intact breast and chest-wall cancer patients treated between January 2021, and January 2023 were analysed. These patients were planned using an automated VMAT planning script using python programming on a Pinnacle treatment planning system with adaptive convolution algorithm. Bilateral intact breast and chest-wall patients as well as patients with boost doses were excluded from the study (Acquah *et al.*, 2023).

3.2.2.2 Patient Dose Planning CT Simulation

To initiate radiation therapy planning, radiation oncologists at the study site would request for a pretreatment CT simulation scan. During scanning, patients assume a supine position, entering the scanner headfirst with their arms elevated above their head. For optimal comfort and positioning,

patients' arms were supported by a dedicated breast board, while a Kneefix was placed under their knees. To maintain patient dignity, only the upper body on the affected side is exposed, from the waist up. A suitable headrest was utilised to stabilise the patient's head, which was gently turned away from the affected breast side. These measures ensure precise and comfortable CT simulations for effective radiation therapy planning.

To facilitate accurate visualisation, radiopaque wires were carefully positioned along the surgical scar and surrounding breast tissue. Utilising laser guidance, permanent reference marks (tattoos) were applied to the patient's thoracic region during simulation to ensure precise setup alignment. Three strategic locations received these tattoos: the left and right lateral aspects, as well as the anterior surface, with small ball bearings (BBs) assisting in their precise placement. To guide target delineation, radiopaque wires were meticulously positioned along the breast and chest-wall scars. All patients underwent CT scanning using the MinFound ScintCare Blue 755 scanner (Minfound Medical, 2023), employing the facility's standardised free-breathing protocol with a slice thickness of 2.5 mm. The acquired CT DICOM dataset was exported to the local image server and subsequently uploaded to the ART-PLAN automated contouring software and TPS for further processing and planning (Acquah *et al.*, 2023).

3.2.2.3 Patient Automated 3-D Volume Delineation

The CT scan data was seamlessly imported into ART-Plan (Version 1.11.3; TheraPanacea, Paris, France), the facility's designated automated contouring software. ART-Plan efficiently contoured associated organs-at-risk and breast/chest-wall volumes, leveraging its advanced algorithms. Figure 3.2. demonstrates the software's exceptional accuracy in breast contouring, exceeding 90%, with only minor adjustments occasionally required by radiation oncologists. The system precisely delineated critical structures, including the heart, ipsilateral and contralateral lungs, and

contralateral breast. Although ART-Plan automatically contoured intact breast and chest-wall volumes, radiation oncologists reviewed and validated these contours to ensure accuracy. Upon approval, the verified 'RTStructure' set comprising clinical target volumes and OARs was exported to Pinnacle via DICOM application (Acquah *et al.*, 2023).

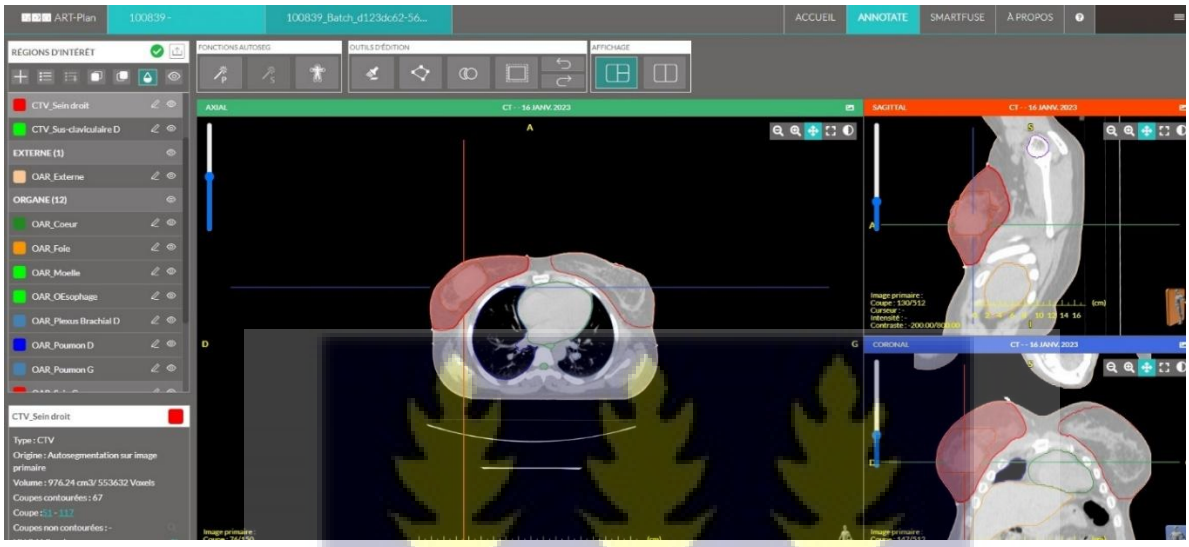


Figure 3. 2: Axial, sagittal, and coronal views of an automated intact breast target volumes with its associated OARs done by the ARTPLAN software.

3.2.2.4 VMAT Automated Patient Treatment Planning

The validated contoured patient dataset was exported to Pinnacle[3] Treatment Planning System-version 16.2.1 (Philips Medical Systems, Fitchburg, WI, USA). The contours were seamlessly integrated into patient images, which already contained demographic information stored in the TPS. The appropriate CT number to electron density conversion table was selected to ensure accurate calculations. The couch top was excluded from the patient scan, and a laser coordinate system origin (represented by three BBs) was established at the laser centre, designated as reference point R. A parallel-running Python script, triggered by Pinnacle's launch, automated the planning process on the TPS computer. The script-initiated dosimetry calculations by clicking the

'dosimetry' button and selecting the patient's prescribed PTV. The script prompted selection of breast cancer type (intact breast or chest-wall) and laterality from dropdown options. With these parameters set, scripted plans were automatically generated by sequentially clicking script buttons.

The automated process begins with external/body volume creation using 0.3/0.5 cm skin padding. PTVs were generated using facility-defined CTV-PTV margins if required by the clinician. Intact breast and chest-wall PTVs were refined by excluding lung and heart intersections. PTV optimisation volumes were created by subtracting external-skin and contracted ROIs. Plan setup includes isocentre, dose prescription, and global dose volumes definitions. OAR dose constraints and weightings/priorities were also defined. 6 MV photon beams with dynamic partial arcs were configured whiles static open beams were set for imaging fields. Next, dose constraint objectives for the PTVs were established and prioritised according to departmental protocol. The final script button generated digital reconstructed radiographs (DRR) filter settings for megavolt (MV) imaging. The plan was optimised using two partial arcs via smart arc optimisation (Figure 3.3) and an adaptive convolution dose computation algorithm.

Figure 3.3: Intact breast VMAT plan automation with 2 partial arcs using Pinnacle TPS script programming [Beam planning interphase].

Optimisation ceased when the optimiser achieved the best solution aligned with the objectives. Additional optimisations may be employed to refine the plan's quality. Following evaluation and approval by the radiation oncologist, the plan was exported for patient-specific QA and subsequent treatment delivery on the Linac (Acquah *et al.*, 2023).

3.2.2.5 Patient-Specific Quality Assurance Measurement

A pretreatment verification plan was created for the patient using a scanned Octavius 4-D phantom in the TPS for patient-QA measurement. Where the dose distribution of the breast treatment plan was recalculated on the CT of the phantom scanned on the MinFound CT scanner. This process is a crucial step because of the plan's complexity and highly sophisticated technology behind the radiation planning and delivery. The Octavius 4-D phantom was set up on the Infinity Linac, and the same designed treatment plan was delivered. It provides a time-resolved dosimetric acquisition as it rotates together with the gantry and allows the reconstruction of a volumetric dose distribution. Pretreatment QA was performed using specialised phantoms, requiring measured doses to meet departmental gamma (γ) analysis criteria of distance-to-dose agreement of ≤3.0 mm and dose difference of ≤3.0%. A gamma index of ≥90% was considered acceptable, indicating successful QA and clearance for patient treatment (Acquah *et al.*, 2023). The γ-index metric, the standard technique used to evaluate the agreement between planned and measured dose (Low *et al.*, 1998), is obtained not only in a two-dimensional way but also three-dimensionally, allowing the evaluation of the whole volumetric dose distribution. The dosimetric verification was carried out, comparing the measured plan with the verification plan.

3.2.2.6 Delivery of Patient Radiation Dose Treatment

The exported plan was imported into MosaiQ (v2.81, Elekta Inc.), a record and verify system (RVS), for treatment delivery. Prior to treatment, the patient was positioned on the treatment

couch, replicating the CT simulation setup, using reference markers/tattoos and the laser system. For position verification, an electronic portal imaging device and iViewGT (v3.4.1, Elekta Inc.) software were used. Portal images were automatically matched with reference images according to the departmental breast imaging protocol, calculating offsets and applying necessary shifts before treatment commencement. The RVS, storing all beam parameters, facilitated the delivery of the two partial arc VMAT treatments to the intact breast or chest-wall (Acquah *et al.*, 2023).

3.2.2.7 Patient Treatment Plan Data Analysis

The collection of clinical data on intact breast and chest-wall plans was done to assess the dosimetric quality over the study period to help establish plan acceptability criteria (PAC). All patient data stored on the TPS's database were manually retrieved and relevant information input into the Microsoft Excel spreadsheet for analysis. From all dosimetric parameters collected, their mean, maximum, minimum and standard deviations of the PTVs and OARs were determined. All derived dose volume histograms for delineated volumes and critical structures were analysed. The PTV volumes used for planning optimisation and then dosimetric analysis were denoted as 'Brst_opt' and 'Chst_opt' for intact breast and chest-wall, respectively. For PTV_opt volume evaluation, there were 41 Brst_opt and 53 Chst_opt volumes analysed.

3.2.2.8 Evaluation of OAR Doses.

The heart is a critical OAR of importance for patients being treated with cancer in the left side of the breast, so data was only analysed for left-sided intact breast and chest-wall. The dose constraint for the heart was recorded by the percentage of heart volume that received 30 Gy (V_{30Gy}(%)) as well as the heart volume that received 5% ($V_{5\%}$(%)) and 20% ($V_{20\%}$(%)) of prescribed dose. Per the facility's protocol, the mean doses to the heart volume were also recorded. Doses received by

the ipsilateral lung (which is a main critical OAR) and that of the contralateral lung were analysed for both intact breast and chest-wall plans. The ipsilateral lung dose constraints were evaluated based on the percentage of lung volume exceeding 20 Gy ($V_{20Gy}(\%)$) and the volumes receiving 5% ($V_{5(\%)}$) and 20% ($V_{20(\%)}$) of the prescribed dose. To minimise radiation exposure, the unaffected breast was designated as an organ at risk during treatment of the intact breast and chest wall. During VMAT planning, the contralateral breast was carefully contoured, and the volume receiving up to 5 Gy was accurately recorded (Acquah *et al.*, 2023).

3.2.2.9 Dosimetric Indices Estimation.

To assess the quality of the VMAT plan, dose metrics were calculated for both the intact breast and chest-wall PTVs. Specifically, homogeneity, uniformity, and conformity were evaluated using the HI, UI, and CI formulas in equations 2.7.1, 2.7.2, and 2.7.3, respectively, providing a quantitative analysis of the plan's performance. Dose homogeneity assesses uniformity within the target volume, while dose conformity evaluates how well the high-dose region matches the target volume (PTV_opt) (ICRU, 2010). The terms dose homogeneity and uniformity of absorbed-dose distribution are interchangeable, describing the consistent and even distribution of radiation doses throughout a targeted area. Treatment plan conformity and uniformity increased as CI and UI values approached one. Meanwhile, HI values closer to zero indicated enhanced homogeneity within the breast volume (Acquah *et al.*, 2023).

3.2.3 Experimental Method for Phase 3 (Proposed planning optimisation criteria).

The third phase of the study was to develop facility-based treatment planning optimisation criteria for VMAT breast planning. The treatment plans generated by the facility's automated VMAT treatment planning workflow were analysed to establish a PAC and then propose a new facility-based planning optimisation criteria (POC) for its breast cancer planning. The established PAC

reiterated conclusions from studies (Hall *et al.*, 2003; Stovall *et al.*, 2008; Keller *et al.*, 2012) that found VMAT breast plans to improve dose coverage of the target at the expense of increased low doses to the critical organs, which in rare cases can increase the risk of secondary cancer. This phase of the study, therefore, proposed the establishment of an optimisation quality metric (OQM) relative scoring method in developing new facility-based POC for breast cancer treatment planning that will improve the overall VMAT plan quality (achieve both target coverage and organ sparing).

Using the established facility's PAC as reference, a newly proposed POC was developed using an OQM scoring process. The final OQM parameter selection was developed through consensus building and meticulous processes which involved iterative planning optimisation of trial-and error processes until an optimal plan for clinical delivery was found. Based on the clinical data analysed, new planning constraints were gradually tightened during optimisation. In this phase of the study, an acceptable benchmark plan was established as the starting point for plan optimisation, which largely eliminated guesswork and adopted protocols in selecting plan objectives/constraints during optimisation.

Twenty left-sided breast cancer patients were randomly selected from the patient Microsoft excel database using the random sample without duplicates (RAND, INDEX and RANK) functions. This is one of the functions available in Excel used to generate random data from a population without repeating the same sample during the selection. To randomise the database, the 61 left-sided patients retrieved from the TPS database were already stored and existed on an Excel spreadsheet. Each of the 61-patient data was listed in columns on the Microsoft Excel spreadsheet. The RAND function; =RAND (), was used to assign random numbers adjacent to cells next to the columns of the 61-patient data. The INDEX and RANK formula; = INDEX (, RANK (,), 1) were used to

generate 10 left-sided intact breast data and 10 left-sided chest-wall data from the 61 randomised database without duplication.

3.2.3.1 Overview of the OQM Selection and Scoring Process

This was to implement relevant metric parameters for optimisation and then score these metrics for plan optimisation development. Majority the parameters considered for inclusion in developing the OQM had the highest relative priorities per current facility's optimisation criteria. Table 3.3 lists these parameters with their corresponding dose constraints for each metric type.

Table 3.3: Current facility's VMAT inverse planning optimisation criteria with constraints priority.

ROI/Contour	Metric type	Constraint/Dose	Relative priority (%)
	Max dose	$V_{105\%}$ / 52.5 Gy	50
PTV	Min dose	$V_{97\%}$ / 48.5 Gy	10
	Uniform dose	$V_{100\%}$ / 50 Gy	15
Heart	Avg. dose	D_{avg} / 7.5 Gy	5
Ipsilateral lung	Avg. dose	D_{avg} / 12.5 Gy	10
Contralateral breast	Max dose	D_{max} / 5 Gy	10
Contralateral lung	Avg. dose	D_{avg}/ 8.5 Gy	10

The final OQM parameter selection process was achieved in the following order of steps:

- **Plan acceptability criteria parameters:** The initial OQM framework was built using collected treatment planning parameters from the clinical breast plan database.
- **Filtering through literature review:** A systematic literature search and review of studies were carried out to reduce the total number of parameters initially collected to only relevant dosimetric

parameters. For a parameter to be included, it had to be relevant to clinical outcomes (Mak *et al.*, 2015; Marks *et al.*, 2010; Travis *et al.*, 2003) and/or recommended for level two reporting by the International Commission on Radiation Units and Measurements (ICRU) Report 83 (ICRU, 2010).

- **Majority rule decision:** The resulting dosimetric parameters were presented to selected radiation oncology team members (two Radiation oncologists and three Medical Physicists) for inclusion. They were to respond "Yes" for a parameter to be included or "No" for it to be excluded. As a result, dosimetric parameters with majority decision (consensus) passed this stage as it was considered very relevant in the planning optimisation phase towards achieving optimal clinical plans per facility's goals.
- **Final parameter prioritisation and scoring:** The included parameters were further reduced, prioritised and scored accordingly based on clinical experiences and anecdotal evidence. Some of the parameters were merged into a single sub-parameter while others were excluded. The final OQM parameters were very vital in achieving overall optimal clinically plans and did not also increase the optimisation time significantly. They were ranked (priority) according to their contribution to the facility's plan goals and awarded score values.

The planning target volume, the heart volume, the ipsilateral lung volume, the contralateral breast volume and the contralateral lung volume were the regions of interest (ROI) used in the OQM parameter selection process. For each ROI, sub-metric parameters were selected, based on their dependence, to set dose objectives during plan optimisation. Prioritisation and score values (minimum and maximum) of OQM parameters were assigned using the results of previous dosimetric analysis in phase two of this study as reference (Acquah *et al.*, 2023). A score value of zero was awarded when objectives were out of the set range and the highest value when set objectives were met for every ROI's sub-metric. A study by Ahmed (Ahmad *et al.*, 2020) using

plan quality metrics employed an approach where parameter selection was based on relevance to clinical outcomes and by recommendation for level two reporting by the ICRU Report 83 (ICRU, 2010).

3.2.3.2 OQM-Based VMAT Replanning

Twenty randomly selected left-sided intact breast and chest-wall patients (training cohort) were re-optimised and scored using the OQM score values for each ROI's sub-metric parameter. The training cohort plan optimisation was done severally (plan trials) with varying prioritisations/weightings of sub-metrics until the highest possible total OQM score was achieved (when variations in ROI's weightings do not affect the overall OQM score). The training cohort planning started with optimising the PTV volumes (PTV_opt) (which were allocated a total of 40 OQM score value) to achieve the desired $V_{95\%}$ dose coverage and lower hotspots below the $V_{105\%}$. Afterwards, all associated organs at risk (which were allocated a total of 60 OQM score value) were included for final optimisation to achieve optimal organ dose sparing. All beams were reset before new trials were loaded for every new plan trail optimisation. The plan whose priorities (objective weightings) generated the highest score in total was chosen as the best possible plan for the selected breast case. The re-optimised plans were clinically possible to be delivered by the linear accelerator and conformed to a typical VMAT plan in terms of treatment delivery time and its efficiency (plan optimisation time). The average priority settings derived from the 20 best possible plans with the highest total OQM score were the proposed optimal planning optimisation criteria.

3.2.3.3 Patient Cohort Comparison

The facility's workflow for automated VMAT treatment planning generation was assessed to establish facility-based plan acceptability criteria for breast cancer patients. For each of the 94 breast cancer patients treated within the selected timeframe, dosimetric parameters from their generated VMAT plans were retrospectively estimated. This was equally performed for the generated VMAT plans using the 20 randomly selected left-sided breast cancer previously treated patients. The training optimised cohort plans were compared with the automated optimised cohort plans in terms of overall breast treatment plan quality. All 40 patient treatment planning data (20 automated optimised plans and 20 training optimised plans) were retrieved from the TPS's database and stored in an Excel spreadsheet for assessment and comparison. The plan quality assurance measurements were also compared.

3.2.3.4 Cohort Dosimetric Comparison.

Dosimetric data of the training plans were compared with their automated optimised cohort plans. Although there is no one agreed best way to evaluate plan quality, plan dosimetric evaluation included dose metrics such as target coverage, OAR constraints, dose homogeneity and conformity (Hernandez *et al.*, 2020). For each patient, dosimetric details of their PTV_opt, heart, ipsilateral lung, contralateral breast, and contralateral lung volumes were evaluated and compared. The dose-volume histograms (DVHs) for these contoured structures were analysed using various percentages of the PD at given volumes. For PTV_opt intact breast and chest-wall volumes, and their $V_{90\%}$, $V_{92\%}$, $V_{95\%}$, $V_{100\%}$, $V_{105\%}$, $V_{107\%}$, $V_{108\%}$ and $V_{110\%}$ (volume receiving a specified percentage of PD) were evaluated. Dose objective constraints for the heart were recorded as a percentage of its volume that received 30 Gy ($V_{30\ Gy\ (\%)}$) and the average dose (D_{avg}) received by

the heart volumes. The percentage of volume that received 20 Gy ($V_{20\ Gy\ (\%)}$) and D_{avg} received by the ipsilateral lung volume were also recorded. Maximum dose (D_{max}) received by the contralateral breast volume as well as the percentage of the contralateral lung volume that received 5 Gy ($V_{5\ Gy\ (\%)}$) were recorded, respectively. For the re-optimised plans, the minimum, maximum, mean values and their standard deviations of dose distributed in the PTV_opt volumes, and OAR were determined (Acquah *et al.*, 2023). Additional plan quality index, quality index (QI) for all PTV_opt volumes were calculated. The QI values were calculated using equation 2.7.4. as introduced by Adnani (Adnani *et al.*, 2020) and was considered clinically acceptable if QI is ≤ 0.3.

3.2.3.5 Cohort Radiobiological Comparison

The biology evaluation tool in Pinnacle TPS was used to evaluate the TCP and NTCP parameters of the targets and the organs at risk, respectively, for the automated optimised plans and their training cohort plans. These two radiobiological parameters evaluated the probability of tumour control in the breast and risk of complications for the OARs based on calculated dose distribution and radiobiological parameters of the ROI. The radiobiological parameters used for evaluation in this study as summarised in table 3.4 were obtained from the Niemierko's model (Niemierko *et al.*, 1993; Gay *et al.*, 2007). The NTCP parameters used for evaluating the contralateral breast volume (normal tissue) were default values provided by the Pinnacle TPS using study done by Korevaar (Korevaar *et al.*, 2002).

Table 3.4: Radiobiological parameters used for evaluating the TCP of the breast tumour and NTCP of the heart and lung.

Radiobiological parameter	ROI	Gamma (γ50)	Alpha/Beta (α/β)	D50 (Gy)	End Point
TCP	Breast	2	10	28	n/a
NTCP	Heart	3	3	49.20	Pericarditis/mortality
NTCP	Lung	2	3	24.5	Pneumonitis
NTCP	Normal tissue*	2.8	3	65	Necrosis

* Parameter used for this ROI were default values provided by TPS (Korevaar *et al.*, 2002)

3.2.3.6 Measured Cohort Plan Dose Comparison

VMAT breast plans deliver heterogeneous dose distributions which provide high doses to the breast volumes while sparing normal tissues. Despite its superior coverage and lower toxicity, VMAT treatment planning and delivery presents additional complexity, thereby increasing the sources of errors. These errors require pretreatment quality assurance (PTQA) or patient-specific QA (PSQA) of the VMAT plans to verify the dose calculation accuracy to the radiation delivery (Miften *et al.*, 2018; Moran *et al.*, 2011). Pretreatment QA measurements were performed for the randomly selected validation VMAT breast plans using the PTW Octavius phantom and the EPIBeam portal imaging method. The agreement between the planned and measured doses for the two QA systems was evaluated using the gamma index analysis.

To validate the significant effect of the proposed OQM-based criteria, the mean values were compared using the paired sample t-test to indicate any significant difference (p-value < 0.05)

between the two optimisation criteria (the current facility's optimisation criteria and the proposed optimisation criteria). The Microsoft excel spreadsheet's data analysis tool was used to run this statistical test between the two optimisation criteria planning data. During the data analysis, the t-test: 'Two sample assuming equal variances' option was selected, and the P(T<=t) two-tail was the most important p-value result recorded.

3.2.3.7 VMAT Efficiency Comparison

The radiation therapy planning and delivery efficiency were evaluated for the two sets of VMAT planning approaches and compared. This was to analyse one of the most important aspects of VMAT technology, planning and delivery time. The parameters used to evaluate the VMAT efficiency were the number of monitor units (MUs), the estimated treatment time (sec), mean dose rate and number of optimisation iterations used. The number of iterations together with the total number of control points were used to analyse the plan optimisation time. The mean dose rates (MU/min) was calculated from the mean monitor units (MU) and the mean delivery times (min) as given below:

$$\check{D}x = \frac{(MU)_x}{(Time)_x} \qquad 3.2.1$$

where;

$\check{D}x$ is the calculated mean dose rate for the VMAT treatment delivered,

$(MU)_x$ is the mean number of monitor units used in the treatment delivery, and

$(Time)_x$ is the mean delivery time for the VMAT treatment plan.

The efficiency parameters evaluated for the 20 randomly selected training plans were compared with their automated optimised cohort plans. The estimated treatment times calculated by the TPS was also compared to the actual delivery times by the Linac as recorded in patient treatment record

system (Onchronos). Onchronos hospital information system (Onchronos RT version, Webtech, Metz, France) is a web-based radiation oncology system used as a verify and record system that is connected to the MosaiQ software. Onchronos, just like the MosaiQ system, records the actual treatment machine parameters which include the monitor units and delivery times.

3.2.4 Experimental Method for Phase 4 (Plan evaluation and Data validation)

Dosimetric data derived from the TPS and that measured using the Octavius and EPID were evaluated in this section. Data validation was also performed for various dosimetric parameters collected, simulated and used in the study.

For the proposed facility-based VMAT planning optimisation criteria evaluation, two medical physicists (Planner 1 and Planner 2) were tasked to manually optimise ten randomly selected left-sided patients each (manually optimised cohort) using the newly developed criteria. The treatment planning experience of the two medical physicists were not the same; while one was a more experienced planner, the other was less experienced. Due to lack of time availability and busy work schedule of the two planners, they were to manually optimise the same five intact breast cases and the same five chest-wall cases each. These ten patients were also randomly selected from the twenty research sample sizes used in phase 3 of this study. Each plan was allowed to have a maximum of two optimisations (1 initialisation optimisation and 1 refinement optimisation) using the set facility-based criteria and then to reduce any unwanted hotspots above 105% of PD according to facility's protocol. All plans were optimised using two partial arcs (start angle of 300 degrees to a stop angle of 150 degrees) with the maximum iterations set to 40 and maximum delivery time per arc set to 180 seconds. This was done to prevent prolonged treatment planning time as well as extremely long treatment delivery time and number of monitor units to be delivered.

The adaptive convolution dose computation algorithm was used for the dose distribution calculations. Selected patients were scanned with free-breathing technique, automatically contoured using ARTPLAN and replanned on the same Pinnacle TPS. During the replanning process, every selected patient plan was duplicated to avoid changes to the original treatment plan (automated optimised cohort). For planning validation assessment, the training cohort - Plan (ref) were also compared to their manually optimised cohorts produced by the two medical physicists (Planner 1 and Planner 2).

3.2.4.1 TPS Plan Dosimetric Evaluation

Dosimetric data of the training plans were compared with the two sets of manually optimised validation cohort plans. For each patient, dosimetric details of their PTV_opt, heart, ipsilateral lung, contralateral breast, and contralateral lung volumes were evaluated.

3.2.4.2 Infinity Linac Commissioning Data Verification

During commissioning, absolute and relative measurements of photon beam data were performed on the Infinity Linac based on the requirement of the Pinnacle TPS for 6 MV photon energy VMAT technology. Photon relative dose measurements included percentage depth dose (PDDs) profiles, cross-plane profiles, in-plane profiles and diagonal profiles. PDD data for the 6 MV energy were also acquired for 3 x 3 cm^2, 5 x 5 cm^2, 10 x 10 cm^2, 15 x 15 cm^2, 30 x 30 cm^2 and 40 x 40 cm^2 field sizes at surface-to-surface distance (SSD) of 90 cm and were normalised to the depth of maximum dose (D_{max}) of the 10 x 10 cm^2 field size. The PDD measurements were done in steps of 1 mm from 0 cm to 3 cm depth and then in 2 mm steps from 3 cm to 30 cm depth using the PTW semiflex 3-D ion chamber (TM31021). The water phantom was set up at 90 cm SSD with a

source-to-isocentre distance (SID) of 100 cm and an isocentre at 10 cm depth for all the Pinnacle photon scanned beam data measurements with the same collimator angle of 0 degree. The measured photon PDD data were compared to reference beam data (golden data) to evaluate the measured data and to ensure its accuracy during the measurement process. The measured photon PDD data taken during this study were also compared to the Elekta Infinity reference beam data set (commissioning data) measured at an SSD of 100 cm for a 10 cm x 10 cm field size. The results of this comparison of the PDD data measurements to commissioning data must be within ≤1.0% for all depths and field sizes. The parameters compared are the depth of dose maximum - R100 (mm), percentage dose at 100 mm - D100(%), percentage dose at 200 mm - D200(%), and beam quality index (Q_i).

The lateral beam profile data, that is the cross-line (X-profile) and in-line (Y-profile) was acquired at SSD of 90 cm for the same field sizes of 3 x 3 cm^2, 5 x 5 cm^2, 10 x 10 cm^2, 15 x 15 cm^2, 30 x 30 cm^2 and 40 x 40 cm^2 at measurement depths of Dmax = 1.5 cm, 5 cm, 10 cm, 20 cm and 30 cm, and were normalised at D_{max} with the 10 x 10 cm^3 field size to the central axis (CAX). All beam data measurements were performed with the PTW BEAMSCAN water phantom. The PTW MEPHYSTO mc^2 data acquisition software version 3.4 was used for data analysis using the Elekta 2020 protocol for beam profile analysis and the AFSSAPS No. 93 protocol for the PDD analysis, respectively (PTW, 2019). The reference measured photon beam data (commissioning data) was used for the configuration of the calculation algorithms in the Pinnacle TPS. The flatness of the beam is defined as the ratio of the maximum absorbed dose (D_{max}) in the flattened area, to the minimum absorbed dose (D_{min}) in the flattened area at the standard depth of measurement (10 cm) as stated below.

$$Flatness = \frac{D_{max}}{D_{min}}\ x\ 100\% \qquad 3.2.2$$

For each beam profile measurement, this ratio must not be more than 106% for field sizes between 10 cm x 10 cm and 30 cm x 30 cm, and 110% for field sizes greater than 30 cm x 30 cm. The symmetry of the beam is also defined as the maximum ratio of the absorbed dose at two points in a flattened area, equidistant from the centre axis measured at the standard depth of measurement (10 cm) as stated below.

$$Symmetry = 100\%\ x\ \frac{max(D_{left},D_{right})}{min(D_{left},D_{right})} \qquad 3.2.3$$

where;

D_{left} and D_{right} are the doses at the points equidistant from the centre axis of the left and right side of the beam, respectively.

For each beam profile measurement, the calculated symmetry must not be more than 103%.

The absolute dose measurements were done according to the IAEA TRS 398 protocol for absorbed dose determination in external beam radiotherapy (Andreo *et al.*, 2000). The PTW beam scan water phantom and the PTW semiflex chamber (TM31010) connected to PTW UNIDOS E electrometer were used to collect charges at SSD of 90 cm for a 10 cm x 10 cm at depth of 10 cm when 200 MUs were delivered. The calibration factor of the chamber used was 9.219 cGy/nC at standard temperature and pressure. The calculated absorbed dose was compared to the reference absorbed dose and must be within ≤1.0% of 1.000 cGy/MU. The absorbed dose to water was calculated by:

$$D_{W,Q} = M_Q N_{D,W,Q_0} k_{Q,Q_0} \qquad 3.2.4$$

where;

$D_{W,Q}$ is the absorbed dose to water at a reference depth in water irradiated by a beam of quality Q,

M_Q is the corrected reading of the ionisation chamber at beam quality Q,

N_{D,W,Q_o} is the calibration factor in terms of the absorbed dose to water for the ionisation chamber at a reference beam quality Q_o,

k_{Q,Q_o} is the correction factor to account for the ionisation chamber response difference between reference beam quality Q_o used for calibration and actual user beam quality Q.

3.2.4.3 Octavius 4-D Commissioning Data Validation

The validation of the PTW Octavius 4-D phantom commissioning data for pretreatment QA was carried out. The implementation of this procedure required beam data collection for VeriSoft software, importing the Octavius phantom into the Pinnacle TPS, and establishing cross calibration and measurement validation. All PDDs were measured using the BEAMSCAN water phantom for field sizes of 4 × 4 cm^2, 5 x 5 cm^2, 8 x 8 cm^2, 10 x 10 cm^2, 15 x 15 cm^2, 20 x 20 cm^2 and 26 × 26 cm^2 measured at 85 cm SSD using a PTW semiflex 0.125 cm^3 chamber (TM31010). The measured data were loaded in the VeriSoft software's menu (Tools – Options – 4-D Dosimetry), and then "merge the PDD files" into a single PDD file (calibration file). For a better model in the Pinnacle TPS, a CT scan of the Octavius 4-D phantom was performed on the MinFound CT scanner and images imported as a patient phantom into the TPS. A QA plan was added to the images after POIs and ROIs were added to the phantom and saved as Octavius QA Phantom. The TPS was used to determine the MUs when a dose of 2.00 Gy (expected dose) was delivered in the Octavius QA phantom for a 10 x 10 cm^2 at 85 cm SSD. A reference point was created at the isocentre of the phantom to calculate the MUs required to deliver the prescribed dose in the TPS. A cross calibration was later performed by measuring the same calculated MUs delivered under the same measurement conditions (10 x 10 cm^2, 85 cm SSD) in the Octavius phantom using a chamber plate

with a PTW semiflex chamber (TM31010) at the isocentre. An open full arc verification plan was performed to validate the expected dose by using a simple open 10 x10 cm^2 arc field with calculated MUs in the Pinnacle TPS at the isocentre. A cross-calibration factor (k_{Cross}) was obtained from the ratio of the expected value ($d_{expected}$) and the measured value ($d_{measured}$) as shown below.

$$k_{cross} = \frac{d_{expected}}{d_{measured}} \qquad 3.2.5$$

- **Experimental setup:** The Linac gantry was set to 0 degree, and the Octavius phantom was set up carefully in the isocentre position under the Linac using its lasers as shown in figure 3.4. The inclinometer was mounted unto a flat portion of the gantry closer to its axis of rotation. The Bluetooth connection was established between the inclinometer and the control unit of the Octavius phantom's component. A test run was performed (full gantry rotation) to make sure all connecting cables are properly connected and out of the way to avoid collision during the gantry rotation.

Figure 3.4: PTW Octavius 4-D phantom setup under the LINAC for pretreatment measurement.

- **VeriSoft setup:** The software was launched, and the devices (detector interface and rotation unit) were selected from the "Tools" menu. The expected dose value (2.00 Gy) and measured dose value (2.092 Gy) were inserted in the "measurement parameters" menu with the cross-calibration option selected. The user factor (k_{User}) was set to 1.000 and a 10 x 10 cm^2 cross calibration static field of 276 MUs delivered by the Linac at gantry and collimator angles of 0 degree. The control unit was powered up for at least 15 minutes to make sure its electronics and detectors were well warmed up and signals very stable before the measurements. The measurements were repeated at least five times until the cross-calibration factor k recorded a constant value. The k factor which was automatically calculated was then accepted and saved in the VeriSoft software.
- **Clinical treatment plan verification:** A 10 x 10 cm^2 static field was planned, delivered and superimposed on its measured field. The planned and delivered static fields were evaluated using Verisoft software. Dosimetric data were assessed by the γ-analysis with acceptance criteria 3%, 3 mm using the local dose gamma analysis.

3.2.4.4 EPIbeam Data Measurement and Validation

Portal images intended for pretreatment beam reference control were acquired with the EPID directly been irradiated with the beams. All patient support systems were removed from the beam path to prevent the beams going through the couch. Measurements were acquired in "open EPID condition" or "attenuation free condition" with no additional build-up materials set on the EPID detector cover. All portal images were acquired in "Open EPID condition" with perfect centring of the EPID (that is no X or Y device translation).

3.2.4.4.1 Beam Library Data Preparation

All the measurements and TPS calculations required for the modelling of the data library for the EPIbeam software are described below:

- **Beam setup planning in the TPS:** Reference dose value was calculated in a PTW slab water-equivalent phantom (RW3) at Source-Axis Distance (SAD = 100 cm) and at a reference depth of 5 cm (d_{ref} depth) in the Pinnacle TPS. A 10 x 10 cm^2 field size (open beam) was used and 100 MUs prescribed to the reference depth on the beam axis to determine the absolute dose value in the RW3 phantom.
- **Dose reference data import from TPS**: The dose reference data was measured and used to establish the dose prediction model and the conversion model for the portal images into dose-to-water map at a reference depth. This was measured perpendicularly to the beam-axis at Source-Axis Distance of the Linac (SAD = 100 cm) and at a reference depth of 5 cm in a homogenous water-equivalent phantom. The dose reference data were extracted from the plan results computed by the Pinnacle TPS. These data were used to build the predicted dose model in EPIbeam, making it and the reference images consistent with the Pinnacle treatment

planning dose calculations. The DICOM RT Dose files, related to the RT Plan files were imported into EPIbeam from the TPS.

- **EPID data acquisitions**: For the Elekta Infinity Linac, the Source-Imager Distance (SID) was 160 cm with the EPID perfectly centred during portal image acquisition (that is no translation in the X and Y direction of the EPID). Portal image measurements for EPIbeam dose calibration beam were acquired with gantry and collimator angles of 0 degree.

3.2.4.4.2 Portal Image Dose Conversion Modeling

- **Dose calibration:** The EPIbeam dose calibration factor is defined as the ratio of dose in water (expected dose-to-water value in cGy), over the pixel value on an imported portal image. It is defined as:

$$C_{calib} = \frac{D_{water}}{R_{pxl}} \qquad 3.2.6$$

where:

D_{water} is the absolute dose (Gy) measured in the RW3 phantom.

R_{pxl} is the raw value at the central pixel of the image.

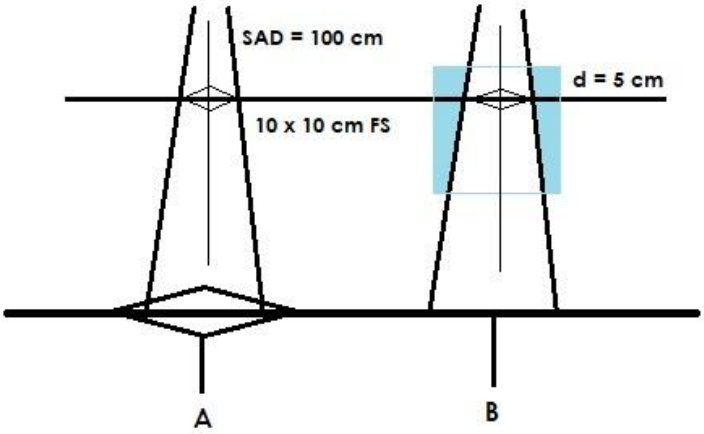


Figure 3.5: Experimental setup of the dose calibration, A is the calibration EPID measurement set-up and B is the dose point measurement in RW3 water phantom.

The D_{water} value was provided by the TPS calculation and the R_{pxl}, from the portal image measurement. The purpose of this measurement is to convert the pixel value of a given portal image into an absolute dose-to-water value in reference geometrical conditions as in Figure 3.5.

- **Non linearity correction:** The dosimetric use of EPID images relies on the linearity between the EPID signal and the dose delivered. However, the EPID images suffer from image-lag and ghosting effects that needed to be accounted for. When acquiring images, a delay of 30 seconds was introduced before the acquisition of the images to correct this ghosting effect. A 10 cm x 10 cm fixed square field planned at isocentre was calculated with increased monitor units from 2 MUs to 500 MUs. Table 3.5 captured the time interval between image acquisitions and the set monitor units. The images were then successfully acquired in that increasing order of the MU values, whiles observing the 30 seconds pause between each acquisition.
- **Correction of gantry sag effect:** To achieve accurate characterisation of the mechanical sag of the EPID during gantry rotation, eight portal images were acquired along the gantry circular trajectory. Symmetric 20 cm x 20 cm square fields were used to acquire electronic portal

images using 100 MUs at regular intervals to cover the 360-degree gantry rotation as captured in Table 3.5.

3.2.4.4.3 Portal Dose Image Prediction Modeling

TPS data (DICOM RT Plan & RT Doses) and EPID images for a set of various field sizes were required to establish the EPIbeam prediction model.

- **Dicom RT Plan and RT Dose files:** From the TPS, DICOM RT Plan and RT Dose files were required for each calculated beam at 95 cm SSD. The field sizes projected at the corresponding SID were smaller or equal to the dimension of the sensitive part of the EPID panel as presented in Table 3.5.

Table 3.5: Various measuring conditions during EPIbeam commissioning.

	Field Sizes (cm^2)	MUs	Gantry Angle (°)
Dose Calibration	10 x 10	100	0
Gantry Sag Effect	20 x 20	100	0 – 315 (in 45° intervals)
Ghosting	10 x 10	2 - 500	0
Dose Prediction	2 x 2 - 24 x 24	100	0
End-to-end Test	10 x 10	100	0

3.2.4.4.4 End-To-End Validation Tests

To verify the prediction and conversion models, EPID images and corresponding DICOM RT Plan and RT Dose files were required for 3 MLC designed fields. Three separate plans were created in the TPS using the MLCs to design three distinct patterns as described in Figure 3.6. These patterns are the letter capital "E", a "Chevron" shape and a "Triangle" planned with 100 MUs at SSD of 95 cm. The DICOM RT Plans were exported to the EPIBeam software while their DICOM RT Plans, RT Dose files and RT images were exported to the record verify system. These plans were then acquired using the open EPID panel and the portal images exported to the EPIBeam software for comparison and analysis, using local gamma analysis with acceptance criteria 2%, 2 mm.

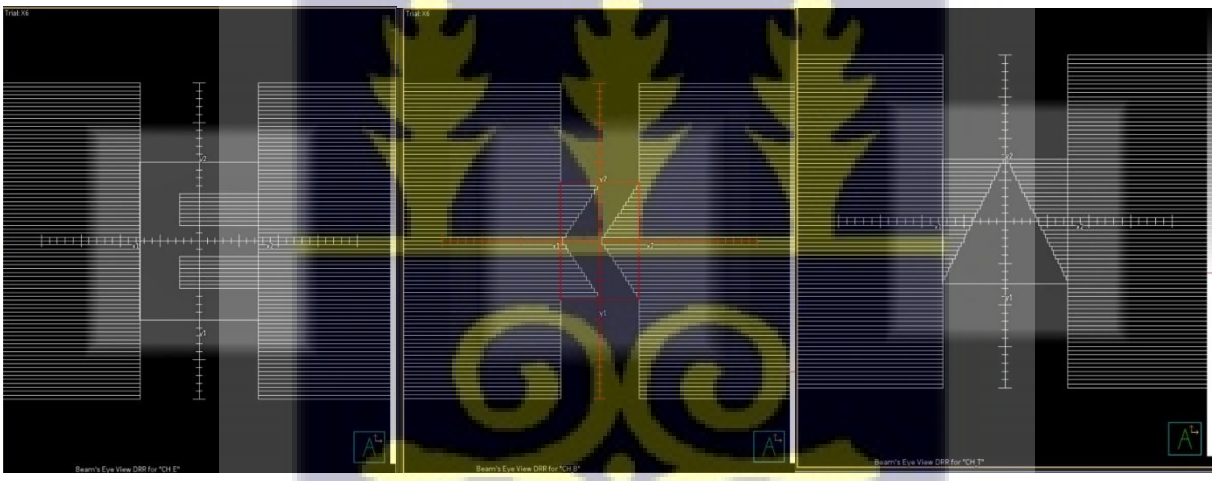


Figure 3.6: The Field E, Chevron and Triangle MLC designed patterns in the TPS for the end-to-end validation test.

3.2.4.4.5 Development of "PlanAccept" for Planning Acceptance

The facility's clinical goals were defined in the Microsoft excel spreadsheet based on the new proposed planning optimisation criteria. It used established grading criteria of multiple goals based on a specific set of plan quality metrics. The grading varied based on how low the doses to the

OARs and dose distribution within the PTV were. Details of each dose objective parameter are summarised in Table 3.6 The "PlanAccept" developed for this study consisted of 11 metrics, each with grading values indicated by colour coding.

Table 3.6: Plan dose objectives parameters for the PTV and OAR used in developing the "PlanAccept" for planning grading.

ROI parameter	Primary dose objective	Secondary dose objective
PTV Min Dose	49.5 Gy	47.5 Gy
PTV Min DVH	49.0 Gy	47.0 Gy
PTV Max DVH	51.0 Gy	53.0 Gy
PTV HI	0.07	0.085
PTV Max Dose	52.0 Gy	52.5 Gy
Heart V_{30Gy}	5%	10%
Heart Davg	4.0 Gy	5.0 Gy
Ipsilateral Lung V_{20Gy}	5%	10%
Ipsilateral Lung Davg	5.0 Gy	8.5 Gy
Contralateral Breast Dmax	4.0 Gy	5.0 Gy
Contralateral Lung V_{5Gy}	20%	30%

CHAPTER FOUR

RESULTS AND DISCUSSION

This chapter outlines the results obtained in the study and the subsequent discussion of these findings. The results obtained from all four study phases are presented and discussed. The first part (Phase 1 study) covers the online-based survey designed for breast cancer external beam radiotherapy in Ghana. Phase 2 of the study covers results from the establishment of breast plan acceptability criteria. The third phase outlines the results from the proposed facility-based treatment planning optimisation criteria for VMAT breast planning. Finally, the last part (Phase 4 study) covers the evaluation of results based on the proposed POC and subsequent data validation of various dosimetric parameters and dose measurements performed during the study.

4.1 PHASE ONE STUDY

Phase one study was a national survey on external bream radiotherapy for breast cancer patients in Ghana. A total of 11 responses were received from the Google web-based questionnaires sent to the targeted radiation oncologists, medical physicists, and radiation therapists in the three radiotherapy facilities in Ghana. There was a 100% facility-response rate as all three radiotherapy facilities participated in the survey. During the survey, CT-based breast planning was recognised as the gold standard and utilised across all three facilities. Most relevant organs at risk associated with breast external beam radiation therapy were well-defined. The three-dimensional conformal radiotherapy forward-planning field-in-field technique emerged as the preferred planning approach. The facilities were equipment with three operational medical linear accelerators and two cobalt-60 treatment units. The three radiotherapy facilities had varying radiation medicine staff

numbers at the time of the survey. SGMC Cancer Centre (Facility A) had employed two radiation oncologists, two medical physicists, and 4 radiation therapy technicians, while NRONMC (Facility B) had 8 radiation oncologists, six medical physicists, twelve radiation therapy technicians, and OD-KATH (Facility C) had eight radiation oncologists, seven medical physicists, and four radiation therapy technicians. Responses to Questionnaire one received from NRONMC were 4, OD-KATH had 1, and SGMC had 3, as shown in Figure 4.1. Questionnaire 2 garnered one response from a radiation oncologist at each facility. For purposes of the results and discussions, the facilities will be referred to as Facility A, Facility B, and Facility C.

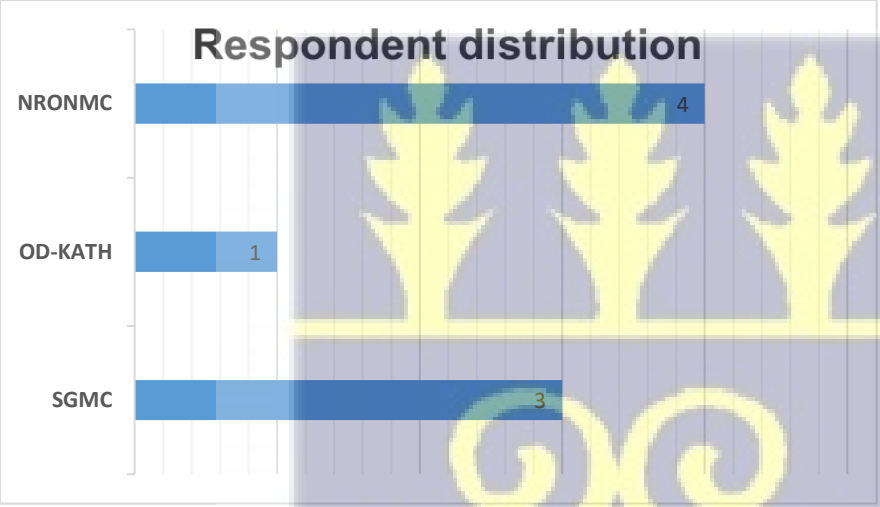


Figure 4.1: Details of facility responses to Questionnaire 1 (Acquah *et al.*, 2022)

4.1.1 Patient Registry

The three radiotherapy facilities treated annually an average of 750 new breast cancer patients with external beam radiotherapy. Approximately two-thirds (500 cases) of the patients were mastectomy (chest-wall irradiation) and one-third (250 cases) were lumpectomy (intact breast irradiation).

4.1.2 Radiation Dose Fractionation Regimens

For both intact breast and chest-wall irradiation, the standard treatment protocol on the linear accelerators was a total dose of 50 Gy delivered in 25 fractions. However, one facility occasionally employed hypofractionation, administering 40.05 Gy in 15 fractions of 2.67 Gy each, to reduce patient visits. To boost treatments, all three facilities used a uniform dose of 10 Gy in 5 fractions of 2 Gy each. Two facilities also had cobalt-60 teletherapy units to manage high patient volumes. At one of these facilities, the Co-60 unit was exclusively used for chest-wall treatments, with a dose fractionation of 42.56 Gy in 16 fractions of 2.66 Gy each, followed by a boost of 16 Gy in 8 fractions of 2 Gy (Acquah *et al.*, 2022).

4.1.3 Pretreatment Simulation

Computed tomography scanners were available for breast cancer pretreatment simulation at all three facilities. Skin markings (tattoos) were used as reference landmarks for patient setup whiles radiopaque wires were used to guide oncologists during chest-wall target volume delineation. Simulations were done in supine position using breast boards for patient immobilisation. The CT images acquired were used in the 3-D treatment planning for the main breast plan and its boost irradiation. Conventional simulators were occasionally used by two facilities for pretreatment simulations to augment the use of the CT scanners. For treatment geometries defined by using conventional simulators, the necessary physical wedge filter was determined by tracing the surface contour along the plane containing the central axes of tangential fields using a lead wire. The lead wire contour was then transcribed onto paper and digitised into the TPS to select the appropriate wedge filter. One facility employed clinical mark-up and manual dose calculations for electron boost treatments, opting out of 3-D treatment planning for chest-wall boost irradiation (Acquah *et al.*, 2022).

4.1.4 Breast Tumour Target Definition and Organs at Risk Delineation

The clinical tumour target volumes and organs at risk were defined by the radiation oncologists in all three facilities. All relevant OARs such as the heart volume, lung volumes, and the contralateral breast were delineated prior to treatment planning. Intact breast delineation was primarily accomplished using mammographic scans and visible glandular tissue in CT images. Surgical clips placed by surgeons aided oncologists in defining the intact breast boost area. For chest-wall targeting, radiopaque wires covering surgical scars during CT simulation served as a reference point. Oncologists from two facilities requested for a 0.5-cm CTV-PTV margin for both intact breast and chest-wall planning. In contrast, one facility used a 1.0-cm margin per their established protocol. Consistently, radiation oncologists included the skin covering the breast of the PTV for both intact breast and chest-wall targets, regardless of disease stage (Acquah *et al.*, 2022).

4.1.5 Radiation Treatment Planning Technique

CT-based treatment planning techniques were employed as standard protocol for both intact breast and chest-wall irradiation in all three facilities. Occasionally, 2-D planning and body outline contours (skin mark-ups) were utilised for some patients in two of the facilities. These two facilities utilised conventional simulators in the determination of irradiation geometries for the 2-D breast planning. Computerised treatment planning systems were used to design 3-D intact breast and chest-wall treatment plans. Motorised wedges and MLCs were used to shape and conform doses to the tumour target for irradiation with the cobalt treatment unit and linear accelerator, respectively. For LINAC-based breast irradiations, FP-FIF techniques were used. Plan acceptance criteria at all three facilities included OAR dose-volume histograms and dose information, following QUANTEC guidelines. Only one facility used a 3.0-cm central lung distance (CLD) and 2.0-cm maximum heart distance (MHD) as its maximum treatment field distances in those OAR

during the planning process. All LINAC-based chest-wall irradiations used various energy-dependent bolus thicknesses during planning, and no boluses were employed for the cobalt-60 based treatment plans (Acquah *et al.*, 2022).

4.1.6 Breast Treatment and Position Verification

Most intact breast irradiations were done using the Linacs available at the three radiotherapy facilities. For chest-wall irradiation, two out of the three facilities used the Linac while the other used the Co-60 unit. Two facilities also used the cobalt-60 unit for selected intact breast and chest-wall patients. One facility does not provide boost irradiation for chest-wall patients treated with the cobalt-60 machine. At the other two facilities, photon beams (6 MV and Co-60) were used for both intact breast and boost plan irradiation. However, one facility utilised electron beams specifically for chest-wall boost irradiation. To ensure accurate positioning, electronic portal imaging devices attached to the Linacs were employed prior to dose delivery. Additionally, portal films were taken for verification purposes when cobalt-60 units were used. For chest-wall irradiation, boluses were applied on alternating days, with thickness varying based on photon beam energy. Typically, a 0.5-cm bolus thickness was used for 6 MV chest-wall plans (Acquah *et al.*, 2022).

4.1.7 Innovative Approach and Modern Technological Advancements

All three facilities acknowledged the need to enhance their treatment planning protocols for intact breast and chest-wall treatments. To achieve this, they implemented advanced techniques and dose reduction strategies. A key adoption across all facilities was the forward planning Field-in-Field technique, replacing traditional wedge-based methods for Linac irradiations. Notably, one facility, which previously relied on motorised wedges, successfully integrated FP-FIF to achieve significant improvements in dose homogeneity within the breast volume. Additionally, this

technique resulted in reduced doses to the lung and heart volumes, while also mitigating dose inhomogeneity issues (Acquah *et al.*, 2017). The use of hybrid treatment planning techniques was introduced by one facility to improve its breast plan quality. The integration of digital megavoltage imaging devices into clinical practice has significantly streamlined and enhanced the accuracy of verification procedures at these facilities. Furthermore, all respondents expressed strong enthusiasm for adopting cutting-edge techniques and technologies to improve breast cancer treatment and planning. Desired advancements include breath-hold technologies, IMRT, VMAT, hybrid irradiation techniques, inverse planning optimisation and advanced imaging systems. The deep inspiration breath hold technique is currently not used in any of the facilities due to its labour intensiveness, time consuming and the cost of this technology.

This survey was the first to be conducted in Ghana in collaboration with the team from the EORTC-ROG breast working group to investigate resources and protocols for breast cancer EBRT practice (Van der Laan *et al.*, 2010). Table 4.1, table 4.2, and table 4.3 summarised the key findings from a survey of three radiotherapy facilities, highlighting their responses to questionnaires. The analysis of these responses offers valuable insights into the current practices of intact breast and chest-wall cancer radiotherapy at these facilities.

Table 4.1: Baseline overview of the current state of intact breast and chest-wall EBRT treatment in facility A (Acquah *et al.*, 2022).

MAIN QUESTION	FACILITY A	
	Lumpectomy (intact breast)	**Mastectomy (chest-wall)**
1. Avg. number of patients per year	47	93
2. Main and boost fractionations	50 Gy/25fr and 10 Gy/5fr	50 Gy/25fr and 10 Gy/5fr
3. Treatment planning technique	FP-FIF	FP-FIF
4. RT type for main and boost	3-D CRT	3-D CRT and 2-D
5.Compensators/wedges/applicators	MLCs	MLCs and applicators
6. Modality / energy	Photons/6MV	Photons/6MV and Electrons/6MeV
7. Beam set up	tangential	tangential and anterior
8.% CT-based planning main/boost	100/100	100/0
9. Reference use at sim for setup	BBs, tattoos	BBs, tattoos
10. Landmark for contouring	surgical clips, Mammo, CT,	Wires, scar for boost
11. Timing for boost treatment	After main treatment	After main treatment
12. CTV to PTV margin	1 cm	1 cm
13. Skin inclusion to PTV	YES	YES

Table 4.1: Continued from previous page

14. OAR contoured	lungs, heart, cord, esophagus	lungs, heart, cord, esophagus
15. Plan acceptance criteria used	DVH	DVH
16. Criteria protocol	QUANTEC	QUANTEC
17. Image verification	MV EPID	MV EPID
18. Bolus usage	NO	YES
19. Bolus thickness and frequency	n/a	0.5cm for half the total fractions
20. New RT plan strategies adapted	FP-FIF	FP-FIF
21. Future technology	IMRT, Inverse planning, DIBH	IMRT, Inverse planning, DIBH

Table 4.2: Baseline overview of the current state of intact breast and chest-wall EBRT treatment in facility B (Acquah *et al.*, 2022).

MAIN QUESTION	FACILITY B	
	Lumpectomy (intact breast)	**Mastectomy (chest-wall)**
1. Avg. number of patients per year	121	242
2. Main and boost fractionations	50 Gy/25fr and 10 Gy/5fr	5 0Gy/25fr and 10 Gy/5fr
3. Treatment planning technique	FP-FIF	FP-FIF
4. RT type for main and boost	Both 3-D CRT/2-D	Both 3-D CRT/2-D
5.Compensators/wedges/applicators	MLCs and wedges	MLCs and wedges
6. Modality / energy	Photons/6MV and Co-60	Photons/6MV and Co-60
7. Beam set up	tangential	tangential
8.% CT based planning main/boost	70	70
9. Reference use at sim for setup	BBs, tattoos	BBs, tattoos
10. Landmark for contouring	CT, Mammo, surgical clips, SIM borders	wires, Mammo, CT, scar
11. Timing for boost treatment	After main treatment	After main treatment
12. CTV to PTV margin	0.5 cm	0 cm
13. Skin inclusion to PTV	NO	NO

Table 4.2: Continued from previous page

14. OAR contoured	Lungs, heart, contralateral breast	lungs, heart, contralateral breast
15. Plan acceptance criteria used	DVH (3D) and max heart dose (2D)	DVH (3D) and max heart dose (2D)
16. Criteria protocol	QUANTEC	QUANTEC
17. Image verification	Portal x-ray images (Co unit), EPID (Linac)	Portal x-ray images (Co unit), EPID (Linac)
18. Bolus usage	YES Sometimes	YES
19. Bolus thickness and frequency	0.5cm for half the total fractions	0.5cm for half the total fractions
20. New RT plan strategies adapted	FP-FIF, Hybrid	FP-FIF, Hybrid
21. Future technology	IMRT, VMAT, Inverse planning, DIBH	IMRT, VMAT, inverse planning, DIBH

Table 4.3: Baseline overview of the current state of intact breast and chest-wall EBRT treatment in facility C (Acquah *et al.*, 2022).

MAIN QUESTION	FACILITY C	
	Lumpectomy (intact breast)	**Mastectomy (chest-wall)**
1. Avg. number of patients per year	82	163
2. Main and boost fractionations	50 Gy/25fr and 10 Gy/5fr	42.56 Gy/16fr and 16 Gy/8fr
3. Treatment planning technique	FP-FIF	FP-FIF
4. RT type for main and boost	Both 3-D CRT/2-D	Both 3-D CRT/2-D
5. Compensators/wedges/applicators	MLCs and wedges	MLCs and wedges
6. Modality / energy	Photons/6MV and Co-60	Photons/6MV and Co-60
7. Beam set up	tangential	tangential
8. % CT based planning main/boost	50	50
9. Reference use at sim for setup	BBs, tattoos	BBs, tattoos
10. Landmark for contouring	CT, surgical clips, SIM borders, Mammo	SIM borders, CT, scar, wire
11. Timing for boost treatment	After main treatment	After main treatment
12. CTV to PTV margin	1 cm	1 cm
13. Skin inclusion to PTV	YES	YES
14. OAR contoured	lungs, heart	lungs, heart

Table 4.3: Continued from previous page

15. Plan acceptance criteria used	DVH	DVH
16. Criteria protocol	QUANTEC	QUANTEC
17. Image verification	MV EPID	MV EPID
18. Bolus usage	YES Sometimes	YES
19. Bolus thickness and frequency	0.5cm for half the total fractions	0.5cm for half the total fractions
20. New RT plan strategies adapted	FP-FIF	FP-FIF
21. Future technology	IMRT, DIBH, inverse planning	IMRT, DIBH, inverse planning

The use of 3-D CRT was observed to be the standard treatment planning protocol currently in the country with few 2-D planning techniques. The FP-FIF planning techniques have also been adopted to improve dose homogeneity, reduce hotspots and doses to critical structures (Ercan *et al.*, 2010; Acquah *et al.*, 2017). The QUANTEC constraint protocols were widely adopted and used in all three facilities (Marks *et al.*, 2010). Plan acceptability criteria were mainly assessed with the use of DVH and the OAR dose constraint table. Each of the three facilities had its own positioning setup correction protocol employed for the positioning shift matching during patient setup.

The survey yielded comprehensive insights into the existing EBRT resources for breast cancer management in Ghana. Although minor variations in protocols were noted among the three facilities, all recognised the need to adopt innovative strategies and technologies to enhance patient outcomes. Desired improvements range from refining departmental protocols to integrating

cutting-edge software and technologies. Furthermore, all participating facilities expressed interest in introducing advanced techniques such as IMRT, VMAT, hybrid planning techniques and DIBH into clinical practice for improved breast cancer radiation therapy (Acquah *et al.*, 2022).

4.1.8 Survey Limitations

Variations in responses to identical questions from the same facilities were observed, indicating potential deviations from established protocols or differing interpretations among staff members. This discrepancy may be attributed to non-adherence to facility protocols, varying understanding of protocols across different professions, or differences in staff experience levels and knowledge. To ensure accuracy and clarify protocol details, the study engaged senior, experienced professionals from each of the three facilities. These individuals contributed to response interpretation and analysis, providing valuable insights into their respective facility's protocols. The survey faced a notable challenge due to widespread apathy and unwillingness to participate among the targeted professionals. The overall response rate was 21%, significantly lower than anticipated. This was largely driven by limited engagement from radiation therapists, who make up the bulk of the target group. Despite accounting for the majority (20 out of 53) across the three facilities, only one response was received from a radiation therapist. Although the survey's response rate was impacted, it remained comparable to a similar study which achieved a 25% response rate (Giro *et al.*, 2009). Notably, the EORTC-ROG survey however reported a higher response rate of 47% (Van der Laan *et al.*, 2010). This disparity can be attributed to the EORTC-ROG survey's targeted focus on radiation oncologists and medical physicists, who are primarily responsible for developing EBRT protocols in radiation therapy facilities. Although the survey's response rate was uneven, the fact that all three targeted radiation therapy facilities in the country participated validates the results. The findings provide insight into current clinical protocols within

these facilities but may not comprehensively represent the full scope of external beam radiation therapy (EBRT) practices. Notably, responses varied significantly across professions and facilities, with some contributing more substantially than others. The analysis of this survey was based and limited to the 21% response rate of the targeted radiation oncology professionals at the three radiotherapy facilities in Ghana. Hence, it is essential to consider the context of this survey when interpreting the results and discussions (Acquah *et al.*, 2022).

4.2 PHASE TWO STUDY

The results for the second phase of the study involved the dosimetric estimation of intact breast and chest-wall VMAT radiation treatment planning database. A total of 94 breast cancer patients planned and treated using automated contouring and VMAT planning techniques from January 2021 to January 2023 were evaluated. The dose distribution parameters and dosimetric data for the selected 94 radiation treatment plans were collected and retrospectively analysed over the study period. The data were evaluated to establish clinical suitability of the current facility's treatment planning protocol and ultimately to establish facility-based breast treatment plan acceptability criteria. The DVHs for all contoured structures were analysed using various percentages of prescribed dose and given volumes. For all PTVs used for optimisation, their $V_{90\%}$, $V_{92\%}$, $V_{95\%}$, $V_{100\%}$, $V_{105\%}$, $V_{107\%}$, $V_{108\%}$ and $V_{110\%}$ (volume receiving a certain percentage of the PD) were evaluated from the DVH.

For each patient, their ages, breast separation, PTV_opt volumes, ipsilateral lung volume, heart volume (for left-sided cases), contralateral lung and contralateral breast volumes were recorded. The number of patients that were planned and treated for intact breast and chest-wall were 41 (43.6%) and 53 (56.4%), respectively. From the data, the incidence of left-sided breast cancer

occurrence was 64.9% (N= 61) as compared to right-sided breast of 35.1% (N=33). The mean patient age was 49 years (ranging from 25 years to 74 years). Figure 4.1 is a graphical representation of the age-distribution of the 94 patients studied in this phase of the work.

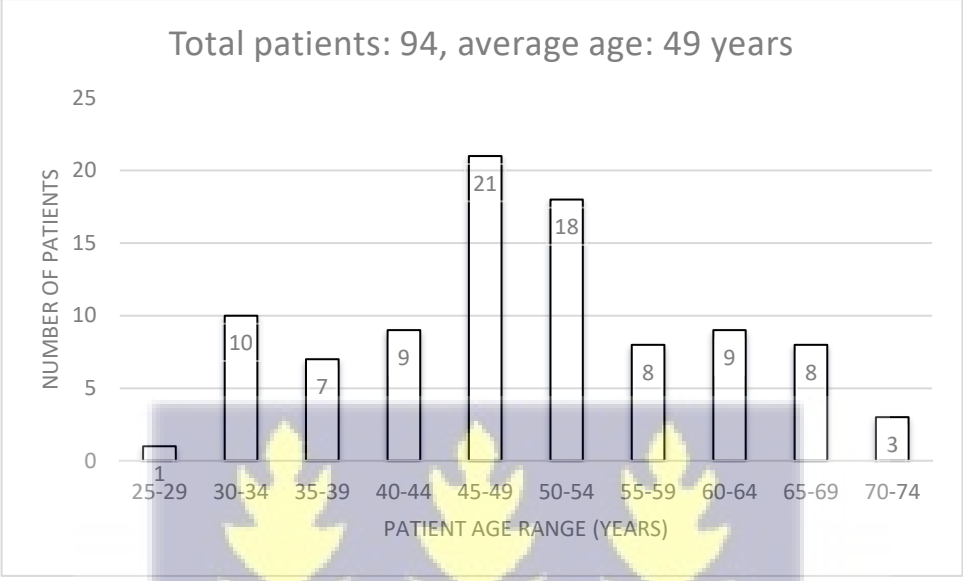


Figure 4.2: Age distribution analysis of patient cohort over 2 years (Acquah *et al.,* 2023)

4.2.1 Planned Target Volume Calculated Dose Indices

Table 4.4 and Table 4.5 show the statistical analysis of the calculated homogeneity index, uniformity index, and conformity index with their respective breast separations for all 94 patients' Brst_opt and Chst_opt volumes, respectively. For the Brst_opt dose indices calculated; the mean homogeneity index was 0.14 ± 0.03, the mean uniformity index was 1.09 ± 0.03, and the mean conformity index was 0.92 ± 0.04. The HI for intact breast volumes ranged from 0.09 to 0.22, UI ranged from 1.04 to 1.18, and CI ranged from 0.81 to 0.96 for all breast separations.

Table 4.4: Statistical analysis summary of calculated plan quality indices for Brst_opt in intact breast patients with breast separations and age distribution (Acquah *et al.*, 2023).

Patient parameter	n	Min	Max	Mean (x)	Standard Deviation
Age (years)	41	25.00	61.00	51.03	12.35
Breast Separation (cm)	41	17.05	32.15	22.97	3.70
Homogeneity Index	41	0.09	0.22	0.14	0.03
Uniformity Index	41	1.04	1.18	1.09	0.03
Conformity Index	41	0.81	0.96	0.92	0.04

For the Chst_opt dose indices calculated, the mean homogeneity index was 0.15 ± 0.04, the mean uniformity index was 1.11 ± 0.03, and the mean conformity index was 0.91 ± 0.04. The corresponding values for chest-wall volumes ranged from 0.09 to 0.24 for HI, 1.06 to 1.19 for UI, and from 0.83 to 0.97 for CI for all breast separations.

Table 4.5: Statistical analysis summary of calculated plan quality indices for Chst_opt in chest-wall patients with breast separations and age distribution (Acquah *et al.*, 2023).

Patient parameter	n	Min	Max	Mean (x)	Standard Deviation
Age (years)	53	33.00	74.00	49.50	10.0
Breast Separation (cm)	53	18.65	32.78	25.47	3.06
Homogeneity Index	53	0.09	0.24	0.15	0.04
Uniformity Index	53	1.06	1.19	1.11	0.03
Conformity Index	53	0.83	0.97	0.91	0.04

The breast separations were sub-divided and classified as small, medium and large sized. For this phase of the study, breast separations less than 20 cm were classified as small, those between 20 cm to 25 cm were classified as medium and those above 25 cm were classified as large size. It was observed that for both intact breast and chest-wall treatment plans, majority of the breast separations fell within the medium and large size range as presented in Table 4.6.

Table 4.6: Classification of breast separation into small, medium and large size for both intact breast cases and chest-wall cases.

Breast Separation	n	Min	Max	Mean (x)	Standard Deviation
Intact Breast cases	41	17.05	32.15	22.97	3.70
Small (cm)	8	17.05	19.87	18.53	0.99
Medium (cm)	24	20.04	24.60	22.40	1.57
Large (cm)	9	25.41	32.15	28.44	2.42
Chest-wall cases	53	18.65	32.78	25.47	3.06
Small (cm)	1	18.65	18.65	18.65	-
Medium (cm)	21	20.56	24.65	22.88	1.42
Large (cm)	31	25.04	32.78	27.54	1.98

It was observed that, the bigger the breast separation using the 6 MV for VMAT planning, the higher the hot spots (which are points of maximum doses within the treatment volume) and hence the worse PTV indices calculated. The hot spots also tend to be greater in patients with larger breast and chest-wall PTV volume sizes. From studies, these high doses can cause unacceptable acute and late toxicities in patients and hence needed to be reduced using creative dose reduction

techniques (Adnani *et al.*, 2020; Acquah *et al.*, 2017; Acquah *et al.*, 2023; Darby *et al.*, 2013). The VMAT intact breast and chest-wall treatment planning technique analysed in this study phase produced a more homogenous dose distribution with lower hot spots but resulted in undesirable high-integral doses to the ipsilateral lung and heart volumes (Acquah *et al.*, 2023).

4.2.2 Planned Target Volume for Optimisation (PTV_opt) Analysed Doses

The mean intact breast volume for optimisation (Brst_opt) was 695.76 ± 269.70 cm^3 (minimum of 379.75 cm^3 and a maximum of 1123.78 cm^3) with a mean breast separation of 22.97 ± 3.70 cm (ranging from 17.05 cm to 32.15 cm). The mean chest-wall volume (Chst_opt) was 506.08 ± 326.34 cm^3 (minimum of 216.88 cm^3 and a maximum of 913.27 cm^3) with a mean breast separation of 25.47 ± 3.06 cm (ranging from 18.65 cm to 32.78 cm). The dosimetric analysis as presented in table 4.7 and table 4.8 are percentages of prescribed planned doses received by the intact breast and the chest-wall volumes, respectively. For the Brst_opt cases, the mean volumes that received 90% ($V_{90\%}$ PD), 95% ($V_{95\%}$ PD) and 105% ($V_{105\%}$ PD) of prescribed dose were 97.32 ± 0.71%, 95.08 ± 1.11% and 1.54 ± 1.02%, respectively. For Chst_opt cases, the mean volumes that received 90% ($V_{90\%}$ PD), 95% ($V_{95\%}$ PD) and 105% ($V_{105\%}$ PD) of prescribed dose were 97.04 ± 0.95%, 94.95 ± 1.19% and 2.28 ± 1.99%, respectively.

Table 4.7: Statistical analysis summary of patient PTV_opt volumes that received various percentages of prescribed dose for intact breast and chest-wall cases.

Volume (cc) receiving % of PD	Breast volume for optimisation				Chest-wall volume for optimisation			
	Min	Max	Mean (x)	SD	Min	Max	Mean (x)	SD
	379.75	1123.78	695.76	269.70	216.88	913.27	506.08	326.34
V_{90} (%)	96.32	98.90	97.32	0.71	96.04	99.91	97.04	0.95
V_{92} (%)	95.92	97.89	96.05	0.90	94.67	97.01	95.88	1.07
V_{95} (%)	92.31	96.16	95.08	1.11	90.29	95.89	94.95	1.19
V_{100} (%)	48.67	50.72	49.49	0.84	41.05	45.21	43.89	1.73
V_{105} (%)	0.55	3.39	1.54	1.02	0.08	7.48	2.28	1.99
V_{107} (%)	0.00	0.56	0.25	0.01	0.00	2.56	1.02	0.45
V_{108} (%)	0.00	0.40	0.18	0.16	0.00	0.20	0.07	0.03
V_{110} (%)	0.00	0.02	0.01	0.00	0.00	0.00	0.00	0.00
Min (% Rx_{min})	12.80	58.70	39.55	9.64	0.81	45.76	22.92	17.84
Max (%Rx_{max})	106.28	113.54	109.52	1.43	106.14	111.52	108.61	1.88
Mean(%Rx_{avg})	98.04	99.92	99.39	0.36	96.06	101.28	99.01	1.52

The mean values of the minimum (%Rx_{min}), maximum (%Rx_{max}) and average (%Rx_{avg}) doses deposited in the Brst_opt volume were 39.55 ± 9.64% (19.77 Gy), 109.52 ± 1.43% (54.76 Gy) and 99.39 ± 0.36% (49.72 Gy) of the prescribed dose, respectively. Those for the Chst_opt volume were 22.92 ± 17.84% (11.46 Gy), 108.61 ± 1.88% (54.31 Gy) and 99.01 ± 1.52% (49.51 Gy) percentage doses deposited, respectively (Acquah *et al.*, 2023).

4.2.3 Organ at Risks Analysed Doses

For every VMAT treatment plan dose distribution, dose parameters and DVH for the heart volume, ipsilateral lung volume, and contralateral lung volume and breast volumes were analysed.

4.2.3.1 Evaluated Heart Doses

For left-sided cases, the mean heart volumes for intact breast and chest-wall irradiated patients were 586.00 ± 51.73 cm^3 (ranging from 453.12 cm^3 to 689.47 cm^3) and 630.21 ± 110.62 cm^3 (ranging from 414.64 cm^3 to 771.32 cm^3), respectively. Table 4.8 captures the statistical analysis parameters of heart volume doses for both intact breast and chest-wall irradiated patients. The mean heart dose recorded were 4.61 ± 1.76 Gy and 5.18 ± 1.55 Gy for intact breast plans and chest-wall irradiated patients, respectively.

Table 4.8: Statistical analysis summary of heart volume that received 5% and 20% of prescribed dose and its volume that received 30 Gy for intact breast and chest-wall cases.

	Intact Breast VMAT plan				Chest-wall VMAT plan			
	Min	**Max**	**Mean (x)**	**SD**	**Min**	**Max**	**Mean (x)**	**SD**
Heart volume(cc)	453.12	689.47	586.00	51.73	414.64	771.32	630.21	110.62
$V_{30\ Gy\ (\%)}$	0.00	1.89	1.03	0.47	0.01	1.92	1.24	0.51
$V_{5\%\ (\%)}$	9.11	99.84	71.39	24.40	10.05	99.92	72.46	22.97
$V_{20\%\ (\%)}$	1.13	19.09	14.05	4.33	1.44	19.67	14.70	4.49
$D_{min(Gy)}$	0.26	2.21	1.04	0.68	0.38	2.53	1.39	0.60
$D_{max(Gy)}$	14.87	51.03	28.72	9.23	16.26	53.95	41.08	9.81
$D_{avg(Gy)}$	1.26	6.85	4.61	1.76	1.56	7.28	5.18	1.55

For the intact breast cases, the mean of the minimum ($\%Rx_{min}$), maximum ($\%Rx_{max}$) and average ($\%Rx_{avg}$) doses deposited within the heart volume were 2.69 ± 1.84% (1.04 Gy), 61.80 ± 18.46% (28.72 Gy) and 9.52 ± 3.52% (4.61 Gy), respectively. Those of the chest-wall cases were 2.78 ± 1.20% (1.39 Gy), 82.17 ± 19.62% (41.08 Gy) and 10.36 ± 3.09% (5.18 Gy) percentage doses deposited, respectively (Acquah *et al.*, 2023).

4.2.3.2 Evaluated Ipsilateral Lung Doses

The mean ipsilateral lung volumes for irradiated patients with intact breast and chest-wall were 799.83 ± 276.01 cm^3 (ranging from 500.12 cm^3 to 2139.49 cm^3) and 809.51 ± 246.58 cm^3 (ranging from 511.89 cm^3 to 2096.94 cm^3), respectively. The mean ipsilateral lung volume that received 20 Gy of prescribed dose were 12.22 ± 3.86% and 13.19 ± 3.74% for intact breast plans and chest-wall plans, respectively. Table 4.9 shows the dosimetric analysis of the ipsilateral lung volumes for both the intact breast and chest-wall VMAT plans treated with 50 Gy dose in 25 fractions.

Table 4.9: Summarised statistical analysis of the ipsilateral lung volumes that received 5% and 20% of PD and its volume that received 20 Gy for intact breast and chest-wall cases.

	Intact Breast VMAT plan				Chest-wall VMAT plan			
	Min	**Max**	**Mean (x)**	**SD**	**Min**	**Max**	**Mean (x)**	**SD**
Ipst. lung volume(cc)	500.12	2139.49	799.83	276.01	511.89	2086.94	809.51	246.58
$V_{20\,Gy}$ (%)	1.78	17.16	12.22	3.86	2.12	18.54	13.19	3.74
$V_{5\%}$ (%)	46.71	99.08	78.11	14.68	47.05	99.28	73.71	14.80
$V_{20\%}$ (%)	10.71	39.77	26.25	8.65	11.53	40.41	26.94	9.02

Table 4.9: Continued from previous page

$D_{min(Gy)}$	0.98	2.18	0.20	0.49	0.99	2.41	0.62	0.55
$D_{max(Gy)}$	47.00	50.69	40.73	2.30	48.14	51.63	41.05	2.12
$D_{avg(Gy)}$	9.03	12.25	4.15	2.06	9.52	12.88	5.21	2.28

4.2.3.3 Evaluated Contralateral Lung Doses

The mean contralateral lung volumes were 906.80 ± 326.97 cm^3 (ranging from 668.15 cm^3 to 2520.69 cm^3) and 899.04 ± 414.25 cm^3 (ranging from 682.33 cm^3 to 3003.07 cm^3) for intact breast and chest-wall irradiated cases, respectively. The dose constraint was a percentage of the contralateral lung volume that received 5 Gy (V_{5Gy} (%)). The dosimetric analysis for the contralateral lung volume is captured in Table 4.10 for both the intact breast and chest-wall VMAT plans.

Table 4.10: Summarised statistical analysis of the contralateral lung volume that received 5 Gy for intact breast and chest-wall irradiated cases.

	Intact Breast VMAT plan				**Chest-wall VMAT plan**			
Cont. lung	**Min**	**Max**	**Mean (x)**	**SD**	**Min**	**Max**	**Mean (x)**	**SD**
volume(cc)	668.15	2520.69	906.80	326.97	682.33	3003.07	899.04	414.25
$V_{5\ Gy\ (\%)}$	0.00	72.10	28.19	19.83	0.00	69.76	27.85	20.04
$D_{min(Gy)}$	0.05	1.84	0.55	0.40	0.04	1.90	0.59	0.75
$D_{max(Gy)}$	2.61	49.51	16.97	12.21	2.53	48.69	14.72	12.56
$D_{avg(Gy)}$	0.42	8.10	3.57	2.15	0.39	7.55	3.95	3.09

4.2.3.4 Evaluated Contralateral Breast Doses

Table 4.11 summarises the statistical analysis of contralateral breast volume dose parameters for intact breast and chest-wall treatment plans. Key findings indicate that mean doses to the contralateral breast were consistently low, under 5 Gy, across both plan types.

Table 4.11: Statistical analysis summary of contralateral breast volume for intact breast and chest-wall irradiated cases.

	Intact Breast VMAT plan				Chest-wall VMAT plan			
	Min	**Max**	**Mean (x)**	**SD**	**Min**	**Max**	**Mean (x)**	**SD**
Cont.breast volume(cc)	329.44	2139.49	743.23	356.07	394.37	2047.03	754.15	400.41
$V_{5\ Gy\ (cc)}$	0.00	799.72	134.30	137.60	0.00	769.71	127.57	120.32
$D_{min(Gy)}$	0.00	1.50	0.56	0.29	0.00	1.39	0.51	0.23
$D_{max(Gy)}$	0.58	7.64	3.66	2.87	0.51	7.28	3.58	2.05
$D_{avg(Gy)}$	0.24	4.92	2.06	1.97	0.20	4.99	1.95	1.81

The rest of the relevant graphical representations obtained from the dosimetric data analysis are presented in the appendix section.

4.2.4 Breast Plan Acceptability Criteria Based on Dosimetric Analysis

This phase of the study analysed patient treatment plan database to define the facility-based plan acceptability criteria (PTV coverage and doses to OARs) for VMAT breast planning. Based on patient dosimetric data analysed, there was lack of consistencies among the facility on what is

considered an acceptable treatment plan. An intact breast plan with as low as 92.31 percentage volume (minimum value recorded) of the PTV being covered by 95 percent of the prescribed dose was accepted. Dose coverage to the target volumes as well as doses to OARs varied from the facility's plan objectives based on the ICRU 83 report ((ICRU), 2010). From the PTV dosimetric parameters analysed, the mean dose that covered 95% of the intact breast PTV was 95.08 ± 1.11% and 94.95 ± 1.19% for chest-wall PTV. The plan acceptability criteria as established for the facility's VMAT breast planning based on dosimetric data analysed are presented in Table 4.12. It is possible to develop acceptable intact breast and chest-wall treatment VMAT plans using the current facility automated treatment planning protocol. Based on the established plan acceptability criteria, acceptable target dose conformance and high dose gradients to contralateral OAR were observed. The plans could be classified as acceptable but not clinically ideal to produce the desired optimal overall treatment outcome.

Table 4.12: Facility-based intact breast and chest-wall VMAT treatment plan acceptability criteria established from dosimetric data analysed over 2 years.

ROI	Breast VMAT plan		Chest-wall VMAT plan	
	Mean (x)	SD	Mean (x)	SD
PTV				
$V_{95\,(\%)}$	95.05	1.11	94.95	1.19
$V_{105\,(\%)}$	1.54	1.02	2.28	1.99
HI	0.14	0.03	0.15	0.04
UI	1.09	0.03	1.11	0.03
CI	0.92	0.04	0.91	0.04

Table 4.12: Continued from previous page

Heart				
V_{30Gy} (%)	1.03	0.47	1.24	0.51
D_{avg} (Gy)	4.61	1.76	5.18	1.55
Ips. Lung				
V_{20Gy} (%)	12.22	3.86	13.19	3.74
D_{avg} (Gy)	4.15	2.06	5.21	2.28
Cont. Lung				
V_{5Gy} (%)	28.19	19.83	27.85	20.04
Cont. Breast				
D_{max} (Gy)	3.66	2.87	3.58	2.05

Both minor and major acceptability deviations (standard deviations) from the planning objectives were observed from the established plan acceptability. It was observed from dosimetric data analysed that out of the 41 intact breast cases; 34 plans met the 95% dose coverage acceptance criteria with 28 plans falling within the mean percentage deviation (95.08%± 1.11%) that were covered by the 95% of the prescribed dose. On the other hand, 7 intact breast plans failed to achieve the expected 95% volume coverage with the 95% of the prescribed dose. It was also observed that 42 chest-wall plans out of the 53 chest-wall cases analysed met the 95% dose coverage while 11 chest-wall plans failed to achieve 95% dose coverage. It is worth mentioning also that 36 plans fell within the mean percentage deviation (94.95 ± 1.19%) that were covered by the 95% dose coverage. The optimised PTV's $V_{95\%}$ and $V_{105\%}$ values were of great importance to the study in establishing the plan acceptability criteria. The dose coverages were more conformed in the intact breast volumes than in the chest-wall volumes. Results showed that 95% of PD covered an average

Brst_opt volume of 95.08 ± 1.11% and an average Chst_opt volume of 94.95 ± 1.19%. Based on this current data, improvements to the facility's breast treatment plan protocol needed to be carried out to achieve at least the mean dose coverage of 95% of PTV volume. For future breast treatment plans, PTV_opt volumes can be assessed against these mean PTV_opt values to guarantee consistency in treatment planning, as advised for Level 2 reporting in ICRU Report 83 (ICRU, 2010). Adnani (Adnani *et al.*, 2020) suggested that limiting the breast volume receiving 105% of the prescribed dose can lead to improved treatment outcomes. The study's results showed that 1.54 ± 1.02% of the optimal breast volume (Brst_opt) and 2.28 ± 1.99% of the optimal Chst_opt received 105% of the prescribed dose (52.5 Gy). Notably, all mean optimal PTV_opt received less than 3% of any hot spot exceeding 105% of the PD. Furthermore, table 4.7 indicates that minimising $V_{105\%}$ to less than 1% can lead to even better outcomes in breast cancer irradiation.

The critical OAR of importance for patients being treated with cancer in the left breast is the heart. The realisation of increased risk of late effects on the heart began as early breast cancer radiation clinical trials began to collect big patient data and longer follow-up analysis (EBCTCG, 2000; EBCTCG, 2005; Barnett *et al.*, 2009; Barton *et al.*, 2014; Chen *et al.*, 2011). Results from this phase of the study show a minimal dose exposure to the heart according to the facility's protocol on heart dose constraint (mean dose of 7.5 Gy). For intact breast irradiation analysed, the mean dose (D_{avg}) received by the heart was 4.61 ± 1.76 Gy (min: 1.26 Gy and max: 6.85 Gy). The mean heart dose (D_{avg}) for the chest-wall cases was 5.18 ± 1.55 Gy (min: 1.56 Gy and max: 7.28 Gy). Darby's study of over 2,000 breast cancer patients treated with radiotherapy over a 43-year period found a direct link between mean heart dose and major coronary events (Darby, 2013). Results showed a 7.4% increase in cardiac mortality risk per 1 Gy of mean heart dose, with effects emerging within 5 years and lasting at least 20 years.

Table 4.8 reveals that intact breast VMAT plans yield lower heart doses compared to chest-wall VMAT plans. This discrepancy may be attributed to the reduced breast tissue and thinner target volumes characteristic of many chest-wall cases. To further evaluate heart dose exposure, two additional objectives were assessed, the V_{30Gy} (%) and $V_{20\%\,(\%)}$ (the heart volume that received 30 Gy and the heart volume that received 20% of prescribed dose, respectively). The study found that the mean heart volume receiving 30 Gy was 1.03 ± 0.47% for the intact breast VMAT plan and 1.24 ± 0.51% for the chest-wall VMAT plan. These values were below the facility's heart objective of $V_{30Gy} < 5\%$ (heart volume receiving 30 Gy should be less than 5%). The mean heart volume receiving 20% of the prescribed dose ($V_{20\%}$) was comparable for intact breast and chest-wall VMAT plans, measuring 14.05 ± 4.33% and 14.70 ± 4.49%, respectively. These values again were below the departmental heart dose objective of $V_{20\%\,(\%)} < 20\%$ (heart volume receiving 20% of PD (10 Gy) should be less than 20%). Based on these current results, the department's VMAT breast treatment planning can be used to achieve heart dose values of 10 Gy and 30 Gy to less than 20% and 5% of the heart volumes, respectively. Same plans would meet the mean dose of less than 7.5 Gy received by the heart volumes.

Radiation treatment for breast cancer often results in significant lung exposure due to their anatomical proximity to the target volumes. To mitigate this, the facility's VMAT breast planning protocol mandates contouring of both ipsilateral (primary organ at risk) and contralateral lung volumes. In accordance with ICRU 83 (ICRU 83, 2010), lung dose-volume specifications require multiple parameters to ensure accurate reporting, considering the parallel nature of lung tissue." So, for the ipsilateral lung, volumes receiving 20 Gy ($V_{20Gy\,(\%)}$) and 30 Gy ($V_{30Gy\,(\%)}$) and mean doses (D_{avg}) received were collected and analysed. The mean absorbed dose recorded was a helpful measure because of the highly non-homogeneous absorbed dose distributions in the lung volumes.

The VMAT planning protocol required the ipsilateral lung to meet the following dose constraints, $V_{20Gy} < 30\%$, $V_{30Gy} < 20\%$ and mean dose ≤ 12.5 Gy. The intact breast VMAT and chest-wall VMAT plans recorded a mean absorbed dose of 4.15 ± 2.06 Gy (min: 9.03 Gy and max: 12.25 Gy) and 5.21 ± 2.28 Gy (min: 9.52 Gy and max: 12.88 Gy), respectively, to the ipsilateral lung volume. The mean lung volume that received 20 Gy was similar for intact breast (12.22 ± 3.86% with mean percentage error of -59.3 ± 12.90%) and chest-wall (13.19 ± 3.74% with mean percentage of -56.03 ± 12.47%) VMAT plans, indicating no significant difference in ipsilateral lung dose. Both plans met facility objectives for lung doses, as seen in Table 4.9.

Volumes that received dose of 5 Gy ($V_{5Gy\ (\%)}$) were also recorded and analysed for the contralateral lung volumes. According to a study conducted by Hall and Wuu (Hall and Wuu, 2003), VMAT breast plans enhance tumour target dose conformity. However, this improvement comes at the cost of increased low-dose radiation exposure to the contralateral lung and breast, potentially elevating the risk of secondary malignancies. The data presented in table 4.10 supports their findings, indicating minimal radiation exposure to the contralateral lung volume for both intact breast and chest-wall cases. Specifically, for intact breast VMAT plan the minimum, maximum, and mean low doses recorded were 0.05 Gy, 1.84 Gy, and 0.55 ± 0.40 Gy, respectively. For the chest-wall VMAT plan, corresponding low doses of 0.04 Gy, 1.90 Gy, and 0.59 ± 0.75 Gy were obtained. These results confirm that low doses of radiation were delivered to the contralateral lung volume in both treatment plans. The mean contralateral lung volume that received 5 Gy was comparable between intact breast (28.19 ± 19.83% with mean percentage error of -6.03 ± 66.10%) and chest-wall plans (27.85 ± 20.04% mean percentage error of -7.17 ± 68.80%). These mean percentage error calculations implied the measured mean OAR dose and volume values were lower than their reference values. While the facility's protocol achieves similar mean doses, increased in low

contralateral lung doses observed require further optimisation improvement in the VMAT planning. When planning and delivering VMAT for breast cancer, the contralateral breast is another critical organ at risk that must be considered. Stovall *et al* examined patient data from 1985 to 1999, where patients received radiation from two opposing tangential beams, with an average dose of 1.3 Gy to the contralateral breast (Stovall *et al.*, 2008). The study found that women under 40 years old are particularly vulnerable, with those receiving an additional 1 Gy or more to the contralateral breast facing a 2.5-fold increased risk of developing secondary breast cancer. Notably, this elevated risk did not apply to women over 40 years of age. Boice (Boice *et al.*, 1992) reported comparable results, revealing a substantial increase in the risk of secondary breast cancer among women under 45 years, with incidence rates climbing from 2.7% to 11.1%. Dosimetric analysis in phase 2 recorded a mean dose of less than 5 Gy to the contralateral breast for intact breast and chest-wall VAMT cases. From Table 4.11, the mean Dmax for the intact breast plan were 3.66 ± 2.87 Gy and 3.58 ± 2.05 Gy for the chest-wall plan, respectively. Current data confirm that the department's VMAT breast planning meets the 5-Gy contralateral breast dose limit. However, just like the contralateral lung, the contralateral breast volume also recorded high low doses in the breast volume for both intact breast and chest-wall VMAT plans. The analysed intact breast plans recorded a maximum dose of 7.64 Gy while the chest-wall plans recorded a maximum dose of 7.28 Gy.

The quality of dosimetric plans was evaluated using a combination of qualitative and quantitative methods. For all 94 patients, each plan underwent quantitative assessment through the calculation of HI, UI, and CI from the optimised planning target volumes. These dose metrics, extracted from the DVH, provided an objective and reliable means of quantifying plan quality in terms of target coverage. Results showed good dose conformity, uniformity, and homogeneity in Brst_opt and

Chst_opt volumes. The mean homogeneity index values of 0.14 ± 0.03 and 0.15 ± 0.04 demonstrated good dose uniformity within the target volumes, respectively. The uniformity and conformity index values further underscored the excellent dose distribution quality. The mean UI values were 1.09 ± 0.03 for Brst_opt and 1.11 ± 0.03 for Chst_opt cases. The calculated mean CI values were 0.92 ± 0.04 for Brst_opt and 0.91 ± 0.04 for Chst_opt cases, respectively. These results indicate optimal dose conformity, with high-dose regions closely aligning with the target volumes, demonstrating a high degree of precision in radiation delivery. The optimised intact breast VMAT plans showed superior dose metrics than the chest-wall plans. However, the facility's VMAT protocol minimised hotspots, maintained improved dose conformity and uniformity across intact breast and chest-wall volumes, underscoring the protocol's effectiveness in delivering quality radiation therapy to the target (Acquah *et al.*, 2023).

4.3 PHASE THREE STUDY

From the result analysis based on the established facility-based plan acceptability criteria in phase two of the study, the facility's VMAT breast treatment planning optimisation criteria were reviewed. Proposed non-generic but data-driven planning optimisation criteria based on patient dosimetric data from the facility were developed. During phase 3, twenty (20) randomly selected left-sided patients (10 intact breast and 10 chest-wall irradiated cases) from the total 61 left-sided patient database retrospectively studied in phase 2 were used. Results obtained during phase 3 are presented and discussed below.

4.3.1 Optimisation Quality Metric Selection and Scoring Process

To establish superior planning optimisation criterion, dosimetric parameters and their appropriate priorities based on the facility's data were used as starting point (reference point). The current

facility's VMAT inverse planning optimisation criteria with constraint priorities used in designing all the breast plans analysed in the phase 2 study were presented in Table 3.3. These parameters formed the basis (plan-overview) in the established proposed planning acceptability criteria as shown in Table 4.12. The scoring parameters selected were relevant to the overall clinical outcome of the treatment plan and were recommended by the ICRU 83 (ICRU, 2010) for level 2 reporting during IMRT treatment planning evaluation. These were the PTVs, ipsilateral lung volume, the heart, contralateral lung and breast volume recorded doses and their DVH evaluations. The current facility's planning optimisation criteria had seven metric types and constraints for its VMAT breast treatment planning. A higher relative 50% optimisation priority was placed on the maximum PTV dose to being limited to a constraint of 105% of the target volume. As described in the methodology pertaining to the processes of selecting the sub-metric parameters in the development of the optimisation quality metric, Table 4.13 presents the number of parameters selected for each step of the process in arriving at the final developed OQM parameters.

Table 4.13: Optimisation quality metric selection data type with the corresponding number of parameters analysed at each selection stage.

Type of data	Number of parameters
Total data types collected (2-year analysis)	81
Dosimetric data	53
Majority rule data	17
Proposed OQM data	11

The eleven developed OQM parameters were for the PTV; the $\mathbf{V_{95\%}}$, $\mathbf{V_{105\%}}$ and for the PTV indices; $\mathbf{D_2}$, $\mathbf{D_{98}}$, and **UI** (D_5/D_{95}). For the Ipsilateral lung volume; $\mathbf{V_{20Gy}}$, $\mathbf{D_{avg}}$, for the heart

volume; **V_{30Gy}, D_{avg}.** and finally, the parameters for the contralateral lung and breast were **V_{5Gy}** and **D_{max}**, respectively.

The score values (minimum and maximum scores) for the PTV and OARs OQM parameters are presented in Table 4.14 and Table 4.15, respectively, based on results from phase 2 dosimetric analysis. The scores ranged from a minimum score value of zero to a maximum score value of twenty (0-20) depending on the priorities of parameters analysed. A total score value of 40 was assigned to the PTV metric parameters while a total score value of 60 was assigned to the OARs. A higher premium score of 15 was placed on the target volume that received 105 percent of the prescribed dose ($V_{105\%}$). An equal maximum score of 10 was assigned to all the remaining 6 different OARs sub-metric parameters, an indication of their importance in achieving optimal VMAT treatment plans with minimal doses to all critical structures.

Table 4.14: The developed PTV OQM metric parameters used to optimise the training plans with their maximum and minimum metric scoring values.

ROI/Contour	Dose Metric	Definition	OQM scoring
PTV	$V_{95\%}$	Volume receiving 95% of prescribed dose	0 (<90%) 10 (100%)
	$V_{105\%}$	Volume receiving ≤ 105% of prescribed dose	0 (>10cm^3) 15 (0cm^3)
	$D_{2\%}$	Dose received by 2% of volume	0 (>110%) 5(<103%)

Table 4.14: Continued from previous page

$D_{98\%}$	Dose received by 98% of volume	0 (<90%) 5 (98%)
Uniform dose	**UI** = D_5/D_{95}	0 (>1.09) 5 (1.00)

Table 4.15: The developed OAR OQM metric parameters used to optimise the training plans with their maximum and minimum metric scoring.

ROI/Contour	Dose Metric	Definition	OQM scoring
Heart	V_{30Gy}	Volume receiving 30Gy	0 (>10%) 10 (<5%)
	D_{avg}	Mean Dose	0 (>10Gy) 10 (<4Gy)
Ipsilateral lung	V_{20Gy}	Volume receiving 20Gy	0 (>10%) 10 (<5%)
	D_{avg}	Mean Dose	0 (>10Gy) 10 (<5Gy)
Contralateral breast	D_{max}	Maximum Dose	0 (>7Gy) 10 (<4Gy)
Contralateral lung	V_{5Gy}	Volume receiving 5 Gy	0 (>30%) 10 (<20%)

4.3.2 Optimisation Quality Metric-Based VMAT Plans.

The twenty randomly selected left-sided breast cancer cases were replanned based on the developed optimisation quality metrics and scoring values as presented in Table 4.16 and Table 4.17.

Table 4.16: PTV OQM parameters with scoring values used in scoring the replanned training plans during the establishment of the proposed new facility-based planning optimisation criteria for breast VMAT planning.

PTV	**Sub-metric**						
OQM scores	min dose (Gy)	OQM scores	max DVH (Gy) 52.5 Gy@2%	min DVH (Gy) 50 Gy@98%	UI = 1	OQM scores	max dose (cc)
10	50.0	**5.0**	< 52.5	50.0	1.00	**15.0**	0.0
9	49.5	**4.5**	52.8	49.5	1.01	**13.5**	1.0
8	49.0	**4.0**	53.0	49.0	1.02	**12.0**	2.0
7	48.5	**3.5**	53.4	48.5	1.03	**10.5**	3.0
6	48.0	**3.0**	53.7	48.0	1.04	**9.0**	4.0
5	47.5	**3.5**	54.0	47.5	1.05	**7.5**	5.0
4	47.0	**2.0**	54.3	47.0	1.06	**6.0**	6.0
3	46.5	**1.5**	54.6	46.5	1.07	**4.5**	7.0
2	46.0	**1.0**	54.9	46.0	1.08	**3.0**	8.0
1	45.5	**0.5**	55.0	45.5	1.09	**1.5**	9.0
0	≤ 45.0	**0.0**	> 55.0	≤ 45.0	≥ 1.10	**0.0**	≥ 10.0

A training patient plan with 10.0 cc or more of its PTV volume receiving a maximum dose ($V_{105\%}$) were scored an OQM score value of 0. The maximum and minimum DVH dose to the PTV that met the new sub-metric objective scored an OQM score value of 5, respectively, while the plan with the best uniformed dose also scored an OQM score value of 5.

Table 4.17: OAR OQM parameters with scoring values used in scoring the replanned training plans during the establishment of the proposed new facility-based planning optimisation criteria for breast VMAT planning.

OAR	**Heart**		**Ips Lung**		**Cont. Brst**	**Cont. Lung**
			Sub-metric			
OQM scores	V30Gy @5%	Davg ≤5Gy	V20Gy @5%	Davg ≤5Gy	dmax ≤5Gy	V5Gy @20%
10	≤5.0	≤5.0	≤5.0	≤5.0	≤5.0	≤20
9	5.5	5.5	5.5	5.5	5.2	21
8	6.0	6.0	6.0	6.0	5.4	22
7	6.5	6.5	6.5	6.5	5.6	23
6	7.0	7.0	7.0	7.0	5.8	24
5	7.5	7.5	7.5	7.5	6.0	25
4	8.0	8.0	8.0	8.0	6.2	26
3	8.5	8.5	8.5	8.5	6.4	27
2	9.0	9.0	9.0	9.0	6.6	28
1	9.5	9.5	9.5	9.5	6.8	29
0	≥10	≥10	≥10	≥10	≥7.0	≥30

During the plan trial simulations of each training plan, the mean OQM total score values of the best plan trials were 89.05 ± 0.58 and 87.95 ± 0.53 (out of a possible total score value of 100) for intact breast and chest-wall, respectively, as presented in table 4.18.

Table 4.18: Mean OQM score values for the best ten training plan trials used in developing the proposed facility-based POC for intact breast and chest-wall planning.

ROI/Contour	OQM Sub-Metric Max score value	10 Intact breast plans Mean ± SD	10 Chest-wall plans Mean ± SD
	Total score for $V_{95\%}$ (max 10)	7.90 ± 0.32	7.45 ± 0.64
PTV	Total score for $V_{105\%}$(max 15)	14.10 ± 1.97	14.05 ± 1.77
	Total score for $D_{2\%}$(max 5)	5.00 ± 0.00	5.00 ± 0.00
	Total score for $D_{98\%}$(max 5)	2.90 ± 0.21	2.45 ± 0.24
	Total score for UI (max 5)	2.15 ± 0.34	2.05 ± 0.46
Heart	Total score for $V_{30\ Gy}$(max 10)	10.00 ± 0.00	10.00 ± 0.00
	Total score for D_{avg}(max 10)	10.00 ± 0.00	10.00 ± 0.00
Ips. lung	Total score for $V_{20\ Gy}$(max 10)	10.00 ± 0.00	10.00 ± 0.00
	Total score for D_{avg}(max 10)	8.00 ± 0.13	7.95 ± 0.21
Contr. breast	Total score for D_{max}(max 10)	10.00 ± 0.00	10.00 ± 0.00
Contr. lung	Total score for $V_{5\ Gy}$(max 10)	9.00 ± 0.04	9.00 ± 0.09
Total OQM score	Total plan score (max 100)	**89.05 ± 0.58**	**87.95 ± 0.53**

From the Table 4.18 above, the sub-metrics with the least OQM score values were the minimum DVH dose to the PTV and the plan's uniformity index. It was observed that the planning objective of the newly introduced sub-metric parameter $D_{98\%;}$ used in the proposed planning optimisation criteria was relatively difficult to achieve compared to the other sub-metric parameters. The desired plan uniformity index was half-way achieved as its mean values indicated in Table 4.18. These represented the best possible plans given the set facility's objective criteria / plan endpoints and the randomly selected test patients' contours used for the manual trial simulations.

4.3.3 Establishment of Proposed Facility-Based Planning Optimisation Criteria

Analysis of the total OQM score values from the training plans led to the establishment of the facility-based planning optimisation criteria. Using these criteria produced high quality optimal VMAT intact breast and chest-wall treatment plans using the optimisation priority values as presented in Table 4.19. The optimisation criteria had both primary/ideal and secondary/acceptable endpoints for all the dose metric objectives.

Table 4.19: Proposed new VMAT breast planning optimisation criteria with primary and secondary endpoint objectives and their respective priority value for each dose metric.

ROI/Contour	Dose Metric	Acceptable (secondary)	Ideal (primary)	Priority
PTV	$V_{95\%}$	≥ 95%	100% (min dose)	10
	$V_{105\%}$	≤ 5.00cc	0.00cc (max dose)	50
	$D_{2\%}$	52.50 Gy	51.50 Gy (max DVH)	5
	$D_{98\%}$	47.50 Gy	49 Gy (min DVH)	5

Table 4.19: Continued from previous page

	Uniform Dx	= 1.04	1.00 (uniform dose)	5
Heart	V_{30Gy}	≤ 10%	≤ 5%	10
	D_{avg}	≤ 5Gy	≤ 4 Gy	5
Ips. lung	V_{20Gy}	≤ 10%	≤ 5%	10
	D_{avg}	≤ 8.5 Gy	≤ 5 Gy	5
Contr. breast	D_{max}	≤ 5 Gy	≤4 Gy	3
Contr. lung	V_{5Gy}	≤ 30%	≤ 20%	2

The newly proposed optimisation criteria did not only reduce normal tissue exposure but also achieved target coverage for both the intact breast and chest-wall PTVs. This planning optimisation criteria represents a promising optimisation alternative for improving long-term breast cancer treatment outcomes.

The maximum score values of all the ROI's sub-metrics adapted in the establishment of the proposed planning optimisation criteria are presented in Table 4.20. The sub-metrics associated with the PTV were the $V_{95\%}$, $V_{105\%}$, D_2, D_{98}, uniformity index ($UI = D_5/D_{95}$) and that for the OARs were the V_{30Gy}, D_{avg} for the heart, V_{20Gy}, Davg for the ipsilateral lung, D_{max} for the contralateral breast and V_{5Gy} for the contralateral lung. Where D_2, D_5, D_{95}, and D_{98} represent the doses received by 2%, 5%, 95%, and 98% volumes of the PTV_opt, respectively. $V_{95\%}$, and $V_{105\%}$ are the volumes of PTV_opt covered by 95% and 105% isodose lines, and V_{5Gy}, V_{20Gy} and V_{30Gy} are the ROI volume that received 5 Gy, 20 Gy and 30 Gy, respectively. D_{avg} and D_{max} represent the average and maximum doses received by the specific ROI. Sub-metrics with their respective OQM score values were established with the highest priority being placed on $V_{105\%}$ sub-metric.

Table 4.20: VMAT planning objectives used in establishing the proposed new facility-based planning optimisation criteria with maximum metric value.

ROI/Contour	Sub-Metric	Endpoint	Max metric value
	$V_{95\%}$	≥ 95% Vol	50 Gy (min dose)
PTV	$V_{105\%}$	receiving ≤ 105%	52.5 Gy (max dose)
		of PD	
	$D_{2\%}$	Dose received	52.5 Gy (max DVH)
		2% of vol.	
	$D_{98\%}$	Dose received	50 Gy (min DVH)
		by 98% of vol.	
	Uniform dose	= 1.00	50 Gy (uniform dose)
Heart	$V_{30\ Gy}$	≤ 10%	30 Gy ($V_{5\%}$)
	D_{avg}	≤ 5 Gy	5 Gy (average dose)
Ips. lung	$V_{20\ Gy}$	≤ 10%	20 Gy ($V_{5\%}$)
	D_{avg}	≤ 8.5 Gy	5 Gy (average dose)
Contr. breast	D_{max}	≤ 5 Gy	5 Gy (max dose)
Contr. lung	$V_{5\ Gy}$	≤ 20%	5 Gy ($V_{20\%}$)

The maximum OQM metric score value represented the highest possible value (Ideal) for which each sub-metric may achieve the highest endpoint allocated. They were set higher than the planning objective criteria/endpoint (acceptable) and had tighter constraints to produce plans of higher quality (ideal). The minimum dose of 50 Gy and maximum dose of 52.5 Gy to the PTV_opt were very important as the targets achieved optimal dose coverage without hotspots.

4.3.4 Patient Cohort Plans Comparison

4.3.4.1 Cohort Dosimetric Results

The statistical comparison between the intact breast and chest-wall manually generated training and automated-generated cohort VMAT plans with respect to PTV_opt and OAR sub-metrics analysis are presented in this section. Figure 4.3 shows the dose distribution within an intact breast plan using the PAC and POC. It shows the transverse, coronal and sagittal dose distribution views for one selected patient's treatment plan. PAC as used represents the optimisation criteria used in establishing the facility's breast plan acceptability criteria (automated plans) and POC represents the newly proposed facility-based planning optimisation criteria (training plans).

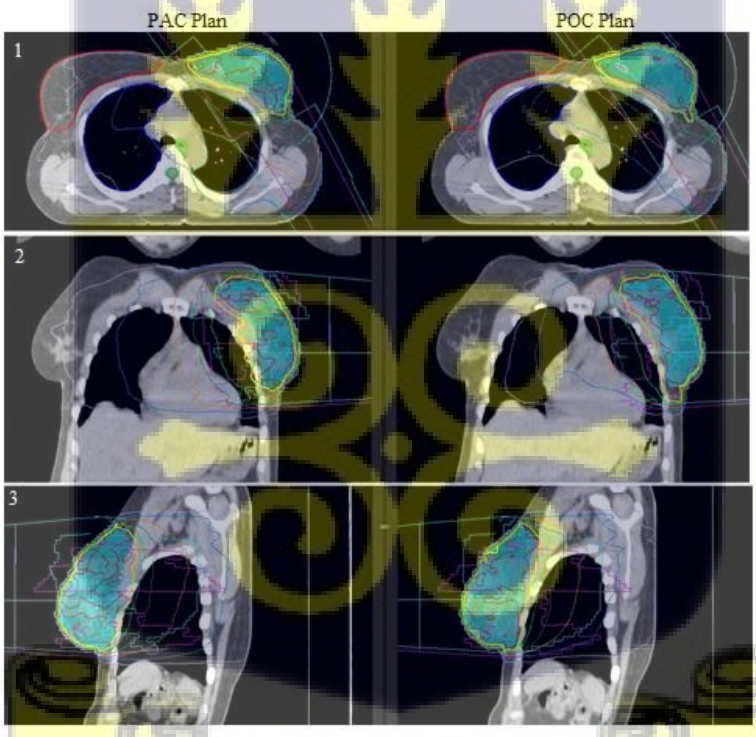


Figure 4.3: Pinnacle TPS interphase showing 95% isodose distribution (yellow colour) of prescribed dose in transverse, coronal and sagittal sections for the PAC and POC plans, respectively.

From Figure 4.3, it was observed that the POC plan had a better breast tumour target dose distribution and a lower maximum dose within the target area as compared with the PAC plan. However, there were significant low dose areas in the patient's contralateral OARs for the PAC plan which were less visible in the POC plan.

Table 4.21 and Table 4.22 show the mean values with their standard deviations (SD) and the calculated p-values for each paired sub-metric. From the results as presented in Table 4.21, the automated cohort plans had slightly higher PTV_opt mean values than their training cohorts optimised plans although both achieved the planning objective set for the PTV_opt. Important observations were the mean target volumes values of $V_{95\%}$ and $V_{105\%}$ for both the training and automated plans. Their recorded mean values exhibited no significant statistical difference as their calculated p-values were greater than the 5% significance level. There was also no statistically significant difference observed between the means of the two cohort plans in terms of their calculated dose indices; that is the HI, UI, CI, and the additional QI calculated for both the intact breast and chest-wall plans. The notable significant difference observed for all the PTV_opt were the $V_{90\%}$ and $V_{92\%}$ for both intact breast and chest-wall plans.

Table 4.21: Quantitative analysis of PTV sub-metrics for the original automated PAC plans and the training replanned POC plans.

	Intact breast PTV Volume		Chest-wall PTV Volume	
Sub-metric	**Mean ± SD (%)**	**p-value**	**Mean ± SD (%)**	**p-value**
	PAC		**PAC**	
	POC		**POC**	
$V_{90\%}$	99.20 ± 0.30	1.69E-05	98.74 ± 0.54	2.07E-04
	98.38 ± 0.32		98.16 ± 0.47	
$V_{92\%}$	98.56 ± 0.37	3.49E-06	97.85 ± 0.56	1.93E-05
	97.32 ± 0.46		97.21 ± 0.59	
$V_{95\%}$	95.81 ± 0.64	0.154697	95.11 ± 0.72	0.356681
	95.46 ± 0.40		95.04 ± 0.61	
$V_{100\%}$	65.11 ± 6.08	0.263945	67.87 ± 5.97	0.279255
	61.52 ± 7.76		59.13 ± 5.74	
$V_{105\%}$	0.76 ± 0.68	0.411718	0.87 ± 0.16	0.542725
	1.04 ± 0.81		1.43 ± 0.39	
$V_{107\%}$	0.34 ± 0.32	0.912751	0.39 ± 0.30	0.994352
	0.36 ± 0.50		0.42 ± 0.65	
$V_{108\%}$	0.07 ± 0.08	0.570796	0.08 ± 0.05	0.651530
	0.10 ± 0.10		0.12 ± 0.03	
$V_{110\%}$	0.02 ± 0.02	0.882149	0.01 ± 0.00	0.724315
	0.01 ± 0.02		0.01 ± 0.00	

Table 4.21: Continued from previous page

HI	0.09 ± 0.02	0.10516	0.12 ± 0.02	0.395491
	0.10 ± 0.02		0.12 ± 0.03	
UI	1.04 ± 0.02	0.106717	1.08 ± 0.02	0.448953
	1.05 ± 0.02		1.08 ± 0.02	
CI	0.96 ± 0.01	0.154697	0.94 ± 0.03	0.108624
	0.95 ± 0.00		0.93 ± 0.02	
QI	0.01 ± 0.01	0.402225	0.01 ± 0.01	0.298911
	0.01 ± 0.01		0.02 ± 0.01	

For the OARs dosimetric comparisons, the calculated p-values were less than 0.05 for all associated organ volumes for both intact breast and chest-wall plans as shown in Table 4.22. There was clearly a statistically significant difference between the calculated means of the two cohort plans indicating an observed effect with respect to doses to the OARs, especially to the contralateral OARs. The p-values of less than 0.001 were calculated for contralateral breast maximum dose comparison between the POC and PAC cohort plans. The observed effects were very significant for the heart and ipsilateral lung volumes. For the intact breast plans, the mean heart volume that received 30 Gy with the POC recorded zero percent while the ipsilateral mean lung volume that received 20 Gy were 6.83 ± 3.66%.

Table 4.22: Quantitative analysis of OAR sub-metrics for the original automated PAC plans and the training replanned POC plans.

		Intact breast OAR Volume		Chest-wall OAR Volume	
OAR	**Sub metric**	**Mean ± SD** **PAC** **POC**	**p-value**	**Mean ± SD** **PAC** **POC**	**p-value**
Heart	$V_{30\ Gy}$	0.93 ± 0.64%	0.001	1.31 ± 0.80%	0.001
		0.00 ± 0.01%		0.08 ± 0.03%	
	D_{avg}	7.45 ± 2.04 Gy	0.001	8.42 ± 2.77 Gy	0.001
		4.84 ± 2.28 Gy		5.19 ± 2.02 Gy	
Ipsilateral lung	$V_{20\ Gy}$	10.14 ± 5.08%	0.004	10.62 ± 5.94%	0.005
		6.83 ± 3.66%		7.08 ± 4.52%	
	D_{avg}	8.16 ± 2.71 Gy	0.001	8.95 ± 3.08 Gy	0.001
		5.13 ± 1.54 Gy		6.41 ± 1.85 Gy	
Contralateral lung	$V_{5\ Gy}$	22.50 ± 13.41%	0.024	23.07 ± 13.01%	0.032
		13.51 ± 7.34%		14.14 ± 7.76%	
Contralateral breast	D_{max}	4.76 ± 1.29 Gy	<0.001	4.98 ± 1.31 Gy	<0.001
		2.35 ± 0.92 Gy		2.75 ± 1.22 Gy	

Utilising the newly proposed facility-based planning optimisation criteria in designing the training VMAT breast treatment plans resulted in decreased low doses to a large volume of normal tissues as shown in Table 4.22, suggesting the possibility of lesser risk for secondary carcinogenesis especially for younger patients. From Figure 4.4, a sample DVH depicted that the training treatment plans generated from the proposed facility-based planning optimisation criteria resulted in relatively better overall treatment plan quality than that of the automated treatment plans.

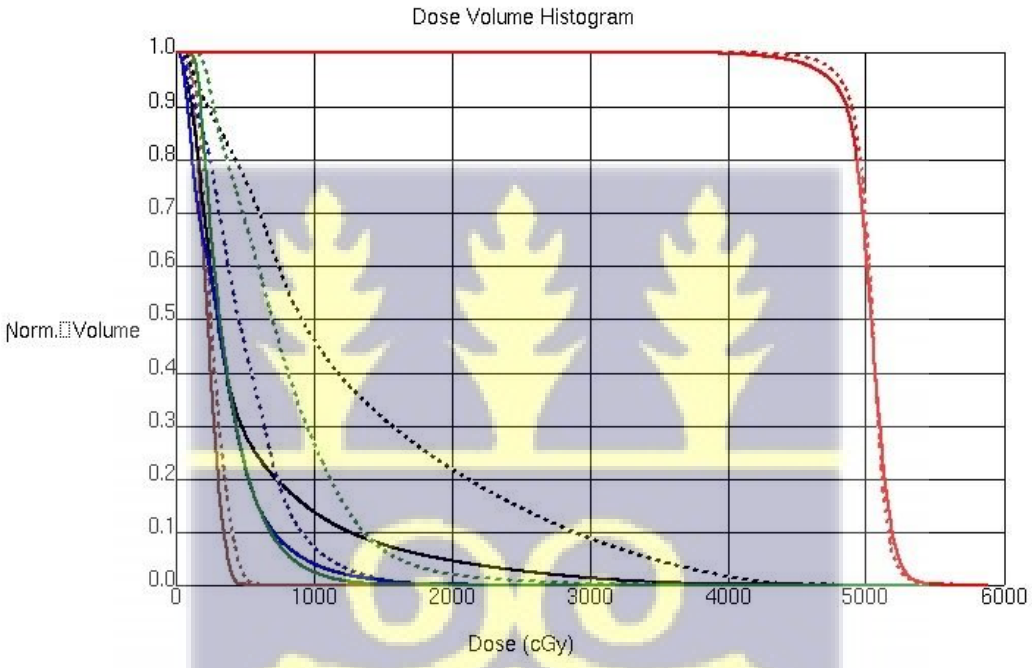


Figure 4.4: Pinnacle TPS plan evaluation interphase showing a sample plan DVHs for tumour target and OARs

Phase 3 compared the observed effects the newly proposed breast planning optimisation criteria had on the overall breast dosimetric plan quality with the automated plans designed with the current optimisation criteria. The mean 95 percent of PD (47.5 Gy) coverage to target volumes were more than the set PTV planning objective of 95% with a mean Brst_opt volume of 95.46 ± 0.40% and a mean Chst_opt volume of 95.04 ± 0.61%. The mean PTV_opt volumes that received

hot spots above 105% ($V_{105\%}$ PD) of the prescribed dose were also restricted to less than a mean value of 1%. The sample DVH obtained from the training a patient's VMAT plan represents solid thick lines, while the automated VMAT plan is represented with dashed thick lines. The various OARs are also represented by the following colours; PTV_opt (red), Heart volume (green), ipsilateral lung volume (black), contralateral lung volume (blue) and contralateral breast volume (brown).

4.3.4.2 Cohort Radiobiological Results

Radiobiological analysis was performed with the inbuilt Pinnacle treatment planning system's biological evaluation option. The TCP for the PTVs and NTCP for the various OARs were analysed for intact breast cases and chest-wall cases for the 20 randomly selected left-sided patients. The results are presented in Table 4.23 for the training plans (POC) and the automated plans (PAC).

Table 4.23: Radiobiological analysis of automated optimised PAC plans and their replanned training optimised POC plans.

ROI/Contour		Intact breast		Chest-wall	
	Index (%)	**Mean ± SD**	**p-value**	**Mean ± SD**	**p-value**
		PAC		**PAC**	
		POC		**POC**	
PTV	TCP	99.0 ± 0.85	0.09	98.2 ± 0.89	0.08
		98.8 ± 1.04		97.9 ± 1.17	
Heart	NTCP	0.42 ± 0.05	0.04	0.51 ± 0.06	0.03
		0.03 ± 0.01		0.05 ± 0.01	

Table 4.23: Continued from previous page

Ipsilateral lung	NTCP	1.25 ± 0.11 0.12 ± 0.02	0.03	1.69 ± 0.14 0.15 ± 0.03	0.03
Contralateral lung	NTCP	0.05 ± 0.01 0.00 ± 0.00	0.02	0.06 ± 0.02 0.00 ± 0.00	0.02
Contralateral breast	NTCP	0.02 ± 0.01 0.00 ± 0.00	0.03	0.02 ± 0.01 0.00 ± 0.00	0.03
P+		97.2% ± 0.07 98.7% ± 0.03	0.04	96.7% ± 0.06 98.1% ± 0.03	0.04

The mean TCP evaluated from the PAC-based plans had a value of 99.0 ± 0.85% (ranging from 98.60% to 99.7%) and 98.8 ± 1.04% with the POC-based plans (ranging from 98.1% to 99.4%) for the intact breast cases. For the chest-wall cases, a mean TCP value of 98.2 ± 0.89% (ranging from 97.7% to 99.1%) was evaluated from the PAC-based plans and a mean value of 97.9 ± 1.17% with the POC-based plans (ranging from 97.2% to 98.8%).

The TCP analysis did not reveal any significant difference for both the intact breast and chest-wall cases with the two OC (p-value of 0.08 and p-value of 0.09, respectively) as no effect was

observed. The mean percentage change calculated for the intact breast plans was -0.20% (a decrease in TCP) and -0.31% for the chest-wall plans (a decrease in TCP) when proposed POC was used.

For selected intact breast cases, the mean NTCP for the ipsilateral lung volume optimised with the PAC was 1.25 ± 0.11% (ranging from 0.97% to 1.41%), and POC-based with a lower mean value of 0.12 ± 0.02% (ranging from 0.09% to 0.16%). The heart NTCP was 0.42 ± 0.05% (ranging from 0.39% to 0.66%) and 0.03 ± 0.01% (ranging from 0.01% to 0.07%) with the PAC and POC, respectively. The mean NTCP for the contralateral lung with the PAC was 0.05 ± 0.01% (ranging from 0.01 to 0.06%), also higher than the POC-based with a mean value of 0.00 ± 0.00%. The contralateral breast NTCP was 0.02 ± 0.01% (ranging from 0.00% to 0.03%) and 0.00 ± 0.00% with the PAC and POC, respectively. The NTCP analysed for the intact breast plans revealed significant differences for all four organs at risk analysed (p-value of 0.04 for the heart, 0.03 for the ipsilateral lung and contralateral breast and 0.02 for the contralateral lung) as effects were observed between the two criteria.

For the chest-wall breast plans on the other hand, the mean NTCP for the ipsilateral lung with the PAC was 1.69 ± 0.14% (ranging from 1.08% to 1.87%), higher than that with the POC with a mean value of 0.15 ± 0.03 % (ranging from 0.11% to 0.20%). The heart NTCP was 0.51 ± 0.06% (ranging from 0.44% to 0.72%) and 0.05 ± 0.01% (ranging from 0.03% to 0.08%) with the PAC and POC, respectively. The mean NTCP for the contralateral lung with the PAC was 0.06 ± 0.02% (ranging from 0.02% to 0.08%), higher than that with the POC with a mean value of 0.00 ± 0.00%. The contralateral breast NTCP was 0.02 ± 0.01% (ranging from 0.00% to 0.03%) and 0.00 ± 0.00% with the PAC and POC, respectively. The NTCP analysed for the chest-wall plans revealed significant differences for all four organs at risk analysed (p-value of 0.03 for the heart, 0.03 for

the ipsilateral lung and contralateral breast and 0.02 for the contralateral lung) as effects were observed between the two criteria. The mean percentage change for the ipsilateral lung was -90.40% and -91.12% (decrease in NTCP values) for the intact breast and chest-wall plans respectively. For the heart, the mean percentage changes were -92.86% for the intact breast plans and -90.19% for the chest-wall plans. These mean percentage changes also exhibited over 90% decreased in NTCP using the new facility-based optimisation criteria. For the contralateral breast and lung, the mean percentage NTCP changes from the initial PAC plans to the new POC were -100% for both the intact breast and chest-wall cases.

The TCP and NTCP curves as seen in Figure 4.5 were largely separated from each other, an indication of maximum dose delivered to breast tumour without any concern of toxicity. This would allow for maximum dose to be delivered to the intact breast and chest-wall volumes while sparing the associated organs at risk, evidence of a higher therapeutic ratio. In addition, Figure 4.5 shows the complication free tumour control probability P+ (Kallman *et al.*, 1992) given by equation 4.1.1.

$$P+ = TCP * NTCP \qquad 4.1.1$$

P^+ was used to evaluate the effectiveness of the dose distribution by comparing its advantages in terms of tumour control probability against its disadvantages in terms of normal tissues complication probability. The relationship between the two evaluated radiobiological indices; TCP and NTCP is termed as the therapeutic ratio. The mean complication free tumour control probability (P^+) for the left intact breast plans was 97.2 ± 0.07% and 98.7 ± 0.03% using the PAC and POC, respectively. For the left-sided chest-wall plans, the P^+ values were 96.7 ± 0.06% and 98.1 ± 0.03% using the PAC and POC, respectively. The p-values as observed for both the intact

breast and chest-wall plans were 0.04, and value less than the statistical 5% significant level set, hence an effect was observed between the two criteria.

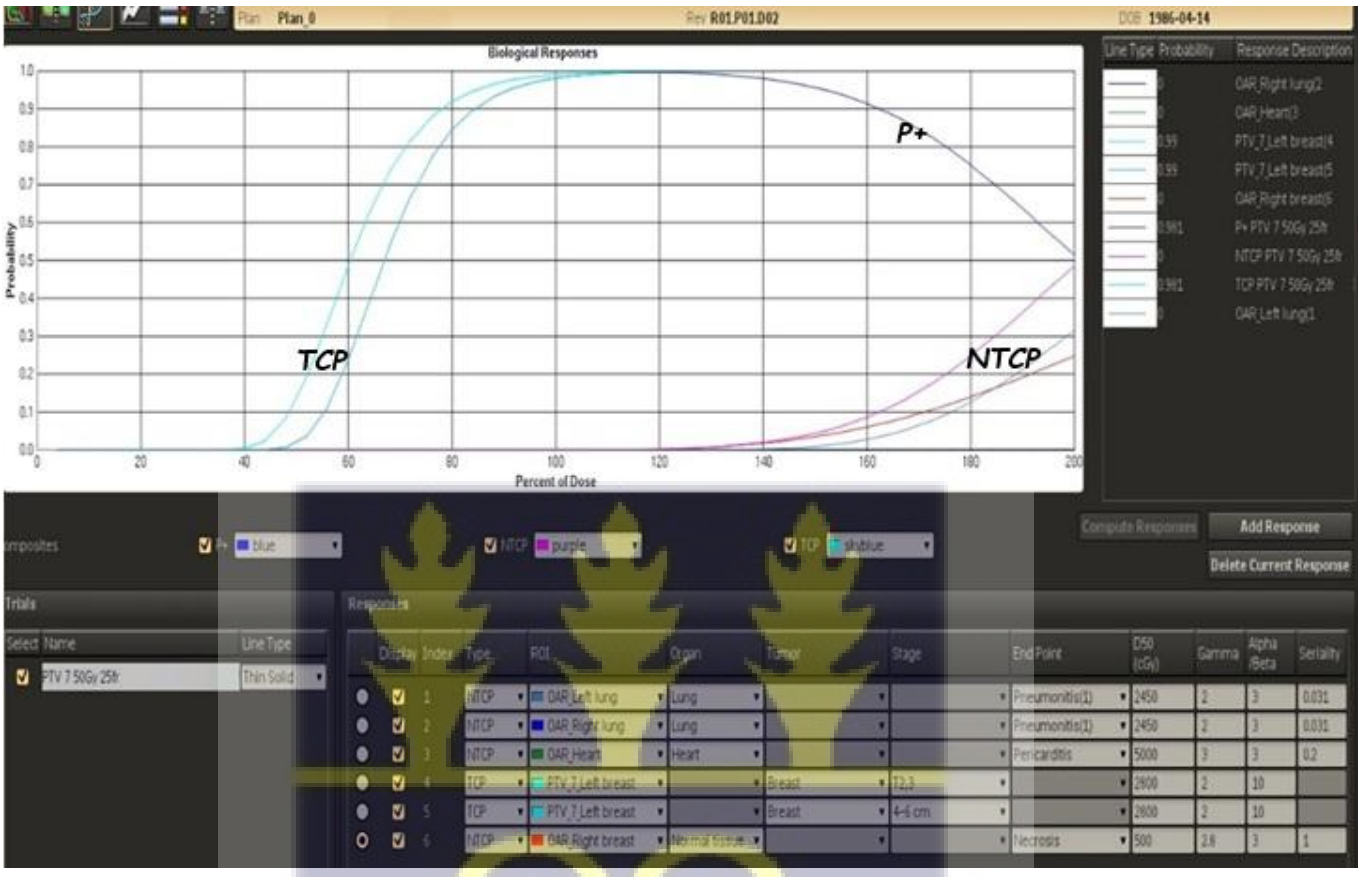


Figure 4.5: Pinnacle TPS biological evaluation window displaying sample results of TCP and NTCP and the principle of therapeutic ratio and the complication free tumour control probability P+ for a left intact breast plan.

The study found significant differences in mean doses (Davg) and percentages of the heart and ipsilateral lung volumes receiving 30 Gy and 20 Gy ($V_{30\,Gy}$ and $V_{20\,Gy}$) for both intact breast and chest-wall plans, indicating a potential improvement in these areas. However, the PTV assessments and dose indices were not significantly different between the two OCs. The proposed POC prioritised critical structures more, which led to these significant differences and could potentially

result in reduced toxicities and improved overall treatment outcomes. In conclusion, while the dosimetric assessment of PTVs showed no significant difference between the two criteria for both intact breast and chest-wall, the POC demonstrated a better focus on critical structures, potentially enhancing treatment effectiveness and safety. The current facility's automation script-based planning optimisation uses a knowledge-based planning (KBP) model to develop a clinically acceptable breast plan and not necessarily the optimal plan as observed from the results. The KBP technique is known to improve planning speed, efficiency and reduced breast treatment planning variability at the expense of the overall plan quality (Shiraishi *et al.*, 2016; Zhang *et al.*, 2010). However, the newly proposed POC did not compromise the treatment planning and delivery efficiency, but importantly improved overall plan quality as seen from the evaluations.

4.3.4.3 Measured Cohort Quality Assurance Results

The pretreatment (patient-specific) quality assurance measurements for the 20 randomly selected intact breast and chest-wall plans (training plans) were carried out and compared with results of their cohort automated plans. Below are the results using both the Octavius 4-D phantom and the EPIbeam web-based software as presented in Tables 4.24 - 4.27.

The percentage difference calculated between the PAC gamma index and the POC gamma index analysis using the Octavius 4-D phantom was less than ± 0.33% for intact breast plans. Mean gamma indices of 94.19 ± 0.89 and 94.21 ± 0.97 were recorded for the PAC and POC analysis, respectively. These gamma values were calculated using the local DD/DTA criteria of 3%, 3 mm QA evaluation criteria and the measurement analysed passed the 90% passing criteria. The calculated p-value indicated no significant difference in terms of intact breast pretreatment QA delivery on the LINAC between the two optimisation criteria.

Table 4.24: The Gamma 3-D analysis for the two partial arcs used in planning the ten intact breast cases with the PAC and POC using the Octavius 4-D phantom

Intact breast plan	PAC gamma value (%)	POC gamma value (%)	PD value (%)
Plan 1	94.1	94.4	0.32
Plan 2	92.8	92.6	-0.22
Plan 3	94.7	94.4	-0.32
Plan 4	93.5	93.7	0.21
Plan 5	95.4	95.3	-0.10
Plan 6	94.3	94.6	0.32
Plan 7	93.8	93.5	-0.32
Plan 8	95.5	95.6	0.10
Plan 9	94.6	94.9	0.32
Plan 10	93.2	93.1	-0.11
Mean(x)	**94.19 ± 0.89**	**94.21 ± 0.97**	
p-value	**0.962**		

Table 4.25: The Gamma 3-D analysis for the two partial arcs used in planning the ten chest-wall cases with the PAC and POC using the Octavius 4-D phantom.

Chest-wall plan	PAC gamma value (%)	POC gamma value (%)	PD value (%)
Plan 1	93.5	93.7	0.21
Plan 2	94.8	94.6	-0.21
Plan 3	92.0	92.1	0.11
Plan 4	94.4	94.7	0.32
Plan 5	93.9	93.8	-0.11
Plan 6	95.5	95.8	0.31
Plan 7	92.3	92.1	-0.22
Plan 8	93.4	93.3	-0.11
Plan 9	94.9	95.3	0.42
Plan 10	94.5	94.3	-0.21
Mean(x)	**93.92 ± 1.13**	**93.97 ± 1.23**	
p-value	**0.925**		

For the chest-wall cases, the percentage difference calculated between the PAC gamma index and the POC gamma index analysis using the Octavius 4-D phantom was less than ± 0.43%. Mean gamma indices of 93.92 ± 1.13 and 93.97 ± 1.23 were recorded for the PAC and POC analysis, respectively. Their gamma values analysed using the same local DD/DTA criteria of 3%, 3 mm QA evaluation criteria had a measurement pass value above the 90% passing criteria. Similarly,

the calculated p-value indicated no significant difference in terms of the chest-wall pretreatment QA delivery on the Linac between the two optimisation criteria.

Table 4.26: The Gamma 3-D analysis for the two partial arcs used in planning the ten intact breast cases with the PAC and POC using the EPIbeam software.

Intact breast plan	PAC gamma value (%)	POC gamma value (%)	PD value (%)
Plan 1	98.98	99.24	0.26
Plan 2	96.44	97.25	0.84
Plan 3	95.54	96.16	0.65
Plan 4	99.74	99.63	-0.11
Plan 5	98.29	98.65	0.37
Plan 6	96.40	96.22	-0.19
Plan 7	99.54	99.40	-0.14
Plan 8	96.43	96.57	0.15
Plan 9	99.38	99.15	-0.23
Plan 10	97.04	97.66	0.64
Mean(x)	**97.78 ± 1.57**	**97.99 ± 1.38**	
p-value	**0.742**		

The percentage difference calculated between the PAC gamma index and the POC gamma index analysis using the EPIbeam software was less than ± 0.85% for the intact breast cases. A mean gamma indices of 97.78 ± 1.57 and 97.99 ± 1.38 were recorded for the PAC and POC analysis,

respectively. These gamma values were calculated using the local DD/DTA criteria of 2%, 2 mm QA evaluation criteria and the measurement analysed passed the 95% passing criteria. The calculated p-value of 0.742 indicated there was no significant difference in terms of the intact breast pretreatment delivery on the Linac between the two optimisation criteria.

Table 4.27: The Gamma 3-D analysis for the two partial arcs used in planning the ten chest-wall cases with the PAC and POC using the EPIbeam software.

Chest-wall plan	PAC gamma value (%)	POC gamma value (%)	PD value (%)
Plan 1	95.47	96.01	0.57
Plan 2	98.36	97.98	-0.39
Plan 3	98.08	98.36	0.29
Plan 4	96.36	97.14	0.81
Plan 5	99.43	99.52	0.09
Plan 6	97.50	97.84	0.35
Plan 7	96.79	97.18	0.40
Plan 8	98.67	98.35	-0.32
Plan 9	95.93	96.21	0.29
Plan 10	97.99	97.48	-0.52
Mean(x)	**97.46 ± 1.28**	**97.61 ± 1.05**	
p-value	**0.779**		

For the chest-wall cases, the percentage difference calculated between the PAC gamma index and the POC gamma index analysis using the EPIbeam software was less than ± 0.82%. Mean gamma indices of 97.46 ± 1.28 and 97.61 ± 1.05 were recorded for the PAC and POC analysis, respectively. Their gamma values analysed using the same local DD/DTA criteria of 2%, 2 mm QA evaluation criteria had a measurement pass value above the 95% passing criteria. Similarly, the calculated p-value indicated no significant difference in terms of the chest-wall pretreatment delivery on the Linac between the two optimisation criteria. The intact breast and chest-wall pretreatment QA analysed using the two different quality assurance systems (Octavius 4-D phantom and the EPID-based EPIbeam software) produced similar gamma index analysis results. The results were not significantly different between the PAC and POC optimised intact breast and chest-wall plans as delivered on the linear accelerator. This shows that the newly proposed planning optimisation criteria was able to produce similar VMAT plans in terms of its complexity and robustness as the current PAC-based VMAT plans. The LINAC was able to deliver the same quality treatment plans as those calculated with the TPS using the proposed POC.

4.3.4.4 VMAT Cohort Treatment Planning and Delivery Evaluation

The VMAT plan efficiency was evaluated in terms of its planning and delivery parameters to maintain a high standard of the plan quality. The efficiency of the VMAT breast plans must be consistent with typical VMAT technique, achieving both fast optimisation and clinically deliverable. The number of iterations and optimisation time may vary depending on the specified planning needs. Table 4.28 presents the number of iterations and total control points used for each randomly selected intact breast and chest-wall VMAT case for the two planning optimisation cohorts. Using the newly proposed optimisation criteria, it was observed that more control points and iterations were utilised by the optimiser in fulfilling the target and OAR objectives. The PAC

used a mean of 20 and 21 iterations for the intact breast and chest-wall plans, respectively, while its POC cohort used a mean of 21 and 22 iterations, respectively. However, there was no direct correlation observed between the number of control points and the total number of iterations used.

Table 4.28: Number of iterations and total control points for optimising intact breast and chest-wall VMAT planning in Pinnacle treatment planning system for POC and PAC plans.

	Intact breast		Chest-wall	
	Optimisation parameters (No. of iterations/total control points)			
No. of Plan	**PAC**	**POC**	**PAC**	**POC**
#1	21/115	20/117	22/108	22/112
#2	17/112	18/113	20/110	21/110
#3	20/106	20/109	23/113	22/114
#4	18/112	19/113	20/104	22/108
#5	22/106	23/108	19/122	19/123
#6	18/102	19/103	21/114	22/119
#7	23/206	25/211	19/120	21/124
#8	22/112	22/113	22/131	23/138
#9	19/115	19/117	24/213	26/221
#10	21/103	22/104	19/114	20/115
Mean (x)	**20/119**	**21/121**	**21/125**	**22/128**
SD	**2.0/31.0**	**2.2/32.1**	**1.8/31.9**	**1.9/33.7**

Figure 4.6 shows a sample left-sided intact breast VMAT optimisation parameters used by the TPS. The total control points per beam and total control points for the whole treatment are displayed.

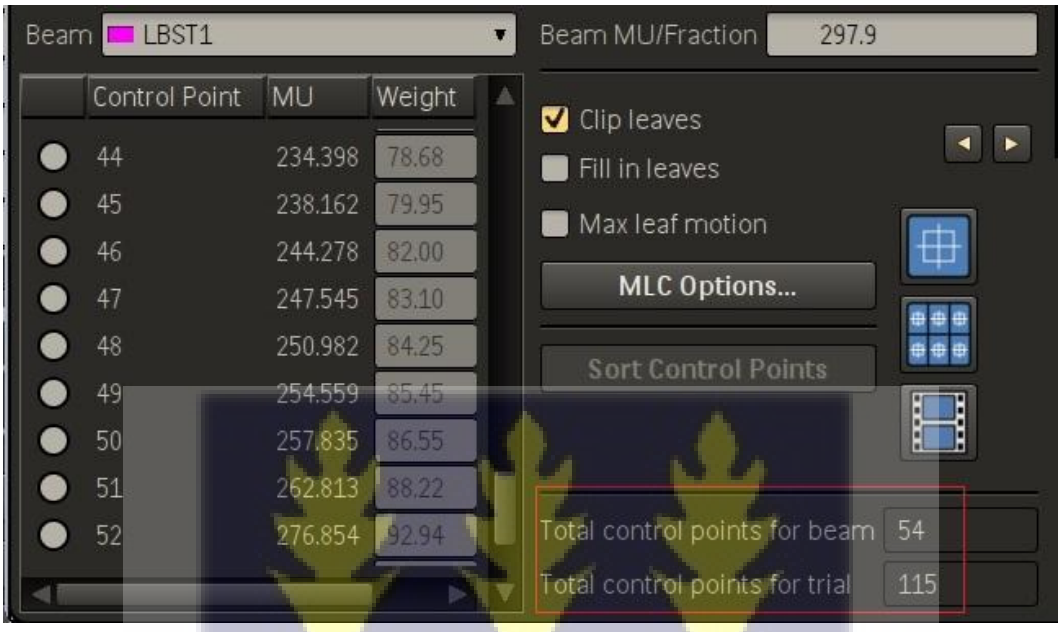


Figure 4.6: Pinnacle TPS optimisation interphase displaying various number of control points.

Figure 4.6 shows a sample VMAT left-sided intact breast treatment plan with total control points for each beam as well as for the plan trail. There are 54 control points used for the first arc (LBST1) and 115 total control points for the whole plan as displayed. The cumulative number of monitor units per control point are also displayed on the left-side of the optimisation interphase with their respective weights.

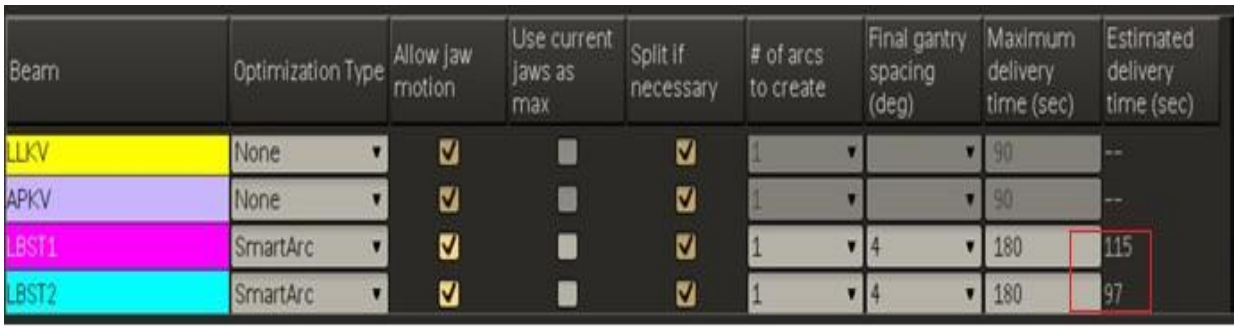
Details of the VMAT estimated delivery efficiency are presented in Table 4.29 for intact breast and chest-wall treatment selected cases for both set of cohort plans. It shows the total estimated delivery time (s) as calculated by the Pinnacle TPS for the 2 VMAT arcs. Figure 4.7 also shows a sample left-sided intact breast VMAT estimated treatment delivery time calculated by the TPS.

Table 4.29: Total estimated intact breast and chest-wall VMAT delivery time (sec) as calculated by the Pinnacle treatment planning system for POC and PAC plans.

	Intact breast		Chest-wall	
	Total estimated delivery time (s)			
No. of Plan	**PAC**	**POC**	**PAC**	**POC**
#1	212	209	251	255
#2	256	252	210	216
#3	236	231	233	229
#4	246	247	249	254
#5	232	230	256	252
#6	214	210	208	215
#7	253	258	246	241
#8	223	227	231	236
#9	246	241	219	225
#10	218	221	227	234
Mean (x)	**233.6**	**232.6**	**233.0**	**235.7**
SD	**16.3**	**16.8**	**17.2**	**14.8**
Mean Dose Rate (MU/min)	**163**	**166**	**161**	**163**

It was noted that similar estimated delivery times were calculated to deliver both the intact breast and chest-wall VMAT plans according to the TPS. The efficiency in treatment delivery did not

significantly differ from the mean estimated delivery times (s) for both cohort plans with a 2.7 sec maximum difference between them.



Beam	Optimization Type	Allow jaw motion	Use current jaws as max	Split if necessary	# of arcs to create	Final gantry spacing (deg)	Maximum delivery time (sec)	Estimated delivery time (sec)
LLKV	None	☑	☐	☑	1		90	--
APKV	None	☑	☐	☑	1		90	--
LBST1	SmartArc	☑	☐	☑	1	4	180	115
LBST2	SmartArc	☑	☐	☑	1	4	180	97

Figure 4.7: Pinnacle TPS interphase displaying calculated sample estimated delivery times (sec).

From figure 4.7, a sample VMAT left-sided intact breast treatment plan with estimated delivery times (sec) calculated in the TPS for 2 arcs are displayed. The first left breast arc (LBST1) shows an estimated delivery time of 115 seconds, and the second left breast arc (LBST2) shows an estimated delivery time of 97 seconds.

The actual Linac delivery time as recorded in Onchronos are also presented in table 4.30; Figure 4.8 shows a sample left-sided intact breast VMAT Linac treatment delivery recorded in Onchronos. It displayed the start time and end time of the 2 VMAT arcs delivered by the Linac. The PAC delivery time data were retrieved retrospectively from the already treated patient files while the POC delivery time data from their cohort plans was delivered during the pretreatment QA session.

Table 4.30: Total actual intact breast and chest-wall VMAT delivery time (sec) as recorded by the Onchronos system for POC and PAC plans.

	Intact breast		Chest-wall	
	Total actual delivery time (s)			
No. of Plan	**PAC**	**POC**	**PAC**	**POC**
#1	189	178	204	201
#2	224	201	198	194
#3	219	210	214	199
#4	231	227	212	220
#5	207	214	215	207
#6	205	189	184	179
#7	241	224	211	223
#8	211	202	200	188
#9	234	214	208	215
#10	201	181	216	204
Mean (x)	**216.2**	**204.0**	**206.2**	**203.0**
SD	**16.4**	**17.0**	**10.0**	**14.0**
Mean Dose Rate (MU/min)	**176**	**190**	**182**	**191**

From the results above, it was observed that the actual LINAC delivery times were shorter than the estimated delivery time calculated by the TPS for both intact breast and chest-wall treatment plans. The mean estimated delivery times calculated for the PAC-based intact breast and chest-

wall were 233.6 ± 16.3 sec and 233.0 ± 17.2 sec, respectively, while their POC-based cohorts were 232.6 ± 16.8 sec and 235.7 ± 14.8 sec. For the proposed optimisation criteria, the VMAT plans designed for both intact breast and chest-wall had a shorter actual Linac delivery time as compared to the PAC plans. The mean actual delivery times by the Linac for the PAC-based intact breast and chest-wall were 216.2 ± 16.4 sec and 206.2 ± 10.0 sec, respectively, while their POC-based cohorts were 204.0 ± 17.0 sec and 203.0 ± 14.0 sec.

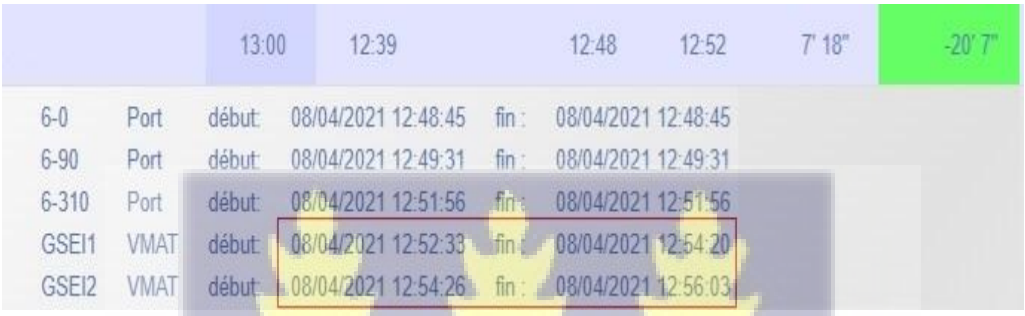


Figure 4.8: Onchronos software interphase showing a sample left-sided intact breast VMAT Linac actual treatment delivery time recorded in Onchronos showing the time recorded from beginning of treatment to end of treatment.

The Onchronos software was in French language, so here are the translations of key words and terms into English. *GSEI1* and *GSEI2* represent "*GAUCHE SEIN*" 1 and 2, respectively, which means left breast 1 and 2. "*Début*" means beginning and "fin" means end.

Table 4.31 equally provides practicable evidence that VMAT intact breast and chest-wall treatment plans produced by the proposed POC can be delivered clinically. It was consistent with the general VMAT plan with respect to total monitor units/treatment time (beam on time) and its efficiency. The difference between the mean monitor units for the VMAT intact breast plan with the proposed POC and the current facility PAC optimised plans was 9.9 MUs. For the VMAT chest-wall cases, the difference between the mean monitor units was 14.6 MUs when comparing the POC and PAC

optimised plans. The PAC and POC monitor units or beam on time were very close with mean values of 634.8 ± 35.4 MUs and 644.7 ± 46.1 MUs for intact breast VMAT plans and mean of 626.8 ± 49.9 MUs and 641.4 ± 45.9 MUs for chest-wall VMAT plans. The proposed optimisation criteria produced plans with a slightly higher time-averaged mean dose rates than their cohort plans for both intact breast and chest-wall cases evaluated. The treatment control system of the Linac adjusted the dose rate to offer the lowest possible delivery time for VMAT treatment taking into consideration the target volume and the proximity of the organs at risk involved. This adjustment in dose rate was very efficient despite both PAC and POC optimised plans having different numbers of MUs but were delivered within almost similar time.

Table 4.31: The total number of monitor units used in planning the ten intact breast and 10 chest-wall cases with the PAC and POC in the TPS.

	Intact breast		Chest-wall	
	Total Monitor Units (MUs)			
No. of Plan	**PAC**	**POC**	**PAC**	**POC**
#1	602.1	592.8	650.3	666.9
#2	659.0	680.7	596.8	626.7
#3	692.7	681.6	683.8	662.8
#4	627.5	654.3	642.4	678.7
#5	609.5	602.9	673.4	671.6
#6	616.1	627.2	584.6	615.4
#7	695.6	740.9	611.8	606.2

Table 4.31: Continued from previous page

#8	622.3	644.6	663.5	689.3
#9	624.6	618.5	518.5	537.6
#10	598.9	603.4	642.6	659.1
Mean (x)	**634.8**	**644.7**	**626.8**	**641.4**
SD	**35.4**	**46.1**	**49.9**	**45.9**

Furthermore, it is established that the POC equally satisfies the main importance of utilising VMAT technology in radiation therapy. It produced treatment plans with very similar planning time (number of iterations and total number of control points) as well as delivery time (estimated and actual times) as compared to the PAC cohort plans.

Finally, this phase of the research has undoubtedly tried to introduce a new optimisation method, grounded in a sufficiently extensive dosimetric, quality assurance and treatment delivery efficiency comparative study. It also went further to present comprehensive assessment of possible clinical outcomes, including key radiobiological metrics such as normal tissue complication probability or tumour control probability.

4.4 PHASE FOUR OF THE STUDY

The results from the fourth phase of the study which involved the validation and evaluation of all measured data and simulated plans performed during the research are presented here.

4.4.1 Plan Dosimetric Evaluation and Validation of Optimisation Criteria

The results presented in Table 4.32 and Table 4.33 compared the PTV and OARs dose metrics evaluated, respectively, from each of the five intact breast plans manually simulated by the 2 medical physicists with their cohort reference plans – Plan (ref). Table 4.34 and Table 4.35 also compared the PTV and OARs dose metrics evaluated, respectively, for the other five chest-wall plans manually simulated by the 2 medical physicists with their cohort plans. These results assessed and validated the proposed facility-based planning optimisation criteria to verify the reproducibility and repeatability of plans using the proposed criteria.

Table 4.32: Intact breast PTV dose metric evaluation for manually simulated treatment plans by the 2 medical physicists used in validating the proposed optimisation criteria.

ROI	Plan(ref)	Planner 1	Planner 2	ANOVA	Post hoc-Test p-valve		
PTV	Mean±SD			p-value	Plan(ref) vs Planner 1	Plan(ref) vs Planner 2	Planner 1 vs Planner 2
$V_{95\%}$	95.68±0.89	95.56±0.90	95.60±0.88	0.974	0.829	0.886	0.941
$V_{105\%}$	0.44±0.28	0.44±0.28	0.43±0.28	0.997	0.981	0.968	0.949
$D_{2(Gy)}$	51.17±0.39	51.21±0.45	51.22±0.51	0.981	0.877	0.861	0.975
$D_{95(Gy)}$	47.70±0.17	47.62±0.13	47.69±0.17	0.712	0.448	0.913	0.513
$D_{98(Gy)}$	44.88±0.52	44.61±0.51	44.83±0.54	0.698	0.433	0.876	0.535
HI	0.13±0.01	0.13±0.01	0.13±0.01	0.645	0.354	0.754	0.576
UI	1.06±0.01	1.06±0.01	1.06±0.01	0.899	0.690	0.968	0.718
CI	0.96±0.01	0.96±0.01	0.96±0.01	0.974	0.830	0.887	0.941
QI	0.00±0.00	0.00±0.00	0.00±0.00	0.997	0.980	0.970	0.949

Table 4.32 and Table 4.33 show the statistical comparison between the intact breast's POC reference plans (Plan (ref)) with the POC- manually generated VMAT plans designed by the two medical physicists (Plan 1 and Plan 2) with respect to their PTV_opt and OAR sub-metrics analysis, respectively. They show the mean values with their standard deviations and the calculated p-values among the three plans and between the selected pairs of plans. It was observed from Table 4.32 that both planners were able to produce intact breast VMAT treatment plans with similar target dose distribution and a lower maximum dose within the target area as comparable with the reference plan. Both plans had similar PTV_opt dosimetric mean values as the reference plan with all three plans achieving the planning objective set for the PTV_opt. Dosimetric parameters of importance were the mean target volume values of $V_{95\%}$ and $V_{105\%}$ recording 95.68 ± 0.89%, 95.56 ± 0.90%, and 95.60 ± 0.88% (ANOVA p-value of 0.974) and 0.44 ± 0.28%, 0.44 ± 0.28%, and 0.43 ± 0.28% (ANOVA p-value of 0.997), respectively. Their recorded mean values exhibited no significant statistical difference as their calculated ANOVA p-values were greater than the 5% significance level. There was also no statistically significant difference observed between the means of their calculated dose indices; that is the HI, UI, CI, and QI calculated for the intact breast plans.

Table 4.33: Intact breast OARs dose metric evaluation for manually simulated treatment plans by the 2 medical physicists used in validating the proposed optimisation criteria.

ROI OAR	Plan(ref) Mean±SD	Planner 1	Planner 2	ANOVA p-value	Post hoc-Test p-valve		
					Plan(ref) vs Planner 1	Plan(ref) vs Planner 2	Planner 1 vs Planner 2
Heart							
V_{30Gy}	0.02±0.02	0.02±0.03	0.01±0.02	0.644	0.961	0.321	0.472
D_{avg}	4.15±1.89	4.16±1.81	4.14±1.92	0.999	0.997	0.988	0.985
I.Lung							
V_{20Gy}	5.73±2.48	5.81±2.45	5.76±2.56	0.998	0.961	0.987	0.974
D_{avg}	5.10±0.71	5.13±0.82	5.11±0.86	0.998	0.956	0.981	0.977
C.Brst							
D_{max}	2.33±0.61	2.36±0.44	2.30±0.62	0.987	0.931	0.946	0.871
C.Lung							
V_{5Gy}	11.12±0.88	11.18±0.66	11.17±0.38	0.987	0.903	0.903	0.982

Table 4.34 and Table 4.35 show the statistical comparison between the chest-wall's POC reference plans (Plan (ref)) with the POC- manually generated VMAT plans designed by the two medical physicists (Plan 1 and Plan 2) with respect to their PTV_opt and OAR sub-metrics analysis, respectively. They show the mean values with their standard deviations and the calculated ANOVA p-values among the three plans and between the selected pairs of plans.

Table 4.34: Chest-wall PTV dose metric evaluation for manually simulated treatment plans by the 2 medical physicists used in validating the proposed optimisation criteria.

ROI PTV	Plan(ref) Mean±SD	Planner 1	Planner 2	ANOVA p-value	Post hoc-Test p-valve		
					Plan(ref) vs Planner 1	Plan(ref) vs Planner 2	Planner 1 vs Planner 2
$V_{95\%}$	95.50±0.64	95.13±0.60	95.31±0.73	0.691	0.867	0.829	0.908
$V_{105\%}$	1.33±0.24	1.47±0.67	1.36±0.65	0.932	0.964	0.937	0.917
$D_{2(Gy)}$	52.07±0.24	52.23±0.27	52.11±0.20	0.561	0.850	0.883	0.961
$D_{95(Gy)}$	47.70±0.18	47.63±0.19	47.65±0.10	0.787	0.437	0.929	0.539
$D_{98(Gy)}$	45.81±0.34	45.94±0.22	45.70±0.50	0.626	0.503	0.891	0.697
HI	0.13±0.01	0.13±0.01	0.13±0.01	0.898	0.422	0.806	0.785
UI	1.07±0.01	1.08±0.01	1.07±0.01	0.479	0.698	0.986	0.761
CI	0.95±0.01	0.95±0.01	0.98±0.01	0.691	0.844	0.867	0.959
QI	0.01±0.01	0.02±0.01	0.01±0.01	0.929	0.961	0.982	0.934

From Table 4.34, it was also observed that both planners were able to produce chest-wall VMAT treatment plans with similar target dose distribution and a lower maximum dose within the target area as comparable with the reference plan. Both plans had similar PTV_opt dosimetric mean values as the reference plan with all three plans achieving the planning objective set for the PTV_opt. The mean target $V_{95\%}$ and $V_{105\%}$ recorded 95.50 ± 0.64%, 95.13 ± 0.60%, and 95.31 ± 0.73% (ANOVA p-value of 0.691) and 1.33 ± 0.24%, 1.47 ± 0.67%, and 1.36 ± 0.67% (ANOVA p-value of 0.932), respectively. Their recorded mean values also did not exhibit any significant statistical difference as their calculated ANOVA p-values were equally greater than the 0.05

significance level used. There was also no statistically significant difference observed between the means of their calculated dose indices; that is the HI, UI, CI, and QI calculated for the chest-wall plans.

Table 4.35: Chest-wall OARs dose metric evaluation for manually simulated treatment plans by the 2 medical physicists used in validating the proposed optimisation criteria.

ROI	Plan(ref)	Planner 1	Planner 2	ANOVA	Post hoc-Test p-valve		
OAR	Mean±SD			p-value	Plan(ref) vs Planner 1	Plan(ref) vs Planner 2	Planner 1 vs Planner 2
Heart							
V_{30Gy}	0.03±0.03	0.03±0.03	0.03±0.03	0.952	0.954	0.361	0.462
D_{avg}	4.83±0.95	4.87±0.94	4.84±0.76	0.997	0.991	0.984	0.981
I.Lung							
V_{20Gy}	6.38±0.77	6.61±1.00	6.45±0.89	0.921	0.979	0.985	0.967
D_{avg}	6.27±0.59	6.41±0.65	6.25±0.67	0.911	0.935	0.974	0.959
C.Brst							
D_{max}	2.89±0.38	2.96±0.34	2.80±0.22	0.723	0.943	0.960	0.884
C.Lung							
V_{5Gy}	11.67±0.44	11.79±0.53	11.66±0.37	0.873	0.912	0.929	0.987

For the OARs dosimetric comparisons, the calculated ANOVA p-values were greater than 0.05 for all associated organ volumes for both intact breast and chest-wall plan as shown in Table 4.34 and Table 4.35. There was clearly no statistically significant difference in the OARs dosimetric values between the calculated means of the three cohort plans and among any pair of plans

compared (Post hoc test). These results represented a positive exploration into the practical implication of the proposed optimisation method, particularly in terms of treatment planning reproducibility and repeatability.

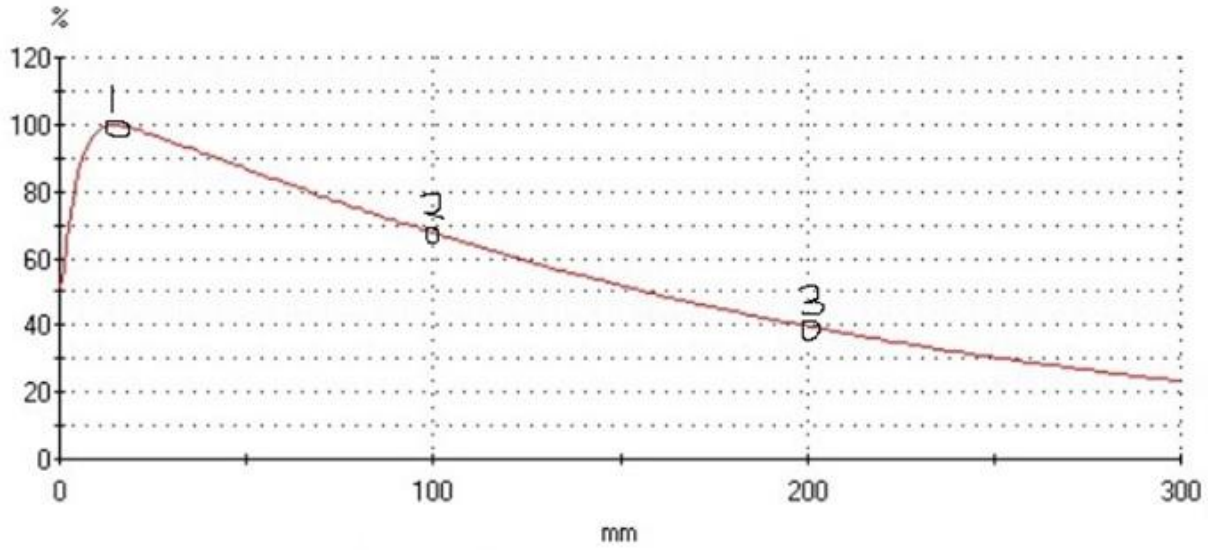
4.4.2 Infinity Linac Commissioning Data Verification

The measured photon percentage depth dose data as shown in Figure 4.9 were compared with the reference beam data obtained during LINAC commissioning to verify the machine accuracy as a form of machine quality control. The measured PDD (10 cm x 10 cm field size at 100 cm SDD at a depth of 10 cm) taken during the study was compared to the LINAC's reference beam data set (commissioning data). The results of this comparison are presented in Table 4.36 and are within ≤ 1.0% of the reference value.

Table 4.36: PDD data for LINAC reference verification at depth of 10 cm (D100).

LINAC parameter	R100 (mm)	D100 (%)	D200 (%)	Qi
Reference value	14.80	**67.51**	39.69	0.5880
Measured value	15.20	**67.92**	40.05	0.5896

The measured PDD of 67.92% differed from the reference PDD value by 0.60% and had beam quality index (Q_i) within 0.27% of the reference Q_i value measured during LINAC commissioning. This quality assurance step ensured that the treatment equipment delivered radiation dose output within the acceptable deviation of within ± 1.0% during the study.



Analyze Results
Protocol: AFSSAPS No 93

R100 [mm]	D100 [%]	D200 [%]	Qi [ ]
15.20	67.92	40.05	0.5896

Figure 4.9: Percentage depth dose taken to verify the reference commissioning data with analyse results,1. denoting R100 (mm), 2. denoting D100 (%) and 3. denoting D200 (%).

Additional PDD measurements and beam profiles were measured and compared with their respective reference values at 90 cm SSD at various depths. This was to verify the TPS data measured during its commissioning as requested by the TPS vendor. The 10 cm x 10 cm field size in-line and cross-line symmetry and flatness measured at specified depths were analysed and then compared with the reference profiles as shown in Table 4.37 and Table 4.38, respectively, using the Elekta 2020 analysis protocol in the software (PTW, 2019).

Table 4.37: Relative difference of the symmetry measurement between measured and reference for the 10 cm x 10 cm field size at different depths.

	Symmetry (%)					
Depth (cm)	**In-Line**			**Cross-Line**		
	Measured	**Reference**	**RD (%)**	**Measured**	**Reference**	**RD (%)**
1.5	100.84	100.78	0.06	100.32	100.25	0.07
5	100.69	100.76	-0.07	100.29	100.34	-0.05
10	100.93	100.89	0.04	100.39	100.36	0.03
20	100.66	100.77	-0.11	100.47	100.59	-0.12
30	100.80	100.94	-0.14	100.47	100.63	-0.16

Note: RD = Relative Difference

Table 4.38: Relative difference of the flatness measurement between measured and reference for the 10 cm x 10 cm field size at different depths.

	Flatness (%)					
Depth (cm)	**In-Line**			**Cross-Line**		
	Measured	**Reference**	**RD (%)**	**Measured**	**Reference**	**RD (%)**
1.5	104.12	103.62	0.48	104.31	103.79	0.50
5	104.34	103.76	0.56	104.54	103.68	0.83
10	104.10	103.75	0.34	104.91	104.46	0.43
20	104.16	103.37	0.76	104.61	104.02	0.57
30	104.23	103.65	0.56	104.72	103.94	0.75

Note: RD = Relative Difference

For each measured beam profile, these ratios (beam flatness and symmetry) were less than the 106% and 103% tolerance levels recommended by the vendor (Elekta) during acceptance testing. It was observed that both the measured and reference flatness and symmetry passed these acceptance criteria. The beam symmetry relative differences calculated between the measured and reference symmetry values recorded their highest difference of -0.14% and -0.16% at the deepest depth of 30 cm for the in-line and cross-line measurements, respectively. All the beam symmetry relative differences calculated at standard depth of 10 cm and below recorded lower relative

differences below ± 0.1%. The beam flatness relative differences calculated between the measured and the reference flatness values recorded less than 1.0% difference for all measurement depths.

For the absolute dose determination verification in water, the results of the reference and measured values are presented in Table 4.39. Electrical charges (nC) were collected and all necessary correction factors applied to determine the absolute absorbed dose per the IAEA code of practice for dosimetry in water (IAEA TRS 398, 2000). The temperature and atmospheric pressure measured in the water setup were 23.1°C and 101.43 kPa, respectively. The ionisation chamber correction factors calculated from the measurements were 1.009, 1.000, 1.001, and 1.003 for the temperature-pressure correction (k_{TP}), electrometer correction (k_{elec}), polarity correction (k_{pol}) and ion recombination correction (k_s), respectively (IAEA TRS 398, 2000).

Table 4.39: Absorbed dose determination in water values and charges obtained during the Linac commissioning (reference) and that during the research work (measured).

	Absorbed dose	Average readings (nC) at depth	
		10 cm	20 cm
Reference value	1.001 cGy/MU	21.39	14.59
Measured value	1.003 cGy/MU	21.45	14.53

The percentage difference between the reference absorbed dose and that of the measured value was 0.19%. This was within the ± 1.0% tolerance limit acceptable for Linac outcome comparison.

4.4.3 Octavius 4-D Recommissioning Data

The analysed PDD results obtained during the Octavius 4-D phantom data recommissioning are presented for 4 × 4 cm^2, 5 x 5 cm^2, 8 x 8 cm^2, 10 x 10 cm^2, 15 x 15 cm^2, 20 x 20 cm^2 and 26 × 26

cm^2 field sizes measured at 85 cm SSD. The PDDs profiles for all the field sizes are captured in figure 4.10 below while their analysed data presented in table 4.40.

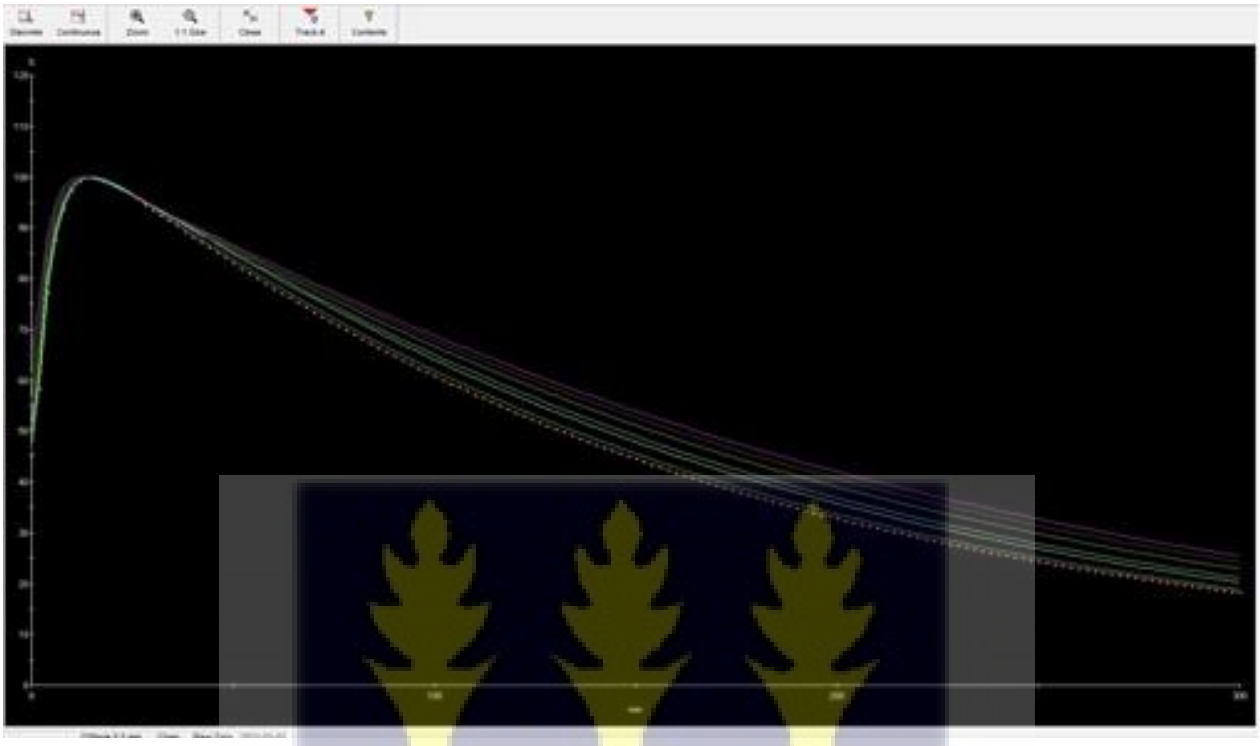


Figure 4.10: A display of the PDD profiles of various field sizes obtained for Octavius phantom data recommissioning.

These PDD data were used to commission the Octavius 4-D phantom VeriSoft software for the pretreatment QA analysis for phase 3 of the study. The measured PDDs were loaded in the VeriSoft software's menu as a single PDD calibration file. The CT images of Octavius phantom were imported into the Pinnacle TPS and saved as Octavius QA Phantom. A calculated monitor unit of 278 MU was obtained from the TPS when the expected dose of 2.00 Gy was delivered to the Octavius QA phantom. The cross calibration performed gave a calibration factor of 0.956 as shown in Figure 4.11.

Table 4.40: PDD analysis for the recommended field sizes taken at SSD of 85 cm for the PTW Octavius phantom commissioning data validation.

Field size (cm x cm)	R100 (mm)	D100 (%)
4 x 4	56.26	60.92
5 x 5	58.06	61.95
8 x 8	60.92	64.07
10 x 10	62.18	64.99
15 x 15	64.42	66.69
20 x 20	66.13	67.85
26 x 26	67.74	68.8

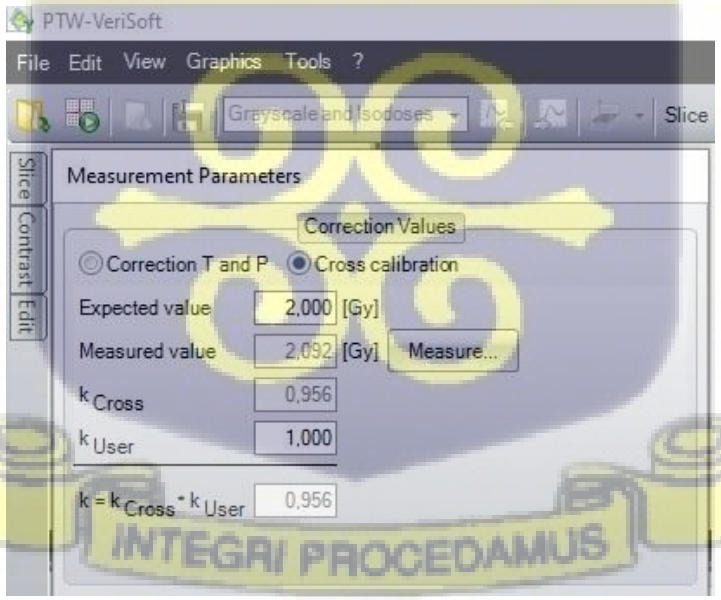


Figure 4.11: PTW VeriSoft software measurement parameters employed in setting up the correction values for QA measurement with the Octavius 4-D phantom.

A k factor of 0.956 calculated automatically was obtained in the VeriSoft software during the Octavius phantom warm up procedure. This value was applied in all the pretreatment QA measurements done during the phase 3 study. For the clinical treatment plan verification measurement done, the gamma index (γ) - analysis was 99.92% acceptance level using the local ±2% DD and DAT dose gamma analysis.

4.4.4 EPIbeam Data Validation

A reference absolute dose calculation was performed with the Pinnacle TPS using CT scanned images of PTW slab water-equivalent phantom as shown in Figure 4.12.

Figure 4.12: Pinnacle TPS dose planning interphase showing the reference absolute dose calculation in the PTW slab water-equivalent phantom.

The DICOM RT Dose file and its related RT Plan file were imported from the TPS into EPIbeam data library to build the predicted dose model. All electronic portal image data acquisitions were done according to the methods described in Chapter three and exported for analysis and validation by the vendor. The results for both EPIbeam acceptance testing and beam data library modelling by the vendor are presented in Figure 4.13.

PERFORMANCE ASSESSMENT – TABLE TO DUPLICATE AND FILL FOR EACH TREATMENT UNIT AND BEAM ENERGY					
Treatment Unit	INF1– Chevron, Triangle and E fields				
Beam Energy	6MV				
Ghosting	☒ User data				
Sagging	☒ User data				
Kernel Conversion	☒ User data				
Calibration	☐ User data		Dose at 5cm = 100 cGy		
Test description	**Tested Fields**	**GAI (%)**	**Protocol**		**Performance is accepted ***
			DTA criterion (mm)	**Dose criterion (%)**	
PERFORMANCE TEST: PHOTON BEAM, ELEMENTARY GEOMETRY					
Field 1: Chevron	☒	100	2	2	☒
Field 2: E	☒	100	2	2	☒
Field 3: Triangle	☒	100	2	2	☒

Figure 4.13: A snapshot from the EPIbeam acceptance testing result for system performance and beam data library modeling.

*This acceptance criterion is set to ±2% variation in gamma index agreement, with a 95% acceptance level.

User data measurements (that is Ghosting, Sagging and Kernel conversion) acquired at the study site for the Infinity LINAC (INF 1) were used in the modeling of the beam data library as shown in the Figure 4.13. All the portal images obtained from the various correction measurements are presented in the appendix section. During the end-to-end validation testing of the model, the local γ-analysis for the three planned MLC designed fields were also within the acceptance criteria of

2%, 2 mm when analysed with the EPIbeam software as shown in the acceptance assessment report in Figure 4.13.

4.4.5 Plan Acceptability "PlanAccept" Evaluation

Finally, an independent "*PlanAccept*" evaluation QA tool for plan acceptability based on the proposed optimisation was developed using Microsoft excel spreadsheet. It was designed with the proposed facility-based clinical goals based on the proposed planning optimisation criteria. A sample verification of this plan acceptability evaluation QA tool was performed by inputting test dose and volume values into the Excel spreadsheet as shown in Figure 4.14.

		IDEAL	*ACCEPTABLE*			
ROI	**Type**	**Primary Goal Dose (Gy) or Volume (%)**	**Secondary Goal Dose (Gy) or Volume (%)**	**Planned dose (Gy)**	**Planned Volume (%)**	**Result**
PTV Breast	PTV Min Dose	49.5 Gy	47.5 Gy	2.0		
PTV Breast	PTV Min DVH	49.0 Gy	47.0 Gy		40.0	
PTV Breast	PTV Max DVH	51.0 Gy	53.0 Gy		53.0	
PTV Breast	PTV HI*	0.07	0.09		0.09	
PTV Breast	PTV Max Dose	52.0 Gy	52.5 Gy	51.0		
Heart	Heart V30Gy	5	10		5.0	
Heart	Heart Davg	4.0 Gy	5.0 Gy	5.0		
Ipslateral Lung	Ipslateral V20Gy	5	10		10.0	
Ipslateral Lung	Ipslateral Davg	5.0 Gy	8.5 Gy	9.00		
Contralateral Breast	Cont Brst Dmax	4.0 Gy	5.0 Gy	5.5		
Contralateral Lung	Cont Lung V5Gy	20	30		12.0	

Figure 4.14: Microsoft excel interphase showing a sample "*PlanAccept*" QA tool showing results in colour coding when input with sample planned dose and volume values.

As indicated by the colour coding, the green colour indicated an ideal/optimal plan parameter that met the primary dose and/or volume goal. The yellow colour indicated an acceptable plan parameter that met the secondary dose and/or volume goal set. The red colour indicated a failed plan parameter that did not meet either the primary or the secondary dose and/or volume goal.

This "*PlanAccept*" evaluation QA tool can be used to evaluate plan quality during the treatment planning process and prior to plan approval to achieve planning and acceptance consistency. This would objectively quantify plan quality by comparing planning parameters without any ambiguity. However, the "*PlanAccept*" evaluation QA tool does not claim to identify the best plan with clinical outcome but rather evaluate breast treatment plans according to clinical intent.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS

The final chapter of the study presents the research conclusion, as well as recommendations based on the results. The recommendations are mainly directed to radiation therapy professionals, radiation therapy facilities, radiation therapy researchers, and relevant national cancer and radiotherapy groups. The limitations and future research areas are also presented in the chapter.

5.1 CONCLUSION

There has been a growing need for the development of facility-based site-specific planning guidelines to minimise patient care variations in external beam radiation treatment planning. This study aims to conduct confirmatory studies to evaluate current VMAT breast treatment planning, which will subsequently inform and justify the development of standardised facility-based VMAT breast treatment planning optimisation criteria. Specifically, the following have been achieved from this study:

1. The confirmatory studies supported the need for further breast plan improvements hence the establishment of the standardised facility-based VMAT breast treatment planning optimisation criteria.
2. A first national survey on external beam radiation therapy for breast cancer patients in Ghana was conducted. This survey was conducted to gain insight into adopted external beam radiotherapy (EBRT) breast cancer treatment guidelines across multi-facilities. With minor inter and intra-facility protocol variations observed, techniques and planning

strategies such as continuous protocol modifications, introduction of commercially available software and technologies were largely desired by all facilities.

3. Plan dosimetric estimation of 94 VMAT treatment planning data were evaluated to determine if the current facility's automated VMAT planning for breast cancer meets institutional treatment goals (plan quality). Based on these dosimetric data analysed, inconsistencies among the facility on what is considered an acceptable treatment plan were identified. It was observed that approximately 17% of analysed 41 intact breast plans failed to meet the set 95 percentage dose coverage acceptance objective while approximately 21% of the analysed 53 chest-wall plans also did not meet the same set objective.
4. Treatment plan acceptability criteria (PAC) were established based on data analysed from the facility's treatment planning database to create a clear benchmark for acceptable plans. Acceptable intact breast and chest-wall treatment plans can be developed using the current facility automated VMAT treatment planning protocol.
5. A new VMAT planning optimisation criteria (POC) was proposed to enhance the overall plan quality (driving continuous improvement). Planning target volume and organs at risk optimisation quality metric (OQM) parameters and relative scoring values were developed to establish the proposed POC. The proposed criteria were local data-based driven with eleven metrics in comparison to the seven used by the facility. The facility's treatment planning objectives were equally tightened not only to reduce significantly normal tissue exposure but also achieve optimal tumour target coverage.
6. Equipment and planning quality control study and the proposed POC standardisation were carried out to validate and demonstrate the consistency of the proposed POC. The proposed POC satisfied key clinical importance of utilising VMAT technology in breast cancer

treatment planning and delivery. It produced improved overall quality breast treatment plan which was replicated by other planners using the same developed facility-based POC guidelines.

Since the radiation therapy facility has been presented with plan acceptable criteria guidelines based on the current breast cancer planning data, uniform plan acceptability criteria for accepting intact breast and chest-wall VMAT treatment plans can be implemented for all patients. Additionally, the newly proposed planning optimisation criteria guideline can help dose planners and medical physicists to produce VMAT breast plans with superior overall plan quality.

In conclusion, the study has demonstrated the possibility of developing local resource-stratified site-specific treatment plan acceptability criteria based on the facility's data to minimise significant variations in patient treatment plans and eventually maximise the overall treatment plan quality. Compared with using the current facility's planning guidelines, the proposed POC approach shows a potential treatment benefit for patients undergoing intact breast and chest-wall irradiations.

5.2 CHALLENGES AND LIMITATIONS OF STUDY

Some of the challenges and limitations that were encountered during the study have been listed below:

1. Survey apathy and the general unwillingness of the targeted professionals to participate in this survey was a big challenge during the first phase of the study. This generally affected the participant response rate to the distributed questionnaires though it was comparable with a similar survey that yielded a similarly low response (Giro *et al.*, 2009).
2. The initial patient data mining method using python programming scripting was not possible due to fear of possible conflict with the facility's own scripting programming

already running on its treatment planning system's database. This resulted in the use of manual data collection and data clean-up which took much longer than anticipated.

3. This research is a retrospective and quality assurance study which does not involve live patients; therefore, actual long term treatment outcomes should be verified clinically.

5.3 RECOMMENDATIONS

5.3.1 Radiation Therapy Facility

1. From the survey, the three radiotherapy facilities should establish their own plan acceptability criteria protocols to have clear benchmarks for acceptable plans based on facility's clinical objectives.
2. The radiotherapy facility should include the plan acceptable criteria into their planning protocols and must be followed to avoid variations in plan quality for all patients.
3. The radiotherapy facility should independently verify the findings of this study to validate the adopted VMAT guidelines currently been used to provide local evidence of their protocols.

5.3.2 Radiation Therapy Professionals

1. To automate this proposed planning optimisation criteria to help increase plan consistency and reduce plan quality variations.
2. Apply homogeneity and conformity indices to evaluate dose distribution quality for a more improved plan quality evaluation assessment.

5.3.3 The Radiotherapy Group

1. Use protocol-based model for its VMAT breast planning automation in scripting the planning and optimisation process in Pinnacle treatment planning system. This automation model would be based on facility's own patient data and will minimise interplanner variability, ensuring uniform quality plans across patients.
2. Should perform periodic audits to include data collection, dosimetric evaluation, and continuous improvement of radiation therapy cancer care to ensure compliance with institutional standards as guidelines evolve.

5.4 FUTURE RESEARCH

In this study, focus was drawn to the systematic collection and periodic analysis of facility's radiation therapy planning data to evaluate possible clinical outcomes based on patient plans. Specifically, Chapter one provided the general background of the inconsistencies in radiation treatment planning processes and an overview of the relevance of using local data in improving therapeutic outcomes. Chapter two described the relevant literature and theories covering all the principles that were utilised in establishing the facility-based plan acceptability and optimisation criteria. Chapter three outlined the equipment, materials and methodologies that were employed throughout the study. It described the PAC development using 2-years' population-based prior patient data, which served as the basis for developing the new POC guidelines. Chapter four outlined the results obtained and subsequently discussed the relevant findings for the four phases of the research study. This chapter (Chapter five) presents the study conclusions, as well as relevant recommendations and discusses the scope for continuing research in the study area and beyond.

1. Similar studies could be conducted for other cancer sites using facility-based prior patient data.
2. Prospective studies could be done to observe clinical suitability of proposed criteria.
3. A 5-year breast cancer survival rate study could be conducted by the facility, if the proposed POC guidelines are implemented in clinical practice to verify treatment outcomes of the study.
4. Monte Carlo simulation research could be conducted and used to simulate the VMAT treatment planning.
5. Periodic review must be conducted to continuously improve overall plan quality and compared with this study.

This study contributed knowledge to treatment planning by establishing data-driven local standards. It demonstrated that treatment plan acceptability criteria can be developed using facility-based planning data, ensuring that established protocols are tailored to institution's equipment and patient population. It also provided evidence for clinical improvement as the findings demonstrate that the proposed protocol offers tangible treatment benefits over existing optimisation guidelines, potentially contributing to better breast cancer patient outcomes.

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APPENDICES

APPENDIX I: UNIVERSITY OF GHANA, ETHICS COMMITTEE FOR BASIC AND APPLIED SCIENCES (ECBAS) - ETHICAL APPROVAL

UNIVERSITY OF GHANA
ETHICS COMMITTEE FOR BASIC AND APPLIED SCIENCES (ECBAS)
P. O. Box LG 1195, Legon, Accra, Ghana

Ref. No: ECBAS 009/21-22

28th April, 2022.

Mr. George Felix Acquah
Department of Medical Physics
University of Ghana
Legon, Accra

Dear Mr. Acquah,

ECBAS 009/21-22: IMPLEMENTATION OF AN AUTOMATED STANDARDIZED HYBRID PLANNING TECHNIQUE FOR BREAST CANCER TREATMENT

This is to inform you that the above referenced study has been presented to the Ethics Committee for Basic and Applied Sciences for a full board review and the following actions taken subject to the conditions and explanation provided below:

Expiry Date:	27/03/2023
On Agenda for:	Initial Submission
Date of Submission:	28/02/2022
ECBAS Action:	Approved
Reporting:	Annually

Please accept my congratulations.

Yours sincerely,

ETHICS COMMITTEE FOR BASIC AND APPLIED SCIENCES APPROVED 28 APR 2022 UNIVERSITY OF GHANA

Professor Dorcas Osei-Safo
ECBAS Chairperson

INTEGRI PROCEDAMUS

APPENDIX II: LETTER OF INTRODUCTION TO STUDY SITE (CICL)

FROM THE DEPARTMENT OF MEDICAL PHYSICS

DEPARTMENT OF MEDICAL PHYSICS
SCHOOL OF NUCLEAR AND ALLIED SCIENCES
University of Ghana – Atomic

Phone: +233 264 945 805
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Office of the Head
P. O. Box AE 1
Atomic Energy
Accra – GHANA

Our Ref: SNAS / MPHY/41
Your Ref:

Date: 21st Feb., 2022.

The Medical Director
Centre de Radiothérapie de Lomé
Rue de l'Eccose BP 6176
Amadanhome, Lomé, Togo

Dear Sir,

LETTER OF INTRODUCTION – MR.GEORGE FELIX ACQUAH

I am writing to introduce to you Mr. George Felix Acquah, a second year MPhil student of the Department of Medical Physics SNAS, with student identification number 10328617.

Mr. Acquah is undertaking his research study under the supervision of Dr. Francis Hasford and Dr. Samuel Tagoe. His research study is titled "Implementation of an Automated Standardized Hybrid Planning Technique for Breast Cancer Treatment." As part of the workplan, he will be using the following equipments:

1. Elekta Linear Accelerator
2. Varian Linear Accelerator
3. Treatment Planning System (Pinnacle and Eclipse)
4. Primo Software
5. Python program language

It will be appreciated if Mr. George Felix Acquah is granted permission to undertake the study at the Radiotherapy Department.

Looking forward to your kind support.

Yours faithfully,

DR. FRANCIS HASFORD
(HEAD)

APPENDIX III: APPROVAL LETTER FROM STUDY SITE (CICL) TO COLLECT CLINICAL DATA FOR THE RESEARCH

The Head of Department

Department of Medical Physics

School of Nuclear and Allied Sciences

University of Ghana

31st March, 2022

Dear Sir / Madam,

EXPERIENTIAL LEARNING AND RESEARCH DATA COLLECTION APPROVAL FOR MR GEORGE FELIX ACQUAH

I hope this letter finds you well.

I am pleased to inform you that the request for experiential learning and data collection for Mr. ACQUAH George Felix has been granted. The purpose of this approval letter is to acknowledge your letter of introduction and to give permission for Mr. ACQUAH to access data from the facility for his research study as stated in the ethical clearance submitted.

The experiential learning will be under the supervision of the Chief Medical Physicist of the organization. All research data must also be protected whiles the results and recommendations shared with the facility at the end of the study.

It is our pleasure to assist Mr. ACQUAH George Felix and wish him all the best in this study. For further information, you can always contact me.

Best regards,

Prof. Adama DIAKITE (M.D)
Medical Director and Radiation Oncologist
Centre International de Cancerologie de Lomé (CICL)
Lomé, Togo.

APPENDIX IV: LIST OF RESEARCH PUBLICATIONS

1. George Felix Acquah, Francis Hasford, Samuel Tagoe, Augustine Kyere, Reynolds Owusu-Kyere, Philip Oppong Kyeremeh, Marianne C. Aznar, and Ernest Osei. Overview of breast cancer external beam radiation therapy in Ghana: Towards the establishment of a national standardized treatment guidelines for improved patient care. Scientific African 17 (2022) e01316.
2. George Felix Acquah, Francis Hasford, Samuel Nii Adu Tagoe, Adama Diakite, Victor Adjenou, and Ernest Osei. Dosimetric evaluation of VMAT automated breast treatment plans: Towards the establishment of an institutional plan acceptability criteria. Pol J Med Phys Eng. 2023;29(4):185-194.

Manuscript Under Review

3. George Felix Acquah, Francis Hasford, Samuel Nii Adu Tagoe, and Ernest Osei. Dosimetric and Radiobiological Evaluation of VMAT Breast Plans: Comparing Facility-Based Optimization and Proposed Data-driven Optimization Criteria. Reports of Practical Oncology and Radiotherapy. RPOR-2025-0088.

COPIES OF RESEARCH PUBLISHED ARTICLES

APPENDIX V: PUBLISHED ARTICLE 1 IN SCIENTIFIC AFRICAN JOURNAL (2022)

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Overview of breast cancer external beam radiation therapy in Ghana: Towards the establishment of a national standardized treatment guidelines for improved patient care

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ABSTRACT

Background and purpose: This paper reports on results from the foremost national survey on external beam radiation therapy (EBRT) treatment practice at the three radiotherapy (RT) facilities in Ghana. It is to survey the current EBRT treatment protocols and its resources available in the country for breast cancer treatment. Results are intended to form the foundation for future clinical research into developing standardized institutional and/or National breast cancer treatment planning guidelines. This will introduce uniformity into EBRT protocols across the three facilities in the country for their breast cancer patients.
Materials and methods: The survey was conducted with two online-based questionnaires; a general questionnaire that targeted radiation oncology professionals working in the three RT facilities in Ghana and a follow-up specifically for the radiation oncologists. The first survey was rolled out from 21st August 2020 to 31st December 2020. The second survey was conducted from 15th February 2021 to 31st March 2021 after the initial analysis of the responses from the first survey. The first questionnaire had 54 general EBRT breast cancer treatment questions. The second questionnaire had 14 questions focusing on dose fractionation regimens, definition of treatment targets and organs at risk (OAR) delineation.
Results: The Google web-based questionnaires had in total 11 responses from the targeted radiation oncologists, medical physicists, and radiation therapists working in the three radiotherapy facilities in the country. The facility response rate was 100% for the survey as there were participation from all three RT facilities. CT-based breast planning was considered standard and used in all three facilities. Reference markers to aid patient positioning and target delineations were employed during simulations. Majority of the relevant OAR associated with breast EBRT were very well defined. 3 dimensional conformal radiother-

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Introduction

According to the latest global cancer statistics (2020 Globocan report), breast cancer is now the most prevalent cancer in the world and most frequent amongst African women [1]. It is also the most frequent cause of cancer-related death in women in Africa. It is estimated that 4600 new cases (out of a total estimated 19,900 new cases for all cancers) will occur amongst Ghanaian women less than 60 years [1] for a projected population of 38 million [2] in 2030. The average age of diagnosis in African women is less than 50 years, which is lower than that in Caucasians [3]. Results from randomized clinical trials in early-stage (I and II) breast cancer have demonstrated enhanced local control in lumpectomy (breast/whole breast/intact breast) with radiation therapy (RT) after breast conserving-surgery (BCS) [4]. The type of treatment depends on the stage of the cancer and may consist of chemotherapy, surgery and radiation therapy or any combination to effectively control or treat the disease. Radiation therapy to the conserved breast after surgery reduces the risk of local recurrence and cancer-related death with a potential survival benefit. For most of breast cancer patients, external beam radiation therapy (EBRT) is an essential aspect of their treatment. However, treatment-related toxicity such as cardiotoxicity and secondary malignancy increases the risk of death and reduces the benefit of radiotherapy [5]. As a result, the best course of treatment for each patient needs to account for individual risk factors.

Global RT clinical research and trials have been fundamental in driving evidence-based changes. They have improved the quality of breast cancer management and reduces its side effects. Notable amongst these changes in breast cancer practice are the importance of EBRT treatment after surgery, hypofractionation courses, partial breast treatment, boost dose and axillary node treatments [4–6]. Unfortunately, in Africa, there is scantiness of research and trials in breast cancer treatment [7]. In the absence of local research, RT facilities in Ghana have adopted international protocols and best practices which were conducted based on resources that may be limited or even lacking in the country as its local protocols.

The use of advanced EBRT treatment planning techniques has improved breast cancer care globally. Although parallel opposed tangential treatment planning technique is considered as the standard, the use of arc or tomotherapy techniques are currently been employed [8]. An increase in accurate dose delivery methods were as a resulted of clinical research/trials into advanced techniques. These include the 3 Dimensional conformal radiotherapy (3DCRT) technique, the field-in-field (FIF) technique, intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) or helical techniques, the hybrid planning technique and proton therapy [9–11]. Image guidance and respiratory motion management have gained momentum in complementing these treatment techniques. Respiratory gating and Deep Inspiration Breath Hold (DIBH) techniques have been found effective in reducing doses to the heart when treating left-sided breast cancer. This eventually translates into clinical benefit by decreasing long term cardiac morbidity and mortality [12].

In an era of evidence-based clinical practice, it may not be absolutely beneficial adopting international protocols and treatment guidelines into local settings without any clinical verification. Institutions must conduct clinical research to investigate the best EBRT planning and delivery technique in the treatment and management of their breast cancer cases. Developing institutional and/or National standardized protocols based on available local resources will be an effective way of introducing uniformity into the treatment breast cancers of that country.

In this study, the three radiotherapy facilities in Ghana were surveyed with respect to their EBRT protocols for breast cancer. These were the two public facilities; The National Radiotherapy Oncology and Nuclear Medicine center (NRONMC), Korle Bu Teaching Hospital in Accra and The Oncology Directorate of the Komfo Anokye Teaching hospital (OD-KATH) in Kumasi. The third was a private facility; The Sweden Ghana Medical Center (SGMC) also in Accra. The questionnaires were intended to capture both resources and the similarities or variations in practice. This would inform the future development of effective resource-stratified standardized guidelines for all three facilities. Radiation oncology professionals from these three RT facilities in Ghana were asked to complete questionnaires for the survey. The questionnaires were designed to solicit answers on available EBRT resources, the current adopted EBRT protocols, ongoing changes in planning techniques and possible future technology to be implemented. The European organisation for Research and Treatment of Cancer (EORTC)-

Radiation Oncology Group (ROG) survey questionnaire was adapted to serve as reference in developing questionnaires for this study.

Materials and methods

Ghana currently have three radiotherapy facilities serving an estimated population of 32 million [2]. The questionnaires were designed and thoroughly reviewed together by members of the research team to solicit answers towards achieving the purpose of this study using the EORTC-ROG [13] survey as a guideline. The survey was administrated in two questionnaires; the initial general questionnaire 1 and an add-on specific questionnaire 2 (which was later developed after the initial analysis of responses from questionnaire 1). The general questionnaire targeted radiation oncology professionals and the follow-up specifically for only radiation oncologists working in the three RT facilities in Ghana. Questionnaire 1 was rolled out from 21st August 2020 to 31st December 2020. The second one was conducted from 15th February 2021 to 31 s t March 2021. The first questionnaire comprised of broader and general details about breast cancer management in Ghana as seen by the three facilities. It was to be answered by radiation oncologists (ROs), medical physicists (MPs) and radiation therapists (RTTs) working at the three RT facilities. Questions ranged from the total number of cases treated yearly, the number of breast and chest-wall patients treated annually. The use of 2D and 3D for treatment planning, treatment planning techniques used and plan acceptance criteria. Target definition, OARs delineation, position verification techniques, radiation types and energies used for treatment. Dose fractionation protocols, the use of bolus, imaging protocols, new strategies used in improving patient care and possibilities of implementing advanced technology in the future. Multiple responses were encouraged per facility to have a clearer picture and to check for consistency with answers. The second questionnaire was a shorter follow-up questions to be answered by only radiation oncologists. It focused on dose fractionations and breast Clinical Target Volume (CTV) to Planning Target Volume (PTV) margins. This was necessary to clarify portions of answers received from questionnaire 1.

Majority of the questions were closed type without the need for inputting further explanations. Questions were made up of multiple-choice questions (MCQs), checkboxes, dropdowns, and quantitative questions. Links to the Google web-based questionnaires were shared on some of the official professional WhatsApp platforms, directly sent to individuals via emails or phones, and re-shared by others to their colleagues. Constant reminders and follow-ups were made to increase the participation rate of the target groups. There were also follow-up discussions with corresponding co-authors from the three RT facilities to seek further clarification where necessary. Responses came from radiation therapy professionals from all the three radiation therapy facilities during the survey. The responses were collected online and later analyzed using Microsoft excel spreadsheet.

Ethical clearance application or informed consent for this particular survey was not necessary as no patient data or involvement with any patient was required for this study. However, permission was sought from the targeted radiation oncology professionals in the three RT facilities (radiation oncologists, medical physicists and radiation therapists) to complete questionnaires on their current breast cancer EBRT protocols.

Results

During the survey period, SGMC cancer center had 2 radiation oncologists, 2 medical physicists and 4 radiation therapists. NRONMC had 8 radiation oncologists, 6 medical physicists and 12 radiation therapists. OD-KATH had 8 radiation oncologists, 7 medical physicists and 4 radiation therapists. For questionnaire 1, four responses were received from NRONMC, one from the OD-KATH and three from SGMC as captured in Fig. 1. For questionnaire 2, there were three responses; one radiation oncologist per facility. For the purposes of results analysis, the radiotherapy facilities will be referred to as facility A, facility B and facility C in no particular order.

Patient database

The three radiotherapy facilities averagely treated in total about 750 breast cancer patients annually using external beam radiotherapy. Approximately two-thirds of these patients were mastectomy cases and the other one-third lumpectomy.

Dose fractionation schedules

For both intact breast and chest-wall radiation therapy treatment, all three facilities treating with the linear accelerator (Linac) used the standard dose fractionation schedule of 50 Gy in 25 fractions (2 Gy per fraction). One facility occasionally used hypofractionation dose schedule of 40.05 Gy in 15 fractions (2.67 Gy per fraction) for some selected patients. For boost treatment, a total dose of 10 Gy in 2 Gy fraction for 5 days is used by all three facilities. Cobalt 60 teletherapy treatment units are also available and used at two facilities to support the high workload of patients treated daily. One such facility used the Co-60 unit solely for chest-wall treatments with a dose fractionation of 42.56 Gy in 16 fractions (2.66 Gy per fraction) and a boost of 16 Gy in 8 fractions (2 Gy per fraction).

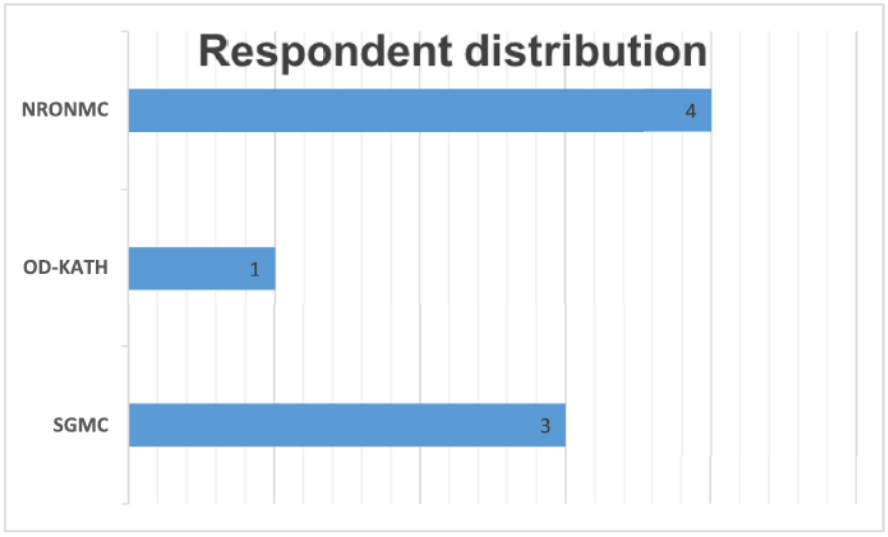

Fig. 1. Details of facility responds to questionnaire 1.

Pretreatment technique

All three facilities used the computed tomography (CT) scanner for breast cancer pretreatment simulations. During CT simulations, tattoos and radiopaque wires are used as reference landmarks for patient setup and to guide oncologists during chest-wall delineation respectively. All simulations were done in supine positions with the use of breast boards for patient immobilisation. The CT images were used for the 3D treatment dose planning for the main plan and its boost treatments. Two of the facilities occasionally used the conventional simulator for breast and chest-wall simulations. For treatment geometries determined with the conventional simulators, the appropriate physical wedge filter to be used was obtained by taken surface contour along the plane harboring the central axes of tangential fields with a lead wire. The contour of the lead wire was transcribed onto a sheet of paper and then digitized into the TPS to determine the appropriate wedge filter. One facility used clinical markup for electron boost hence and no 3D treatment planning for its chest-wall boost.

Breast definition and organ delineation

Target volumes were defined and delineated only by the radiation oncologists in all three facilities. For the organs at risk, the medical physicists (doubles as dose planners/dosimetrists in all three facilities) may delineate the lung volumes. All other OARs like the heart, spinal cord, esophagus, and the contralateral breast were done by the radiation oncologists. Two of the facilities do not delineate the contralateral breast and the esophagus for cases involving supraclavicular node treatments. Breast delineations were done mostly with the aid of mammography images and the visible glandular breast tissue in the CT images. Surgical clips when present helped with the definition of intact breast boost. For chest-wall target definition, the surgical scars normally covered with wires during CT scanning were used by oncologists as a guide. Oncologists from two of the facilities used a 0.5 mm CTV to PTV margins for intact breast and chest-wall target delineations whiles one facility used a 1 cm margin as their protocol. The skin is mostly not excluded from the PTV during both breast and chest-wall target definition by the radiation oncologist regardless of the stage of disease.

Treatment planning technique

CT-based treatment planning for both intact breast and chest-wall cases were used in all three facilities as a standard protocol. Occasionally 2D and body outline contours (skin mark-ups) for planning were used for some cases in two of the facilities. These facilities also utilized conventional radiotherapy simulators in the determination of irradiation geometries for the 2D breast plans. Computerized treatment planning systems (TPSs) were available in creating different treatment plans for intact breast and chest-wall patients. Motorized wedges and MLCs (for treatment planning with Cobalt treatment units and linear accelerators respectively) were used in creating treatment plans for 3D treatments. The forward planning field-in-field treatment technique was employed for Linac treatment. All three facilities used the OARs dose-volume histogram (DVH) and dose information as criteria for plan acceptance according to the QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) constraints. The use of central lung distance (CLD) and maximum heart distance (MHD) is employed during the planning process by one facility. The maximum treatment field distance in the lung and heart should not exceed 3 cm

Table 1
Baseline overview of the current state of breast and chest-wall radiotherapy treatment in facility A.

Main Question	Facility A *Lumpectomy(intact breast)*	*Mastectomy(chest-wall)*
Avg. number of patients per year	47	93
Standard main and boost fractionations	50 Gy/25fr and 10 Gy/5fr	50 Gy/25fr and 10 Gy/5fr
Treatment planning technique	FP-FIF	FP-FIF
RT type for main and boost	Both 3DCRT	3DCRT and 2D
Compensators/wedges/applicators	MLCs	MLCs and applicators(boost)
Modality / energy	Photons/6MV	Photons/6MV and Electrons/6MeV (boost)
Beam set up	tangential	tangential and anterior (boost)
% CT based planning main/boost	100/100	100/0
Reference use at sim for setup	BBs, tattoos	BBs, tattoos
Landmark for contouring	surgical clips, Mammo, CT,	Wires, scar for boost
Timing for boost treatment	After main treatment	After main treatment
CTV to PTV margin	1cm	1cm
Skin inclusion to PTV	YES	YES
OAR contoured	lungs, heart, cord, esophagus	lungs, heart, cord, esophagus
Plan acceptance criteria used	DVH	DVH
Criteria protocol	QUANTEC	QUANTEC
Image verification	MV EPID	MV EPID
Bolus usage	NO	YES
Bolus thickness and frequency	n/a	0.5 cm for half the total fractions
New RT plan strategies adapted	FP-FIF	FP-FIF
Future technology	IMRT, Inverse planning, DIBH	IMRT, Inverse planning, DIBH

and 2 cm respectively. Bolus is used in the planning of the chest-wall cases when treated on the Linac and not employed in planning for use on the Cobalt treatment units.

Breast treatment and position verification

All three facilities used the Linac to treat intact breast cases. For chest-wall cases, two out of the three facilities used the Linac. Two facilities also used the cobalt unit for both intact breast and chest-wall treatment for some selected cases. One facility does not give a boost plan for chest-wall patients treated on the Cobalt machine. All three facilities used photon beams (6 MV and Co) for both the breast treatment and boost plan except for one facility that used only electron beams for chest-wall boost treatment. Electronic portal imaging devices attached to the Linacs are used for position verifications before dose delivery. Portal films are taken to aid position verification when Cobalt treatment units are used for treatment delivery. Boluses for chest-wall treatments are used on alternative days and its thickness depends on the energy of the photon beam though 0.5 cm bolus thickness is usually used for the 6MV breast plans.

New technique and future advanced technology

All three facilities recognised the importance of introducing new treatment planning techniques and strategies into their breast and chest-wall treatment planning procedures. All facilities have adapted the use of the FP-FIF planning technique, doing away with the use of wedges. One such facility that has used motorized wedges for years introduced this technique to significantly improve breast dose homogeneity. Doses to the lung and heart were reported to have reduced using this method of planning while dose inhomogeneity problems were equally reduced [15]. The introduction of digital MV imaging devices into clinical practice also made verification procedure less cumbersome and accurate for these facilities.

All respondents expressed keen interest in their facilities implementing more advanced techniques and technologies in planning and treating breast cancer patients in the future. These new techniques and strategies included breath-hold, IMRT, VMAT, advanced imaging, and inverse planning. DIBH is currently not used in any of the facilities due to its labor intensiveness, time consuming and the cost of this technology.

The three tables below represent an abridge version of questionnaire and responses received from the three radiotherapy facilities during the survey. Analysis of results gave a clear overview of the current breast and chest-wall cancer RT practice in the three facilities as presented in the tables below. (Tables 1–3).

Discussion

This survey is the first to be conducted in Ghana to investigate EBRT breast cancer clinical practice in the three RT facilities. The survey team in collaboration with the team from the EORTC-ROG breast working group developed similar questionnaires for this survey. From the survey, chest-wall/mastectomy was the common breast cancer type treated annually with EBRT. CT-based treatment planning has become the standard in the country though few patients are simulated on a conventional radiotherapy simulation machine. During simulations, radiopaque wires and reference markers (tattoos) are

Table 2
Baseline overview of the current state of breast and chest-wall radiotherapy treatment in facility B.

MAIN QUESTION	FACILITY B *Lumpectomy(intact breast)*	*Mastectomy(chest-wall)*
Avg. number of patients per year	121	242
Standard main and boost fractionations	50 Gy/25fr and 10 Gy/5fr	50 Gy/25fr and 10 Gy/5fr
Treatment planning technique	FP-FIF	FP-FIF
RT type for main and boost	Both 3DCRT/2D	Both 3DCRT/2D
Compensators/wedges/applicators	MLCs and wedges	MLCs and wedges
Modality / energy	Photons/6MV and Co-60	Photons/6MV and Co-60
Beam set up	tangential	tangential
% CT based planning main/boost	70	70
Reference use at sim for setup	BBs, tattoos	BBs, tattoos
Landmark for contouring	CT, Mammo, surgical clips, SIM borders	wires, Mammo, CT, scar
Timing for boost treatment	After main treatment	After main treatment
CTV to PTV margin	0.5	0
Skin inclusion to PTV	NO	NO
OAR contoured	Lungs,heart, contralateral breast	lungs, heart, contralateral breast
Plan acceptance criteria used	DVH (3D) and max heart dose (2D)	DVH (3D) and max heart dose (2D)
Criteria protocol	QUANTEC	QUANTEC
Image verification	Portal x-ray images (Co unit), EPID (Linac)	Portal x-ray images (Co unit), EPID (Linac)
Bolus usage	YES Sometimes	YES
Bolus thickness and frequency	0.5 cm for half the total fractions	0.5 cm for half the total fractions
New RT plan strategies adapted	FP-FIF	FP-FIF
Future technology	IMRT, VMAT, Inverse planning, DIBH	IMRT, VMAT, inverse planning, DIBH

Table 3
Baseline overview of the current state of breast and chest-wall radiotherapy treatment in facility C.

MAIN QUESTION	FACILITY C *Lumpectomy(intact breast)*	*Mastectomy(chest-wall)*
Avg. number of patients per year	82	163
Standard main and boost fractionations	50 Gy/25fr and 10 Gy/5fr	42.56 Gy/16fr and 16 Gy/8fr
Treatment planning technique	FP-FIF	FP-FIF
RT type for main and boost	Both 3DCRT/2D	Both 3DCRT/2D
Compensators/wedges/applicators	MLCs and wedges	MLCs and wedges
Modality / energy	Photons/6MV and Co-60	Photons/6MV and Co-60
Beam set up	tangential	tangential
% CT based planning main/boost	50	50
Reference use at sim for setup	BBs, tattoos	BBs, tattoos
Landmark for contouring	CT, surgical clips, SIM borders, Mammo	SIM borders, CT, scar, wire
Timing for boost treatment	After main treatment	After main treatment
CTV to PTV margin	1	1
Skin inclusion to PTV	YES	YES
OAR contoured	lungs, heart	lungs, heart
Plan acceptance criteria used	DVH	DVH
Criteria protocol	QUANTEC	QUANTEC
Image verification	MV EPID	MV EPID
Bolus usage	YES Sometimes	YES
Bolus thickness and frequency	0.5 cm for half the total fractions	0.5 cm for half the total fractions
New RT plan strategies adapted	FP-FIF	FP-FIF
Future technology	IMRT, DIBH, inverse planning	IMRT, DIBH, inverse planning

used for easy target definition and patient positioning respectively. The use of surgical clips to guide oncologists in boost target delineation is fast catching up. Surgeons are constantly being reminded to leave these clips at the location of the tumor during surgery. Mammogram images are standard guiding tools to aid in accurate breast target delineation. Most of the critical associated OARs for breast radiation therapy are well delineated.

The conventional standard dose fractionation of 50 Gy in 25 fractions is used for intact breast cases and the majority of chest-wall cases. A sequential boost of 10 Gy in 5 fractions is also given after the main treatment is done. Only one facility uses electrons to boost the scar whiles another uses the Co-60 treatment units to treat the chest-wall together with the scar. Using the cobalt unit increases skin dose hence very good for chest-wall cases with skin involvements. 3DCRT is the standard treatment planning currently in the country with few 2D cases. The forward planning field-in-field planning techniques have also been adopted to improve dose homogeneity and to reduce hotspots [14,15].

The QUANTEC OAR constraint protocols/tables are widely adapted and used in all three facilities [16]. Plan acceptance criteria are mainly assessed with the use of DVH and meeting the OAR dose constraint. The use and emphasis on central lung distance and maximum heart distance are practically not enforced as more weight is placed on dose coverage, OAR DVH and the constraint tables.

Linac fitted with multi-leaf collimators (MLCs) for better dose conformance and OAR sparing are now available at each of the three facilities. The use of physical wedges is being discontinued whiles motorized wedges in planning are also gradually being replaced with open beams in the FP-FIF technique. The use of bolus on chest-wall of patients treated on the Linacs is determined by the energy used; which most of the time is the 6 MV photon beam. A bolus thickness of 0.5 cm is commonly used on alternative days to improve cosmetic outcomes whiles increasing dose coverage to the skin. All three facilities do not use bolus for intact breast planning except for very rare special cases where the breast surface needs to be covered. For image verification, no patient is treated without imaging, each facility has a form of an imaging device and its associated software. During the imaging procedure, one anterior and one lateral isocentric fields (isofields) are used in obtaining portal images and matched with the reference digitally constructed radiographs (DRRs) prior to beam delivery. Each of the three facility has its own positioning set-up correction protocols employed for the shifts matching during patient treatment

All three facilities in the country have recognised the importance and clinical relevance of consciously implementing new strategies and techniques to improve patient outcomes. These new strategies and techniques could be small changes in departmental protocols to an introduction of commercially available software and technology. The possibility of introducing future techniques like IMRT, VMAT, and DIBH into breast cancer radiation therapy clinical practice were desired by all participating facilities.

Limitations of this survey

It was noted that there were few different answers to same questions from same facilities where more than one response was received. This might suggest that there might not be a clear internal protocols on breast and chest-wall or the lack of strict adherence if those protocols exited. It was also noted that different professions might have a different understanding of department protocols, hence the lack of uniformity in answers to the same questions. Staff experience levels and knowledge might also have contributed to these difference. To get the accurate details of each facility's protocol, a senior radiation oncology professional from each of the three facility was involved in this study and contributed to the preparation of this paper. Survey apathy and the general unwillingness by majority of the targeted professionals to partake in this survey was a big challenge as well. The participant response rate was 21% to the distributed questionnaires. This low rate was mainly due to the very limited participation from the radiation therapists (RTTs) from the three RT facilities. Only one response was received from a RTTs although they form the majority of radiation oncology staff in all three facilities in the country (20 RTTs out of 53 targeted radiation oncology staff). This greatly affected the response rate though it was comparable with a similar survey that yielded a response rate of 25% [17]. The EORTC-ROG survey [13] recorded a response rate of 47% as it main targeted groups were the radiation oncologists and medical physicists. These two groups are largely responsible for and in charge of the development of EBRT treatment protocols in RT facilities. This does not however invalidate the results of this survey as there were responses from all three targeted radiation therapy facility in the country. While the results give an indication of current clinical protocols within the three RT facilities in the country, they may not necessarily reflect the entire EBRT clinical practice in those facilities. Some of the targeted professions and facilities generated a much larger response than others. The response was limited to 21% of the targeted radiation oncology professionals at the three radiotherapy facilities in the country. Hence the results from this survey should therefore be interpreted with this in mind.

Conclusion

This survey has provided an overview and baseline of the current EBRT clinical practices of breast cancer clinical treatment protocols in the three RT facilities in Ghana. The facilities have adopted well-known international breast cancer protocols and best practices in the management of the disease. From the data analysis, it is emphatic that the facilities acknowledge the need for introducing strategies and investing in future advanced techniques to deliver quality breast treatment whiles reducing long-term side effects. This survey has not only provided the current state of breast radiotherapy clinical practice but also provided an avenue for future studies into consolidating these different facility protocols into a more improved standardized facility and/or national guidelines. These guidelines when properly done may be adapted by all three current RT facilities and by future facilities in the management and treatment of breast and chest-wall cancer patients based on local resources. The variations in some of the findings on one hand, and the similarities in resources give credence to the need to harmonize protocols by establishing standardized radiotherapy guidelines for breast cancer. Similar survey aiming at a much larger participation from radiation oncology professionals in the three RT facilities is recommended. With such results, an inter-comparison study between EBRT resources and practices in Ghana and that of the EORTC-ROG countries can be carried out later for breast cancer treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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APPENDIX VI: PUBLISH ARTICLE 2 IN THE POLISH JOURNAL OF MEDICAL PHYSICS AND ENGINEERING (2023)

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Scientific Paper

Dosimetric evaluation of VMAT automated breast treatment plans: Towards the establishment of an institutional plan acceptability criteria

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Abstract

Introduction: To evaluate the clinical suitability of the current facility-based treatment plan protocol in establishing acceptability criteria.

Material and methods: Automated Volumetric Arc Therapy (VMAT) treatment plans were retrospectively evaluated for intact breast and chest-wall cancer patients from January 2021 to January 2023.

Results: A total of 94 patients were planned and treated using automated contouring and VMAT planning technique. The number of patients planned and treated for intact breast and chest-wall were 41 (43.6%) and 53 (56.4%), respectively. The mean intact breast volumes for optimization (Brst_opt) receiving 95% and 105% of the prescribed doses were 92.80% ± 1.11 and 1.54% ± 1.02, respectively. Their corresponding mean chest-wall volumes for optimization (Chst_opt) were 90.65% ± 3.19 and 2.28% ± 2.99, respectively. For left-sided cases, the mean heart dose received was 4.61 Gy ± 1.76 and 5.18 Gy ± 1.55 for intact breast plans and that for chest-wall plans, respectively. The mean ipsilateral lung volume receiving 20 Gy of the prescribed dose was 12.22% ± 3.86 and 13.19% ± 3.74 for intact breast plans and chest-wall plans, respectively. For the Brst_opt and Chst_opt dose metrics were calculated; the mean homogeneity index (HI) was 0.14 ± 0.03 and 0.15 ± 0.04, mean uniformity index (UI) was 1.09 ± 0.03 and 1.11 ± 0.03, and mean conformity index (CI) were 0.92 ± 0.04 and 0.91 ± 0.04, respectively.

Conclusions: The dosimetric evaluation shows a good dose distribution in the target volumes with minimal doses to the organs at risk (OAR). Assessment of the current data affirms the clinical usefulness of the facility-adopted protocol in achieving quality treatment plans for intact breast and chest-wall irradiations. The establishment of plan acceptability criteria will help achieve improved overall treatment outcomes.

Keywords: dosimetric indices; breast radiotherapy; plan quality; VMAT plan; acceptability criteria.

Introduction

Breast cancer, according to the current GLOBOCAN report, is the most prevalent cancer in the world and most frequent among African women in terms of incidence and mortality.[1] The treatment of breast cancer depends on the stage and consists of a combination of chemotherapy, surgery and radiation therapy to effectively manage it. For most patients, external beam radiation therapy (EBRT) is an essential component of their treatment after breast-conserving surgery (BCS), known as lumpectomy (intact breast) or the total removal of the breast, known as mastectomy (chest-wall).[2] As compared to other cancers, curative doses used in breast cancer are relatively lower and do not require dose escalation for tumour control. A conventional dose fractionation schedule of 50 Gy in 25 fractions (2 Gy per fraction) over 5 weeks was prescribed. This was followed by a boost dose of 10 Gy delivered in 5 fractions to the tumour bed in selected patients. Key issues of concern that

Authors' contribution:
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article.

require critical attention are contour irregularities, dose planning process variations, risk of long-term toxicity and secondary carcinogenesis due to high doses to critical organs.[3] Modern treatment planning and dose delivery techniques such as Volumetric Modulated Arc Therapy (VMAT) offer the freedom of delivering dynamic intensity-modulated radiotherapy with leaf sequencings of the multileaf collimator system to provide beam intensity modulations coupled with simultaneous gantry rotations to achieve better dose coverage to the tumour and reduction of doses to organs at risk. Treatment delivery with VMAT is faster, more efficient, and better dose conformity of the target, and additionally can provide differential dose distributions, allowing the simultaneous integrated boost (SIB) delivery.[4] Results from EBRT breast cancer treatment survey conducted in Ghana[5] identified certain variations in treatment planning guidelines, hence the need for this new facility to establish a standardized institutional-based protocol. Studies were carried out to focus on developing consistent breast-specific treatment planning guidelines through contouring and planning automation.[6,7] This was to improve plan quality and maintain uniformity in treatment planning protocols within the facility for all breast cancer patients after breast-conserving surgery and mastectomy.[8]

With the majority of the chest-wall and intact breast tumour volumes assuming irregular shapes with critical OAR in close proximity to the tumour volumes, tailoring the dose distribution to conform to the target volume during treatment planning requires a very high level of competence and expertise due to these complexities.[9] The conventional process is highly manual, requiring several iteration processes, fine-tuning and adjustments to produce an optimal plan worthy of approval for treatment delivery. Utilizing automated scripting eliminates unnecessary human errors and introduces constancy in the planning process.[10,11] Evaluation of departmental protocol is key in assessing the clinical suitability of planned dose distribution and plan quality that is expected from a treatment plan. Systematic collection and analysis of clinical data is recommended in understanding the possible clinical outcome based on individual patient plans. Well-defined criteria for treatment plan acceptability should be established based on the results from the above-analyzed clinical data.[12,13] This study tends to evaluate the automated VMAT departmental intact breast/chest-wall planning protocols and to establish plan acceptability criteria for the same.

For future studies, these established plan acceptability criteria would be quantified by developing institutional-based plan quality metrics (PQM) in assessing the quality of plans.[14,15] With these PQMs, the automated intact breast and chest-wall plans can be compared and quantified to determine which plan has the highest plan quality.

Materials and Methods

The treatment plans of low-risk intact breast and chest-wall cancer patients treated with the VMAT technique at a new cancer centre over the first 2-year period were evaluated. All conserved breast and lumpectomy patients treated with a standard 50 Gy in 2 Gy per fraction within the time frame were selected. For each patient, data on their ages, the volume of the Plan Target Volume used for optimization (PTV_opt), ipsilateral lung volume, heart volume (for left-sided cases), contralateral lung volume and contralateral breast volume were recorded. For each VMAT treatment plan dose distribution, the minimum, maximum, mean and standard deviation of the Brst_opt/Chst_opt, ipsilateral lung, heart, contralateral lung and breast were determined. The DVHs were used to analyze the dose distribution in all contoured structures. For all PTV volumes used for optimization, their $V_{90\%}$, $V_{95\%}$, $V_{100\%}$, and $V_{105\%}$, (volume receiving 90, 95, 100 and 105 percentages of the PD, respectively) were evaluated from the DHV and recorded. Special attention was given to volumes receiving 95% (47.5 Gy) and 105% (52.5 Gy) of the prescribed dose. The PTV dose indices: Homogeneity index (HI), Uniformity index (UI), and Conformity index (CI) for the optimized tumour volumes were then calculated using **Equations 1**, 2 and 3.

Ethical clearance was applied for and approved (ECBAS 009/21-22) to retrospectively collect and analyze patient data. Informed consent for the study is not necessary since no direct involvement with any patient is required. However, permission was sought from the department to access its treatment plan database. All patient data were made anonymous by excluding their identities so they could not be linked back to any patient by another person. Data collected were also kept safe and were only accessible by the main investigator(s) during the research period.

Patients' characterization

Data of all ninety-four (94) intact breast and chest-wall cancer patients planned and treated from January 2021 to January 2023 were collected and retrospectively studied. These patients, as represented graphically in **Figure 1**, were planned using an automated VMAT treatment planning (inverse planning technique) script with a dose prescription of 50 Gy in 25 fractions. Bilateral intact breast and chest-wall patients were excluded from this analysis as well as patients with boost doses. The script for the intact breast and chest-wall VMAT planning automation was written using the Python programming language. The Pinnacle treatment planning system (TPS) was used for the VMAT treatment planning. It comes with three calculation options – fast convolution, adaptive convolution and collapsed-cone (CC) convolution. The adaptive convolution dose calculation algorithm was used in all treatment planning.

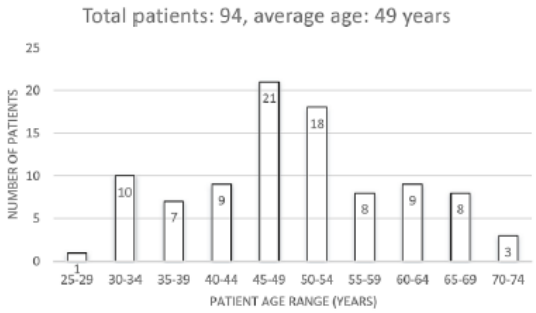

Figure 1. A plot of age distribution of total number of patients studied within the 2-year period

Patient dose planning CT simulation

A computed tomography (CT) pretreatment simulation scans are requested by the Radiation oncologist. For the scanning protocol at this facility, the patients were scanned in the supine position, head first into the scanner, with both arms raised above the head. Their arms were supported in a comfortable position with a breast board and a Kneefix placed under their knees. During the scan, only the upper body on the affected side was exposed from the waist up to maintain the patient's dignity. The head was positioned on an appropriate head rest and turned away in the opposite direction from the affected side of the breast. Radio-opaque wires were placed on the scar and on the surrounding breast for visualization on the radiograph. During simulation, with the aid of lasers, tattoos (permanent marks) were made on the skin of the patient's thorax as reference points for setup. These tattoos were placed at the left and right laterals as well as on the anterior of the patient with the aid of small ball bearings (BB). Additionally, radiopaque wires were placed on the breast and chest-wall scar to guide the oncologists during target delineation. All patients are scanned with a MinFound ScintCare Blue 755 CT scanner (MinFound Medical Systems Co., Ltd, Zhejiang Province, P.R. China) using the institutional free breathing protocol with a slice thickness of 2.5 mm. The acquired CT Dicom dataset were then exported to the facility's local image server for onward upload/import into the automated software for contouring and to the TPS for planning.

Patient automated 3D volume contouring

The CT scan Dicom data were then automatically imported into ART-Plan (Version 1.11.3; TheraPanacea, Paris, France). ART-Plan is the facility's automated software used for contouring of all the associated OARs and the breast/chestwall volumes. As shown in **Figure 2**, the accuracy of this automatic contouring software for the breast is over 90% accurate, which may require minimal adjustments by the radiation oncologist. The software accurately contours the heart, ipsilateral lung, contralateral lung and contralateral breast volumes. The intact breast and chest-wall volumes were also contoured by the system, but this process requires the radiation oncologist to review them and approve the volumes for treatment planning. Only the approved 'RTStructure' set – clinical target volumes (CTVs) and OAR were then exported via the DICOM application to Pinnacle.

Figure 2. Axial, sagittal, and coronal views of an automated intact breast volume with its associated OARs done by the ARTPLAN software.

Patient automated VMAT treatment planning

The approved contoured patient dataset with all its associated reference points was then exported into the Pinnacle^3 TPS (Version 16.2.1; Philips Medical Systems, Fitchburg, WI, USA). The correct CT number to the electron density convention table was selected. The couch top is excluded from the patient scan and laser coordinate system origin (represented by the 3 BBs) created at the laser center (referred to as the reference point R). The Python script program for treatment planning workflow automation started running when Pinnacle planning software was launched. From the script, the 'dosimetry' button is clicked, and the corresponding patient PTV is selected per the oncologist's prescription. The breast cancer type (intact breast or chest-wall) and its laterality are selected from the dropdown button. Automatically generated scripted plans were produced by clicking the script buttons. The automated process is streamlined as follows;

Creation of external/body volume, where skin padding of 0.3 cm or 0.5 cm was applied to create 'external-skin' volume depending on the extent of skin involvement. Next is the creation of the PTVs according to the facility's given CTV-PTV margins of 0 mm for intact breast and chest-wall and 7 mm for nodal involvement. The intact breast and chest-wall PTVs were also created by eliminating the intersected regions with the ipsilateral lung and heart volumes. Their corresponding PTV volumes used for optimization (PTV_opt) are created by subtracting the 'external-skin' volume from the PTV and any other regions of interest (ROI). The plan's isocenter, dose prescription and global dose volumes are created afterwards. Dose constraint objectives for the OARs with its optimization priorities, irradiation geometry (a 6 MV photon treatment beam placement and dynamic partial arc) and imaging fields (static open beam) were created. Then, the dose constraint objectives for the PTVs with its set priorities were created according to the departmental protocol. The script for the DRR creation was activated to create the appropriate digital reconstructed radiographs (DRRs) filter settings to be used for MV imaging. The plan was optimized using two partial arcs (smart arc optimization), as shown in **Figure 3**, with an adaptive convolution dose computation algorithm. The Treatment planning system software used the inverse planning technique in designing breast plans. The software optimizer used the facility's set planning objectives for the PTV and organs at risk together with their set priorities to design the treatment planning accordingly. The optimizer only stops optimizing when all the criteria are met (best result per the given objectives). One or two more optimizations were done by the dose planner by changing the priorities to improve the plan's quality (reducing hotspots and further reducing doses to organs) after the initial optimization. The plan was then evaluated and approved by the radiation oncologist to be exported for patient-specific QA and onward treatment delivery on the Linac.

Patient radiation dose treatment delivery

The exported plan was imported into MosaiQ (Version 2.81, Elekta Inc., Sunnyvale, CA, USA), which is a record and verify system (RVS). A treatment verification plan was created for the patient using an Octavius 4D-phantom (PTW-Freiburg, Germany) in the TPS for patient-QA measurement. The measured doses with the phantom must pass the departmental/local gamma analysis criteria (3.0 mm distance-to-dose agreement and 3.0% dose difference) before the patient's first treatment session. A gamma index of more than 90% was considered to be acceptable to pass the plan for treatment.

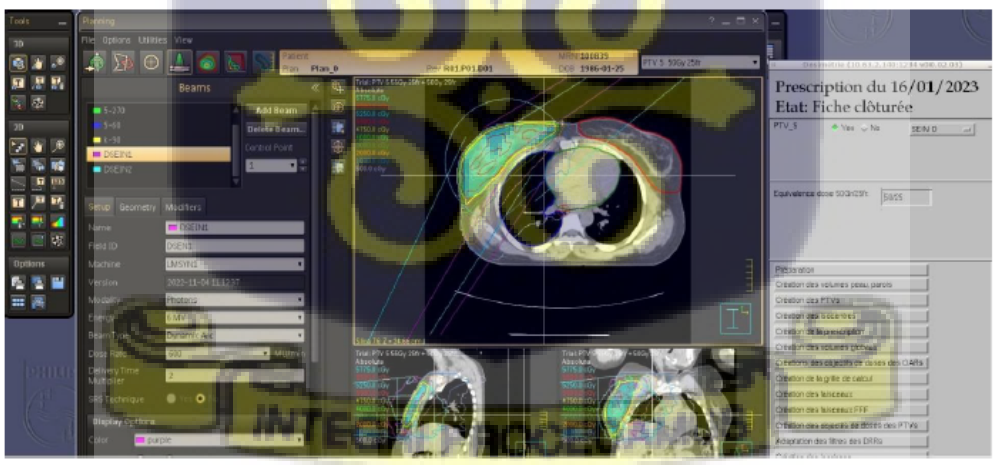

Figure 3. An automated VMAT intact breast plan using 2 partial arcs performed with a script programming running on a Pinnacle TPS. [Beam planning interphase]

During treatment, the patient was first positioned on the treatment couch, the same as during the CT simulation, with the aid of the reference markers/tattoos and the laser system. Electronic portal imaging device (EPID) attached to the treatment machine and iViewGT (Version 3.4.1, Elekta Inc., Sunnyvale, CA, USA) software was used for position verification before dose delivery. The portal images taken were automatically matched with their references according to departmental breast imaging protocol. The calculated offsets and resulting shifts after imaging were corrected before treatment. The RVS, which stores all beam parameters, was used to deliver the two partial arc VMAT treatments to the intact breast or chest-wall volumes.

Data analysis

Selected intact breast and chest-wall plan dosimetric data were collected from the TPS database and entered into a Microsoft Excel spreadsheet for analysis. The mean, maximum and minimum values together with their standard deviations were determined. The derived PTV and OAR dose-volume histogram (DHV) were also analyzed. The PTV volumes used for optimization and analysis were termed as 'Brst_opt' and 'Chst_opt' for intact breast and chest-wall, respectively.

Evaluation of OAR doses

The dose constraint for the heart was recorded by the percentage of heart volume that received 30 Gy ($V_{30Gy\ (\%)}$) as well as the heart volumes that received 5% ($V_{5\%(\%)}$) and 20% ($V_{20\%(\%)}$) of the prescribed dose. Per the departmental protocol, the mean doses (D_{avg}) to the heart volumes were also recorded.

For the ipsilateral lung, the dose constraint was recorded by the percentage of lung volume that received 20 Gy ($V_{20Gy\ (\%)}$) as well as the lung volumes that received 5% ($V_{5\%(\%)}$) and 20% ($V_{20\%(\%)}$) of the prescribed dose.

The other healthy breast was considered an organ at risk and protected during irradiation of the diseased intact breast and chest-wall. For all automated VMAT plans, the contralateral breast was contoured and its volume that received a maximum dose of 5 Gy were recorded.

Dosimetric indices evaluation

The derived DVH of the dose distributions were very useful in the evaluation of the dosimetric plan quality. Dose metrics, including homogeneity, uniformity and conformity, were calculated for both intact breast and chest-wall PTV volumes used for VMAT plan optimization.

The plan quality was quantitatively evaluated by calculating the homogeneity index (HI), uniformity index (UI) and conformity index (CI) for intact breast and chest-wall volumes used for optimization. Dose homogeneity and dose conformity are independent specifications of the quality of the absorbed dose distribution. Dose homogeneity characterizes the uniformity of the absorbed-dose distribution within the target volume, while dose conformity characterizes the degree to which the high-dose region conforms to the target volume, usually the PTV_opt.[16] The HI values are calculated using Yoon M. et al.'s formula[17] as:

$$HI = \frac{(D_2 - D_{98})}{D_{PD}} \quad \text{Eq. 1}$$

Subsequently, the uniformity and conformity indexes were calculated respectively as:

$$UI = \frac{D_5}{D_{95}} \quad \text{Eq. 2}$$

$$CI = \frac{V_{RI}}{TV} \quad \text{Eq. 3}$$

where D_2, D_5, D_{95}, and D_{98} represent the doses received by 2%, 5%, 95%, and 98% volumes of the PTV_opt, respectively. D_{PD} is the prescribed dose of 50 Gy, V_{RI} is the volume of PTV_opt covered by the reference isodose line (95% isodose line using the ICRU-83), and TV is the target volume (Brst_opt and Chst_opt in this study). The closer the values of CI and UI are to 1 indicates greater conformity and uniformity, and values of HI closer to zero indicate greater homogeneity.

Results

The mean breast volume for optimization (Brst_opt) was 695.76 cm^3 ± 269.70 cm^3 (minimum of 379.75 cm^3 to maximum 1123.78 cm^3) and that for the chest-wall volume (Chst_opt) was 506.08 cm^3 ± 326.34 cm^3 (minimum of 216.88 cm^3 to maximum 913.27 cm^3). The mean breast separation for intact breast was 23.66 cm ± 3.92 cm (ranging from 16.80 cm to 32.78 cm), and that for chest-all was 26.77 cm ± 3.37 cm (ranging from 21.41 cm to 34.90 cm).

Table 1 and **Table 2** show the statistical analysis summary of the calculated HI, UI, and CI for all 94 patients' Brst_opt and Chst_opt volumes, respectively.

For the Brst_opt cases, the mean volume receiving 90% ($V_{90\%\ PD}$), 95% ($V_{95\%\ PD}$) and 105% ($V_{105\%\ PD}$) of the prescribed dose were 97.32% ± 0.71%, 92.80% ± 1.11% and 1.54% ± 1.02% respectively. For Chst_opt cases, the mean volume receiving 90% ($V_{90\%\ PD}$), 95% ($V_{95\%\ PD}$) and 105% ($V_{105\%\ PD}$) of the prescribed dose were 97.04% ± 1.59%, 90.65% ± 3.19% and 2.28% ± 2.99% respectively. Results for all optimized target volumes receiving various percentages of the prescribed 50 Gy dose are presented in **Table 3**.

The averages of the minimum (%Rx), maximum (%Rx) and mean dose(%Rx) deposited in the Brst_opt volume were 39.55% ± 9.64% (19.77 Gy), 109.52% ± 1.40% (54.76 Gy) and 99.43% ± 0.37% (49.72 Gy) of the prescribed dose respectively. That for the Chst_opt volume were 22.92% ± 17.84% (11.46 Gy), 108.61% ± 1.88% (54.31 Gy) and 99.01% ± 1.52% (49.51 Gy) percentage doses deposited, respectively.

Table 1. Summary of the statistical analysis of the homogeneity Index, the uniformity Index, and the conformity index for the Brst_opt for all the intact breast patients studied

	n	Minimum	Maximum	Mean (x)	Standard Deviation
Age (years)	41	25.00	61.00	51.03	12.35
Homogeneity Index	41	0.09	0.22	0.14	0.03
Uniformity Index	41	1.04	1.18	1.09	0.03
Conformity Index	41	0.81	0.96	0.92	0.04

Table 2. Summary of the statistical analysis of the homogeneity Index, the uniformity Index, and the conformity index for the Chst_opt for all the chest-wall patients studied

	n	Minimum	Maximum	Mean (x)	Standard Deviation
Age (years)	53	33.00	74.00	51.03	12.35
Homogeneity Index	53	0.09	0.24	0.15	0.04
Uniformity Index	53	1.06	1.19	1.11	0.03
Conformity Index	53	0.83	0.97	0.91	0.04

Table 3. Statistical analysis summary of patient PTV_opt volume receiving 90, 92, 95, 100, 105, 107, 108 and 110% of the prescription dose for both intact breast and chest-wall patients

Volume (cc) receiving the % of the PD	Breast volume for optimization				Chest-wall volume for optimization			
	Minimum	Maximum	Mean (x)	SD	Minimum	Maximum	Mean (x)	SD
	379.75	1123.78	695.76	269.70	216.88	913.27	506.08	326.34
$V_{90\,(\%)}$	96.89	98.90	97.32	0.71	95.2	99.91	97.04	1.59
$V_{92\,(\%)}$	95.92	97.89	96.05	0.90	92.67	97.01	94.88	1.77
$V_{95\,(\%)}$	92.31	94.76	92.80	1.11	86.29	95.19	90.65	3.19
$V_{100\,(\%)}$	48.67	50.72	49.49	0.84	41.05	45.21	43.89	1.73
$V_{105\,(\%)}$	0.55	3.39	1.54	1.02	0.08	7.48	2.28	2.99
$V_{107\,(\%)}$	0.00	0.56	0.25	0.01	0.00	2.56	1.02	1.05
$V_{108\,(\%)}$	0.00	0.40	0.18	0.16	0.00	0.20	0.07	0.03
$V_{110\,(\%)}$	0.00	0.02	0.01	0.00	0.00	0.00	0.00	0.00

Table 4. Summary of the statistical analysis of heart volume receiving 5%, 20% of the prescribed dose and volume receiving 30 Gy for both intact breast and chest-wall patients

Heart volume (cc)	Breast VMAT plan				Chest-wall VMAT plan			
	Minimum	Maximum	Mean (x)	SD	Minimum	Maximum	Mean (x)	SD
	453.12	689.47	586.00	51.73	414.64	771.32	630.21	110.62
$V_{30\,Gy\,(\%)}$	0.00	1.89	1.03	0.47	0.01	1.92	1.24	0.51
$V_{5\%\,(\%)}$	9.11	99.84	71.39	24.40	10.05	99.92	72.46	22.97
$V_{20\%\,(\%)}$	1.13	19.09	14.05	4.33	1.44	19.67	14.70	4.49
$D_{min(Gy)}$	0.26	2.21	1.04	0.68	0.38	2.53	1.39	0.60
$D_{max(Gy)}$	14.87	51.03	28.72	9.23	16.26	53.95	41.08	9.81
$D_{avg(Gy)}$	1.26	6.85	4.61	1.76	1.56	7.28	5.18	1.55

Table 5. Summary of statistical analysis of the ipsilateral lung volume receiving 5%, 20% of the prescribed dose and volume receiving 20 Gy for both intact breast and chest-wall patients

Ipst. lung volume(cc)	Breast VMAT plan				Chest-wall VMAT plan			
	Minimum	Maximum	Mean (x)	SD	Minimum	Maximum	Mean (x)	SD
	500.12	2139.49	799.83	276.01	511.89	2086.94	809.51	246.58
$V_{20\,Gy\,(\%)}$	1.78	17.16	12.22	3.86	2.12	18.54	13.19	3.74
$V_{5\%\,(\%)}$	46.71	99.08	78.11	14.68	47.05	99.28	73.71	14.80
$V_{20\%\,(\%)}$	10.71	39.77	26.25	8.65	11.53	40.41	26.94	9.02
$D_{min(Gy)}$	0.98	2.18	0.20	0.49	0.99	2.41	0.62	0.55
$D_{max(Gy)}$	47.00	50.69	40.73	2.30	48.14	51.63	41.05	2.12
$D_{avg(Gy)}$	9.03	12.25	4.15	2.06	9.52	12.88	5.21	2.28

Table 6. Summary of statistical analysis of the contralateral lung volume receiving 5 Gy for both intact breast and chest-wall patients

Cont. lung volume(cc)	Breast VMAT plan				Chest-wall VMAT plan			
	Minimum	Maximum	Mean (x)	SD	Minimum	Maximum	Mean (x)	SD
	668.15	2520.69	906.80	326.97	682.33	3003.07	899.04	414.25
$V_{5\,Gy\,(\%)}$	0.00	72.10	28.19	19.83	0.00	69.76	27.85	20.04
$D_{min(Gy)}$	0.05	1.84	0.55	0.40	0.04	1.90	0.59	0.75
$D_{max(Gy)}$	2.61	49.51	16.97	12.21	2.53	48.69	14.72	12.56
$D_{avg(Gy)}$	0.42	8.10	3.57	2.15	0.39	7.55	3.95	3.09

Table 7. Summary of statistical analysis of contralateral breast volume for both intact breast and chest-wall patients

Cont.breast volume(cc)	Breast VMAT plan				Chest-wall VMAT plan			
	Minimum	Maximum	Mean (x)	SD	Minimum	Maximum	Mean (x)	SD
	329.44	2139.49	743.23	356.07	394.37	2047.03	754.15	400.41
$V_{5\,Gy\,(cc)}$	0.00	799.72	134.30	137.60	0.00	769.71	127.57	120.32
$D_{min(Gy)}$	0.00	1.50	0.56	0.29	0.00	1.39	0.51	0.23
$D_{max(Gy)}$	0.58	7.64	3.66	2.87	0.51	7.28	3.58	2.05
$D_{avg(Gy)}$	0.24	4.92	2.06	1.97	0.20	4.99	1.95	1.81

The mean heart volumes for patients treated with intact breast and chest-wall were 586.00 cm^3 ± 51.73 cm^3 (ranging from 453.12 cm^3 to 689.47 cm^3) and 630.21 cm^3 ± 110.62 cm^3 (ranging from 414.64 cm^3 to 771.32 cm^3) respectively. **Table 4** captures the statistical analysis of heart volume dose parameters for both the intact breast and chest-wall plans.

For the intact breast cases, the averages of the minimum (%Rx), maximum (%Rx) and mean dose(%Rx) within the heart volume were 2.69% ± 1.84% (1.04 Gy), 61.80% ± 18.46% (28.72 Gy) and 9.52% ± 3.52% (4.61 Gy) respectively. That for the chest-wall cases were 2.78% ± 1.20% (1.39 Gy), 82.17% ± 19.62% (41.08 Gy) and 10.36% ± 3.09% (5.18 Gy) percentage doses deposited, respectively.

The mean ipsilateral lung volumes for all patients treated with intact breast plan and chest-wall plan were 799.83 cm^3 ± 276.01 cm^3 (ranging from 500.12 cm^3 to 2139.49 cm^3) and 809.51 cm^3 ± 246.58 cm^3 (ranging from 511.89 cm^3 to 2096.94 cm^3) respectively. **Table 5** shows the dosimetric analysis of the ipsilateral lung volumes for both the intact breast and chest-wall VMAT plans treated with 50 Gy dose in 25 fractions.

The mean contralateral lung volumes were 906.80 cm^3 ± 326.97 cm^3 (ranging from 668.15 cm^3 to 2520.69 cm^3) and 899.04 cm^3 ± 414.25 cm^3 (ranging from 682.33 cm^3 to 3003.07 cm^3) for intact breast and chest-wall cases, respectively. The dose constraint was a percentage of the contralateral lung volume receiving 5 Gy ($V_{5Gy\,(\%)}$). The dosimetric analysis for the contralateral lung volume is captured in **Table 6** for both the intact breast and chest-wall VMAT plans. **Table 7** below captures the statistical analysis of the contralateral breast volume dose parameters for both the intact breast and chest-wall plans. The mean doses received by the contralateral breast were less than 5 Gy for both intact breast and chest-wall cases.

In **Table 1** and **Table 2**, these dose metrics are presented for 41 intact breast plans and 53 chest-wall plans. The mean HI, UI, and CI for intact breast (Brst_opt) volume were 0.14 (ranging from 0.09 to 0.22), 1.09 (ranging from 1.04 to 1.18), and 0.92 (ranging from 0.81 to 0.96), respectively. The corresponding values for chest-wall (Chst_opt) volume were 0.15 (ranging from 0.09 to 0.24), 1.11 (ranging from 1.06 to 1.19), and 0.91 (ranging from 0.83 to 0.97), respectively.

Discussions

This study was to evaluate the dose distribution of VMAT treatment plans used in treating patients with breast cancer (intact breast and chest-wall) at a new cancer facility over the first two years and establish plan acceptability criteria. Dosimetric estimation for 94 breast patient treatment planning data was done, and facility-based plan acceptability criteria were developed. The dosimetric estimation was done for intact breast volume and chest-wall volume contoured for VMAT planning optimization as well as the OAR structures. The PTVs for optimization were created by eliminating the intersected PTV regions with the ipsilateral lung and heart volumes. These volumes presented the actual intact breast and chest-wall target volumes used for dosimetric analysis purposes. This prevented the overestimation of the target volumes, which would have affected the dosimetric analysis of the PTVs. The minimum, maximum, mean and standard deviations were determined from the PTV volumes and OARs for intact breast and chest-wall. Subsequently, dose metrics were evaluated from the DVH for the two PTV_opt volumes.

The optimized PTV volumes receiving 95% ($V_{95\%\,PD}$), and 105% ($V_{105\%\,PD}$) of the PD were of great importance to this study in establishing the plan acceptability criteria. According to the recommendation for level 2 reporting by the ICRU report 83[16], at least 95% of the treatment volume must receive at least 95% of the prescribed dose. A study by Adnani et al. [18] has also shown that minimizing the breast volume receiving 105% of the PD leads to better treatment outcomes. From the studied data, the average of the mean percentage dose (%Rx) and maximum

percentage dose (%Rx_{max}) in the intact breast volume were 99.43% ± 0.37% (49.72 Gy) and 109.52% ± 1.40% (54.76 Gy), respectively. Those for the chest-wall volumes were 99.01% ± 1.52% (49.51 Gy) and 108.61% ± 1.88% (54.31 Gy) percentage doses, respectively. This shows that, on average, the target volumes received more than the 95% prescribed dose recommended by ICRU. However, the maximum percent doses were also higher than the recommended value of 105% of the prescribed dose. This has the risk of increased treatment complications and should be minimized as recommended for better treatment outcomes. The absorbed dose coverage was better with the intact breast volumes than the chest-wall as expected. This was mainly due to the smaller volume of the chest-wall as compared to that of the intact breast. The smaller the chest-wall volume, the lesser the dose coverage unless bolus are used to increase coverage. From the dosimetric data analysis, 95% of the prescribed dose (47.5 Gy) covered an average intact breast volume of 92.80% ± 1.11 and an average chest-wall volume of 90.65% ± 3.19. These average values did not meet the 95% dose coverage to 95% of PTV per departmental protocol. However, this does not necessarily mean all studied patients had inferior PTV dose coverage, **Table 3** shows a maximum volume coverage of approximately 95% for Brst_opt and over 95% for Chst_opt. Based on currently established plan acceptability criteria, further improvement in the department's breast treatment planning optimization criteria needs to be developed to increase overall average dose coverage for the PTV volume to at least 95%. PTV_opt volumes for future breast treatment plans can be evaluated along these mean PTV_opt values to ensure consistency in treatment planning. According to the results, 1.54% ± 1.02 and 2.28% ± 2.99 of the mean Brst_opt and Chst_opt volumes received 105% or more of the prescribed dose, respectively. This restricted all the mean PTV_opt volumes receiving a hot spot of 105% ($V_{105\%PD}$) of the prescribed dose to less than 3%. Based on the results as shown in **Table 3**, $V_{105\%}$ can be further minimized to less than an average of 1% for better outcomes in breast radiation treatments.

The critical OAR of importance for patients being treated with cancer in the left breast is the heart. Increased risk of late effect of high radiation to the heart has been established from big data collection and longer follow-up analysis. Results from such a study recorded a minimal heart dose exposure similar to the heart dose constraint as established by our department (mean dose of 7.5 Gy). For the intact breast cases, the average dose (D_{avg}) received by the heart was 4.61 Gy ± 1.76 (min: 1.26 Gy and max: 6.85 Gy). The average heart dose (D_{avg}) for the chest-wall cases was 5.18 ± 1.55 (min: 1.56 Gy and max: 7.28 Gy). A study conducted by Darby et al.[3] for over 2,000 women treated with radiotherapy for breast cancer over a period of 43 years found a direct correlation between the average heart dose and major coronary incidents. They concluded that the baseline risk of cardiac mortality increases linearly by 7.4% per 1 Gy of the average heart dose and takes effect within 5 years of treatment and for at least the next 20 years. Results, as captured in **Table 4**, show that the intact breast VMAT planning produces plans with lower heart doses than the chest-wall VMAT plans. This may be due to lesser breast tissues and thinner target volumes presented by many chest-wall cases. Another OAR dose constraint objective used in analyzing the absorbed dose received by the heart was the volume receiving 30 Gy ($V_{30Gy\,(\%)}$). In addition, the heart volumes that received 20% ($V_{20\%(\%)}$); that is 10 Gy of the prescribed dose were equally recorded and analyzed. An average heart volume of 1.03% ± 0.47 and 1.24% ± 0.51 for the intact breast VMAT plan and chest-wall VMAT plan, respectively, received 30 Gy. These values were below the constraints set by the department of $V_{30Gy} < 5\%$. Similarly, the mean heart volume that received $V_{20\%}$ of the PD was 14.05% ± 4.33 and 14.70 ± 4.49 for intact breast and cheat-wall VMAT plans, respectively. These values were below the departmental dose constraint of $V_{20\%(\%)} < 20\%$. Based on these current results, the department's VMAT breast treatment planning can be used in achieving heart dose values of 10 Gy and 30 Gy to less than 20% and 5% of the heart volumes, respectively. The same acceptability criteria can be established using the average dose of less than 7.5 Gy received by the heart volumes.

Due to the close proximity of the lung volume to the breast and chest-wall target volumes, it tends to receive the highest dose during radiation treatment delivery. Per the department protocol for the VMAT planning technique, both the ipsilateral lung (main OAR of interest) and contralateral lung volumes are contoured. For parallel organs such as the lung, ICRU 83 report[16] recommends more than one dose-volume specification to be considered for its reporting. So for the Ipsilateral lung, volumes receiving 20 Gy ($V_{20Gy\,(\%)}$) and 30 Gy ($V_{30Gy\,(\%)}$) and average doses (D_{avg}) received were collected and analyzed for both VMAT plans. The institutional-based automated VMAT planning objective criteria required the ipsilateral lung volume that received 20 Gy and 30 Gy to be less than 30% and 20%, respectively, while an average dose of 12.5 Gy was set as the constraint dose objective for the lung volume. From the dosimetric analysis, the intact breast VMAT and chest-wall VMAT plans gave an average dose of 4.15 Gy ± 2.06 (min: 9.03 Gy and max: 12.25 Gy) and 5.21 Gy ± 2.28 (min: 9.52 Gy and max: 12.88 Gy) respectively to the ipsilateral lung volume. The mean lung volume receiving a dose of 20 Gy was 12.22% ± 3.86 and 13.19% ± 3.74 for the intact breast and chest-wall VMAT plans, respectively. These results indicate that there is no significant difference in ipsilateral lung dose between the two VMAT techniques. From **Table 5**, it was observed that both VMAT plans delivered acceptable doses to the ipsilateral lung volumes according to the departmental plan objective.

For the contralateral lung, $V_{5\,Gy\,(\%)}$ were also recorded and analyzed. A study by Hall and Wuu[19] holds the view that the VMAT breast plan improves dose conformity of the target but at the cost of increased low doses to the contralateral lung and contralateral breast, which may result in an increased risk of

secondary malignancy. The results shown in **Table 6** agree with their findings, as low doses were recorded in the lung volume for both VMAT plans. Minimum, maximum and mean low doses of 0.05 Gy, 1.84 Gy and 0.55 Gy ± 0.40 were recorded for intact breast VMAT plan, and corresponding low doses of 0.04 Gy, 1.90 Gy and 0.59 Gy ± 0.75 were recorded for chest-wall VMAT plan. The mean lung volume that received 5 Gy was 28.19% ± 19.83 for the intact breast plan and 27.85% ± 20.04 for the chest-wall plan. Based on these plan acceptability criteria, similar mean ipsilateral and contralateral lung volumes can be achieved using the departmental optimization criteria. However, the recorded low doses in the contralateral lung volume can be addressed with further improvement to the current VMAT planning optimization criteria.

Another important organ at risk to be considered during VMAT breast planning and dose delivery was the contralateral breast. A study[20] analyzed patient data (from 1985 to 1999) treated with two opposing tangential beams with an average dose of 1.3 Gy to the contralateral breast. Younger women less than 40 years were observed to be at risk, especially those who received 1 Gy more to their contralateral breast, having a 2.5-fold increased risk of developing secondary breast cancer. This excess risk was not so for women over 40 years of age. A similar study by Boice et al.[21] also revealed an increase in risk of secondary breast cancer from 2.7% to 11.1% for women less than 45 years. Results from our dosimetric evaluation show a mean dose of less than 5 Gy to the contralateral breast for both intact breast and chest-wall VAMT plans. The facility-based objective criteria used for the contralateral breast dose was a dose maximum (D_{max}) of 5 Gy. From **Table 7**, the average D_{max} for the intact breast plan was 3.66 Gy ± 2.87 and 3.58 Gy ± 2.05 for the corresponding chest-wall plan. Based on these current mean contralateral breast acceptability criteria, the department's VMAT breast treatment planning optimization can be used in achieving a contralateral breast dose maximum of 5 Gy or less. All these challenges, when not addressed, might present long-term cardiac mortality, symptomatic pneumonitis, secondary malignancy and sometimes disease recurrence[22].

The aim of dosimetric plan evaluation was to assess the plan's quality using qualitative and/or quantitative approaches. Each plan was quantitatively assessed by calculating its HI, UI and CI for the PTV_opt for all 94 patients. These dose metrics derived from the DVH serve as a very useful and objective method of quantifying the plan's quality with respect to target coverage. Values of CI and UI closer to one indicate greater conformity and uniformity, and that of HI closer to zero indicate greater homogeneity. Results from our evaluation show relatively superior average dose conformity, uniformity and homogeneity in the Brst_opt and Chst_opt volumes. The mean HI for the Brst_opt and Chst_opt were 0.14 ± 0.03 and 0.15 ± 0.04 respectively. This demonstrates greater uniformity of the absorbed dose distribution within the various target volumes. The mean UI for the Brst_opt and Chst_opt were 1.09 ± 0.03 and 1.11 ± 0.03, respectively. The mean CI values were 0.92 ± 0.04 and 0.91 ± 0.04 for the Brst_opt and Chst_opt, respectively. The dose conformity demonstrates a greater degree to which the high-dose regions conform to the various target volumes. A detailed summary of the calculated HI, UI and CI values are represented in **Table 1** and **Table 2** for all patients studied in this research. VMAT plans for the optimized intact breast volumes exhibited superior mean dose metrics than those for the chest-wall volumes. However, the department's VMAT breast planning optimization criteria produced smaller hotspots while maintaining improved dose coverage (conformity) and dose uniformity throughout the intact breast and chest-wall volumes.

Conclusion

A facility-based plan acceptability criteria was established using two years of patient data from breast treatment plans dosimetric analysis. These plan evaluations exhibited acceptable dose distributions in the intact breast and chest-wall target volumes with minimal doses to critical organs. The evaluation of patient data affirms the clinical usefulness of the facility's breast planning protocol in achieving quality treatment plans for intact breast and chest-wall irradiations. The clinical implementation of the established plan acceptability criteria for intact breast and chest-wall treatment plan approval can produce clinically acceptable treatment plans while eliminating variations in plan acceptability. The established facility plan acceptability criteria should be periodically evaluated using improved dose reduction strategies to further improve overall treatment plan quality.

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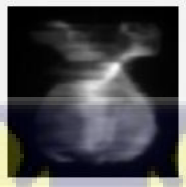
APPENDIX VII: SAMPLE EDPIBEAM ANALYSED PRETREATMENT QA GAMMA RESULTS FOR LEFT INTACT BREAST AND LEFT CHEST-WALL PLANS

Protocole 2%2mmLOCAL 2.0% 2.0mm / local

Résultats

Unité de traitement
BLINF1

#	1	2	
Nom	LBST1	LBST2	Tous les faisceaux
Image brute acquise			
γ-max (1%)	1.47	1.52	
γ-moyen	0.40	0.35	0.38
GAI (>95.0%) %	95.30	96.82	96.01
Recentrage EPID	Non	Expert	
Intégrité CIAO	0.86	0.82	
Protocole	✔	✔	
Visa expert	-	-	

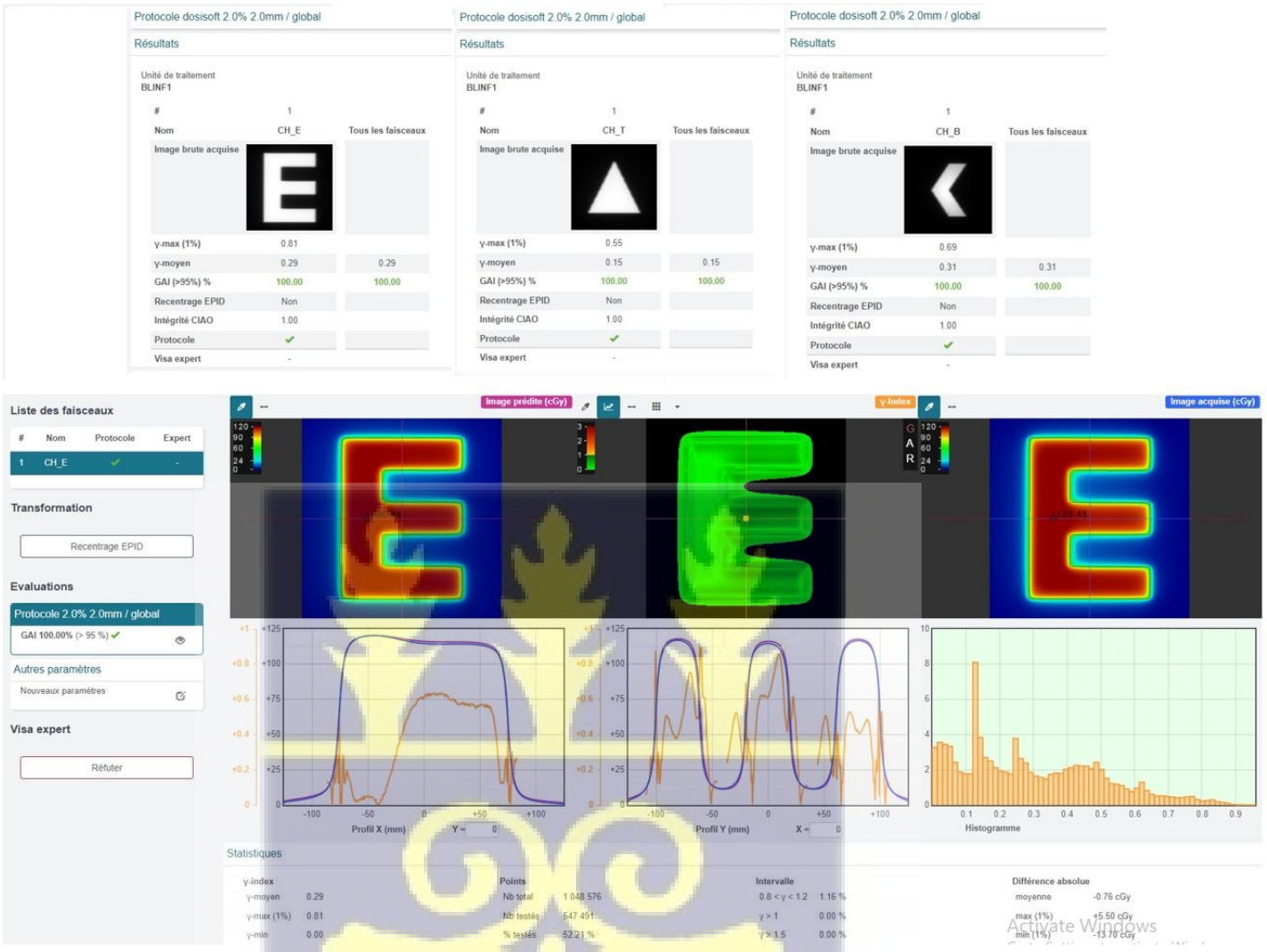
Protocole 2%2mmLOCAL 2.0% 2.0mm / local

Résultats

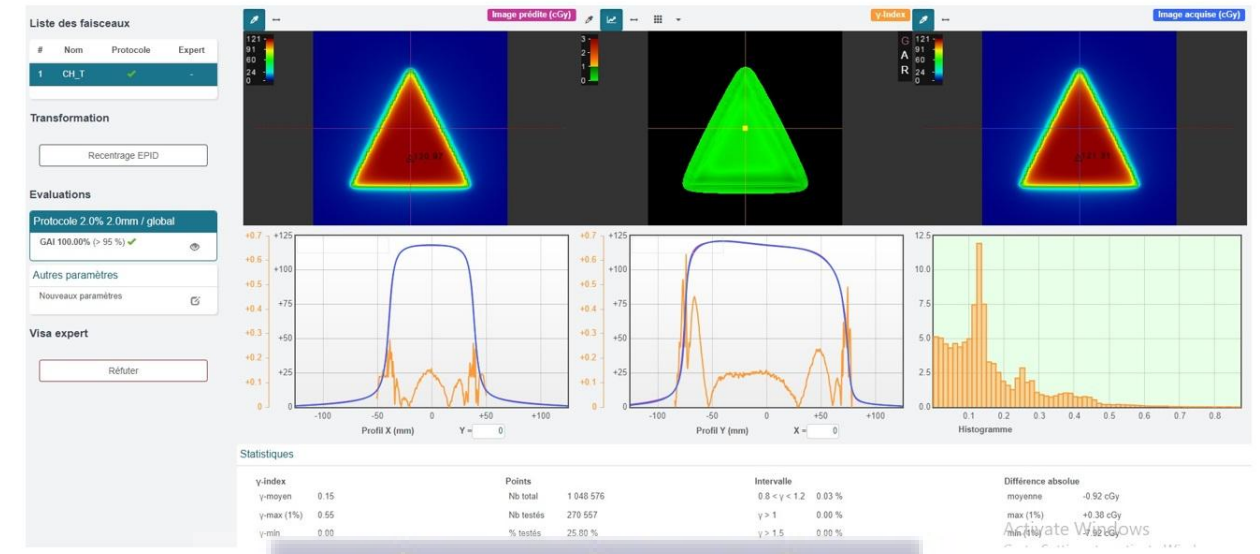
Unité de traitement
BLINF1

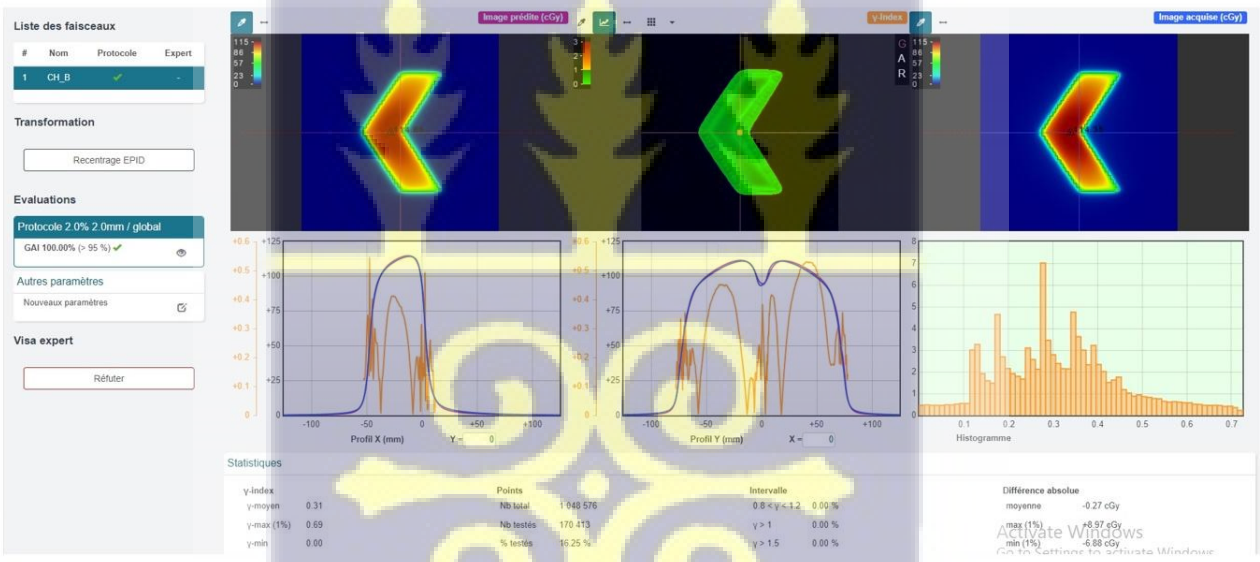
#	1	2	
Nom	LCHT_1	LCHT_2	Tous les faisceaux
Image brute acquise			
γ-max (1%)	1.82	1.72	
γ-moyen	0.32	0.44	0.38
GAI (>95.0%) %	96.57	96.22	96.40
Recentrage EPID	Expert	Non	
Intégrité CIAO	0.81	0.86	
Protocole	✔	✔	
Visa expert	-	-	

APPENDIX VIII: EPIBEAM END-TO-END TEST RESULTS 1

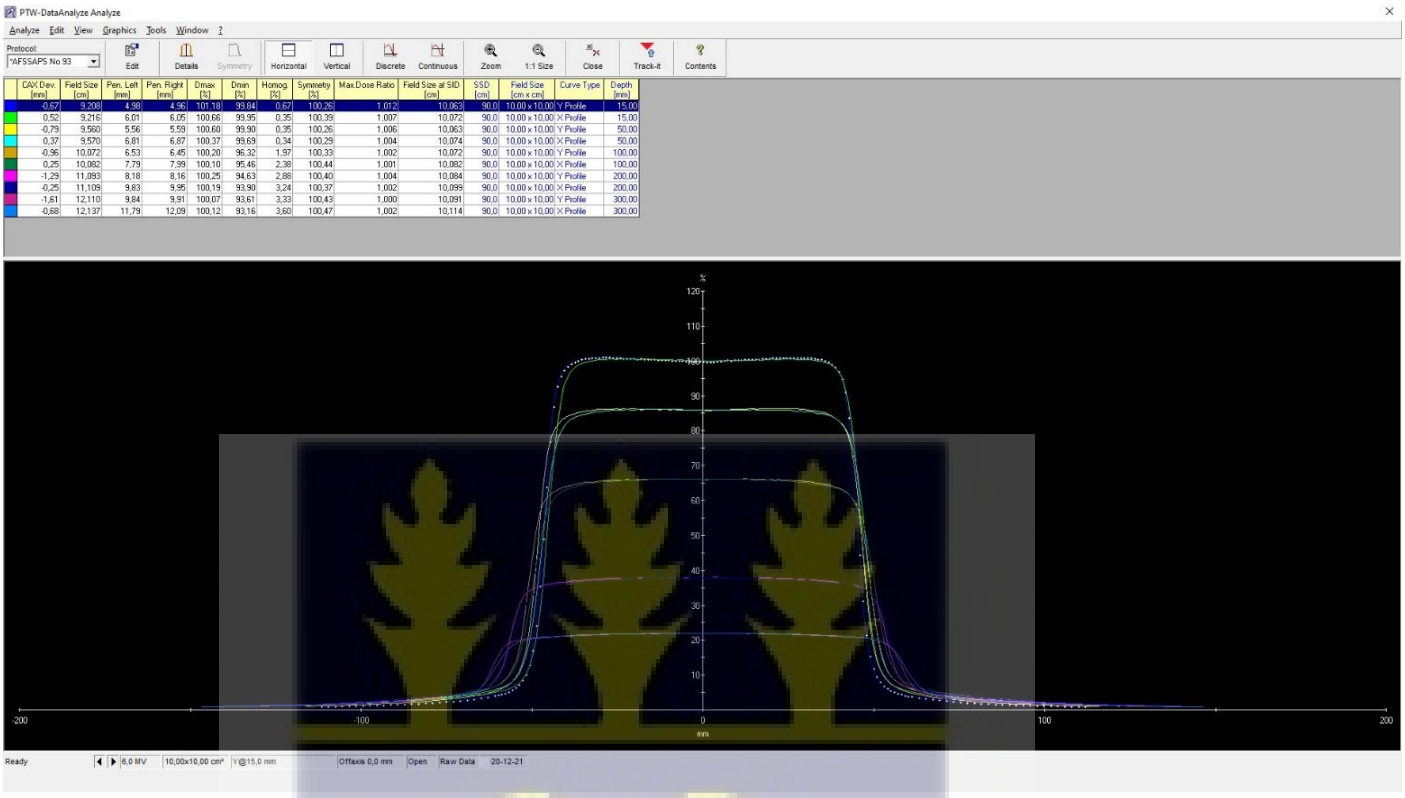


APPENDIX IX: EPIBEAM END-TO-END TEST RESULTS 2

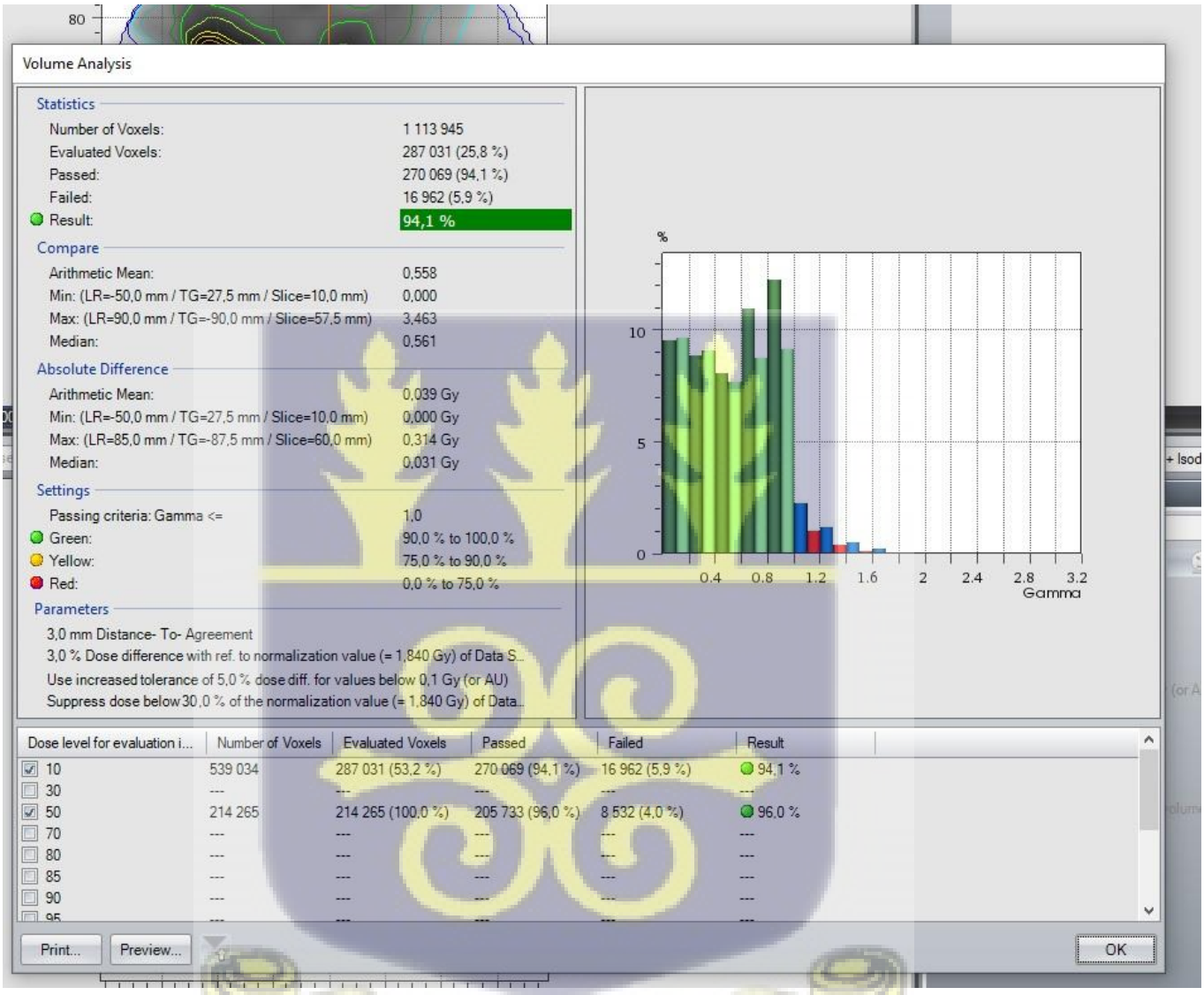




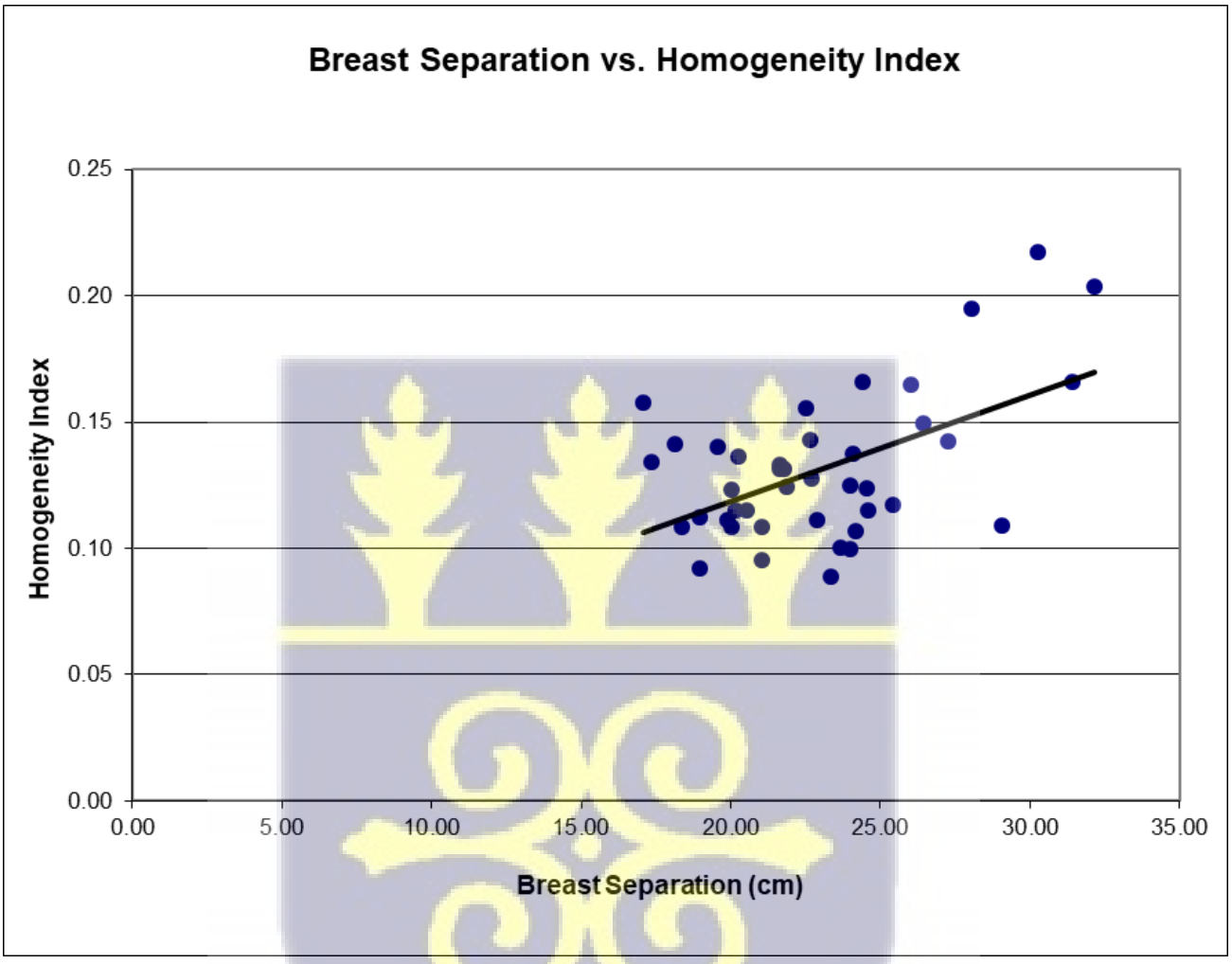
APPENDIX X: IN-LINE AND CROSS-LINE BEAM PROFILES FOR 10 CM X 10 CM FIELD SIZE AT DIFFERENT MEASUREMENT DEPTHS



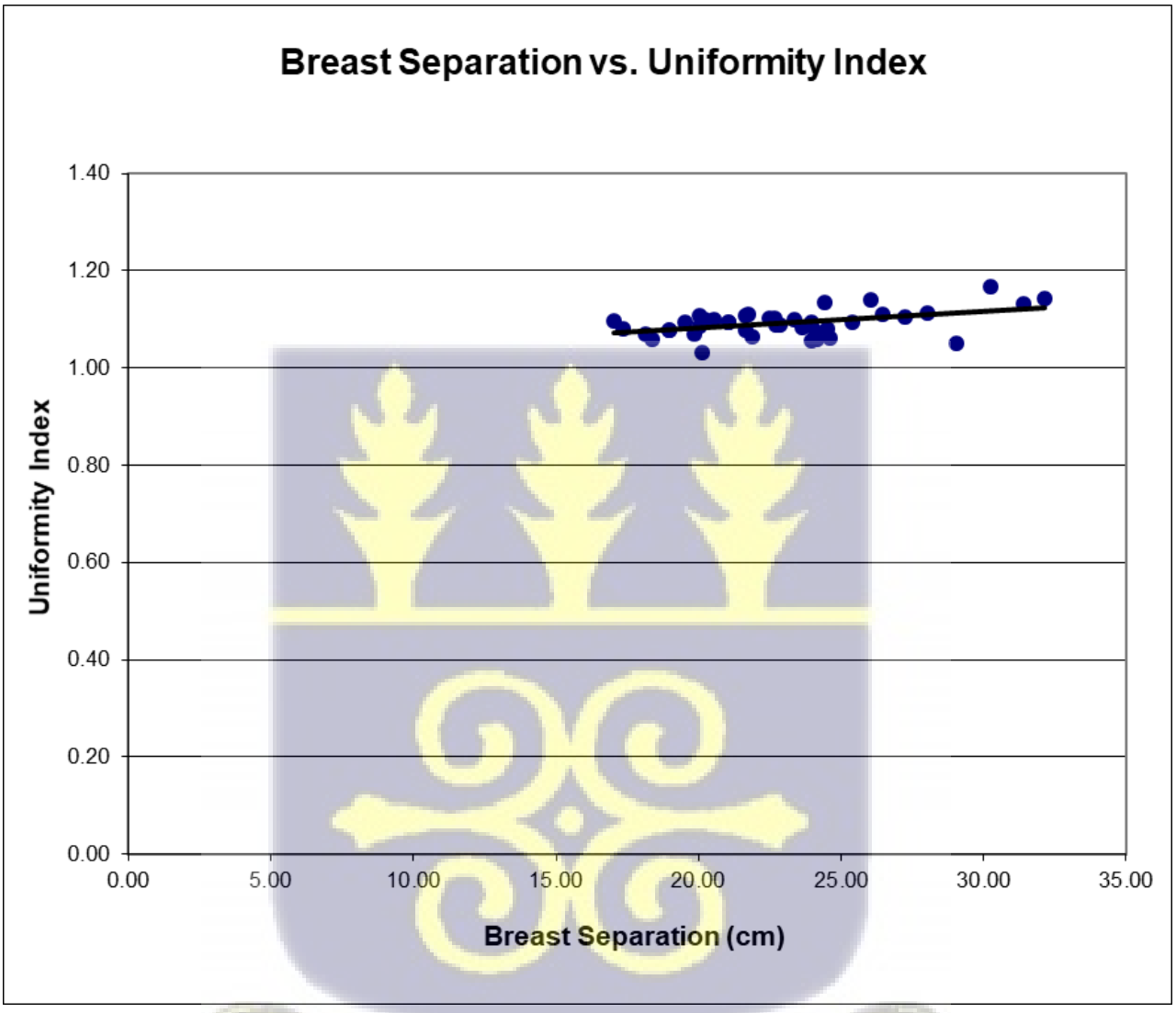
APPENDIX XI: SAMPLE OCTAVIUS 4-D PHANTOM ANALYSED PRETREATMENT QA GAMMA RESULTS FOR LEFT INTACT BREAST PLAN



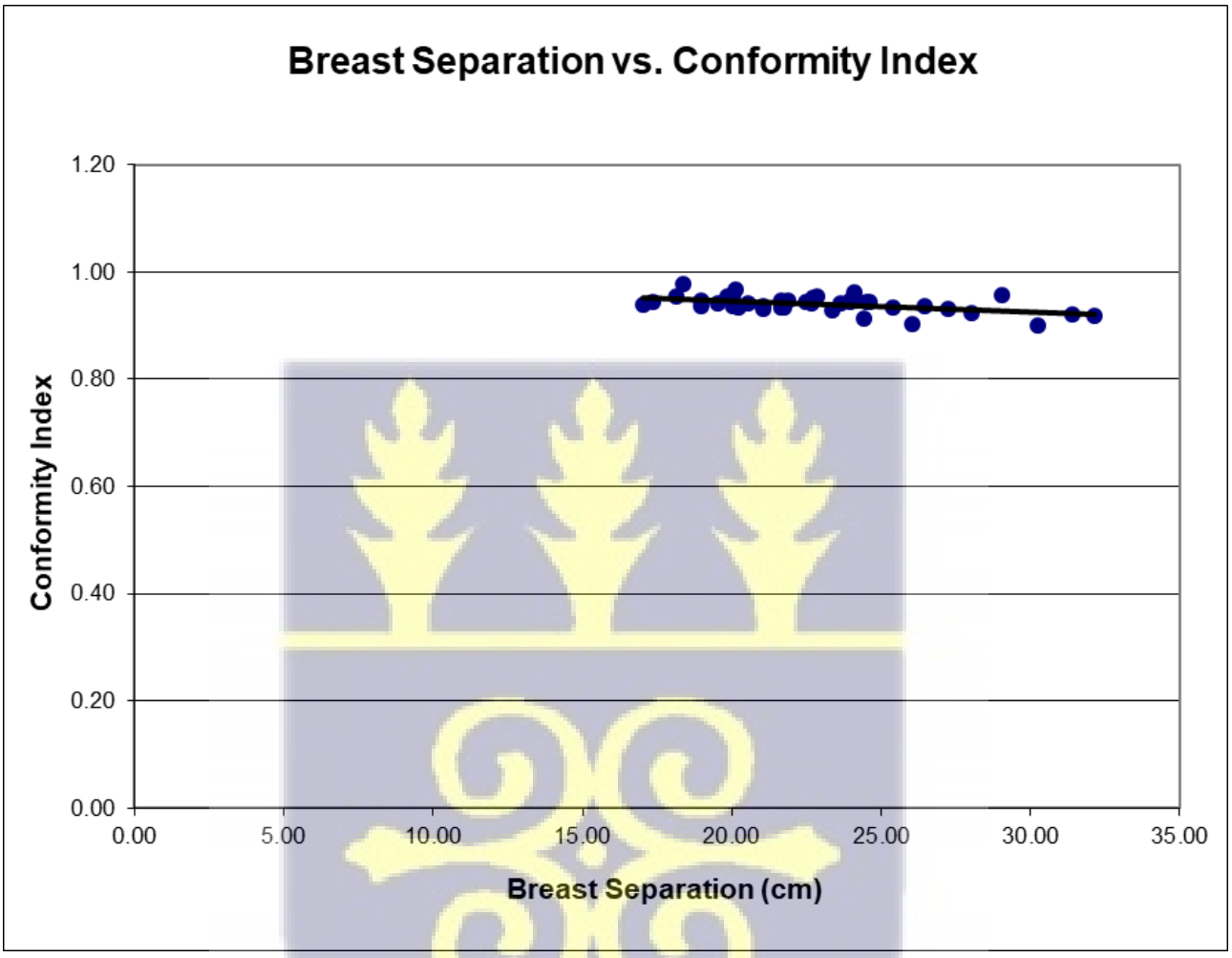
APPENDIX XII: GRAPHICAL REPRESENTAION OF THE EFFECT OF BREAST SEPARATION ON PLAN HOMOGENEITY INDEX FOR THE 43 INTACT BREAST PATIENTS ANALYSED IN PHASE 2



APPENDIX XIII: GRAPHICAL REPRESENTAION OF THE EFFECT OF BREAST SEPARATION ON PLAN UNIFORMITY INDEX FOR THE 43 INTACT BREAST PATIENTS ANALYSED IN PHASE 2



APPENDIX XIV: GRAPHICAL REPRESENTAION OF THE EFFECT OF BREAST SEPARATION ON PLAN CONFORMITY INDEX FOR THE 43 INTACT BREAST PATIENTS ANALYSED IN PHASE 2



APPENDIX XV: GRAPHICAL REPRESENTAION OF THE EFFECT OF BREAST SEPARATION ON PLAN HOT SPOT/HIGH DOSE FOR THE 43 INTACT BREAST PATIENTS ANALYSED IN PHASE 2