CONVENTIONAL VS HYPOFRACTIONATED RADIOTHERAPY: A COMPARISON OF CLINICAL-PATHOLOGICAL CHARACTERISTICS, DOSIMETRIC PARAMETERS AND TOXICITY IN POST-MASTECTOMY PATIENTS AT OCEAN ROAD CANCER INSTITUTE DECEMBER 2019 TO MARCH 2020

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By

Kevin Makori

A Dissertation Submitted in (Partial) Fulfilment of the Requirements for the Degree Master of Medicine (Clinical Oncology) of

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CERTIFICATION

The undersigned certifies that she has read and hereby recommends for acceptance by Muhimbili University of Health and Allied a dissertation entitled; **‘‘Conventional Vs hypofractionated radiotherapy: A comparison of clinical-pathological characteristics, dosimetric parameters and toxicity in post-mastectomy patients at Ocean Road Cancer Institute December 2019 to March 2020’’,** in (partial) fulfilment of the requirements for the degree of Masters of Medicine (Clinical Oncology) of Muhimbili University of Health and Allied Sciences.

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Date

DECLARATION AND COPYRIGHT

I, **Dr. Kevin Makori**, hereby declare that this **dissertation** is my original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature…… **Date**……

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DEDICATION

To my wife Emma: alone and lovingly, you supported this life-changing pursuit. A better definition of love never existed.

To my guardian angel, mum: You told me to pursue knowledge with the fervour of a possessed man; it's not over. It's your prayers that keep me going

To dad, the man of few words: I hope I've made you proud

To Bravian, who is always following in my footsteps-in his own unique way- but unconvincingly denies it: follow me into oncology

To Leslie and Elora; It's been long enough, I'm coming back home

To all cancer patients: your plight shall be my motivation.

ABSTRACT

Background: According to GLOBOCAN 2018, breast cancer amongst females is the most commonly diagnosed malignancy and the leading cause of cancer deaths. In Tanzania, just as in most other sub-Saharan countries, this number is only second to cervical cancer. Radiotherapy, an essential component in the adjuvant management of breast cancer, has traditionally been delivered using standard or conventional fractionation, consisting of a total dose of 50 Gy delivered at 1.8 to 2Gy daily fractions over 5-6 weeks. However, studies have demonstrated that hypofractionation schemes, utilizing lower total doses such as 40 Gy or 42.5 Gy, delivered at more than 2 Gy daily fractions over about 3 weeks offer the same therapeutic benefit and safety profile as standard fractionation. This benefit has mostly been studied post-breast conserving surgery.

Hypofractionation in the post mastectomy setting is slowly being adopted across the world, including Tanzania, where the recent arrival of linear accelerators has facilitated its utilization at Ocean Road Cancer Institute. Despite the foregoing, no data has as yet been published on how post-mastectomy hypofractionation compares to conventional fractionation, with regard to dosimetric parameters and acute toxicities amongst breast cancer patients in Tanzania.

Objective: The aim of this study was to compare the dosimetric parameters and acute toxicities of conventional radiotherapy with hypofractionated radiation therapy in post mastectomy patients with indications for radiotherapy at Ocean Road Cancer Institute.

Methods: This was a prospective comparative study between hypofractionated (HFRT) and conventional (CFRT) schemes of radiotherapy (RT) from December 2019 through March 2020. A total of 74 post-mastectomy patients undergoing adjuvant radiotherapy were conveniently sampled and recruited into the two study groups, with 37 patients in each of the two arms; conventional fractionation (50 Gy in 25 Fractions, 2 Gy/day over 5 to 6 weeks) or hypofractionation (42.5Gy in 16 Fractions, 2.67 Gy/day over 3 weeks). All patients were treated using the linear accelerator, with the 3D conformal technique. Patient demographics, tumour characteristics, management and dosimetric parameters were collected prior to radiotherapy. Evaluation for acute toxicities was conducted immediately upon completion of treatment and within 90 days as per the RTOG radiation toxicity

grading system. Data analysis was done using SPSS and presented in the form of tables and graphs. Independent t test was used to test the mean differences between these two groups and a p value <0.05 was considered statistically significant.

Results: This study recruited 74 post mastectomy patients who were on treatment at Ocean Road Cancer Institute between December 2019 and March 2020. Both HFRT and CFRT were allocated 37 patients each, with fairly equal distribution of social demographic and clinical features. The mean participant age was 51±12 years, with the majority within the age range 41-50. The mean BSA and BMI were 1.7±0.2 and 24.8±7.6 respectively. All participants had a diagnosis of invasive ductal carcinoma. The most common stage was IIIB (27%) and IIIA (29.7%) and grade was III (18.9%) and II (18.9%) in CFRT and HFRT respectively. One third (33%) of all participants had ER positive tumours, while ER-, PR+, HER2+ and HER2- status was documented in 40%,26%,23% and 51% respectively. The maximum dose to the chest wall PTV, as indicated by D2%, was higher with CFRT (mean=55.20 Gy) than with HFRT (mean=47.15Gy). The near minimum dose to the chest wall PTV (D98%) was lower with HFRT (mean=37.61Gy) than with CFRT (39.94%). The mean V95% of the chest wall PTV was 90.19%, in CFRT, and slightly higher at 92.58% in HFRT, a difference that was statistically significant (p=0.001). A statistically significant lower ipsilateral lung V35Gy, V40Gy and mean dose was noted with hypofractionation. Immediately post treatment, no statistically significant difference was noted in the proportions of grade 0 skin toxicities (51.4% in CFRT and 48.6% in HFRT) and grade 1 skin toxicities (48.6% in CFRT and 51.4 in HFRT). No grade 2 or 3 skin toxicities were noted immediately post treatment. Toxicity grade appeared to change at subsequent follow up within 90 days of treatment, with grade 2 and 3 toxicities being noted, respectively, in 43.25% and 10.8% of patients in CFRT, and 45.9% and 8.1% of patients in HFRT.

Conclusion: This study demonstrated that hypofractionation and conventional fractionation regimens have comparable acute skin toxicity profiles, with grade 2 toxicity being the most common and that hypofractionation results in a lower dose to the heart, lung and spinal cord.

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LIST OF ABBREVIATIONS

3DCRT:	3D conformal radiotherapy
CFRT:	Conventionally fractionated radiotherapy
CI:	Conformity index
CL Max dose:	Contralateral lung maximum dose
CL Mean dose:	Contralateral lung mean dose
D1%:	Dose to 1% of the PTV
D2%:	Dose to 2% of the PTV
D5%:	Dose to 5% of the PTV
D95%:	Dose to 95% of the PTV
D98%:	Dose to 98% of the PTV
D99%:	Dose to 99% of the PTV
EBCTG:	Early Breast Cancer Trialists' Collaborative Group
EORTC:	European Organisation for Research and Treatment of Cancer
ER:	Estrogen receptor
GLOBOCAN:	Global Cancer Observatory
Gy:	Gray
HER2:	Human epidermal growth factor receptor type 2
HFRT:	Hypofractionated radiotherapy
HI:	Heterogeneity index
ILV20Gy:	Ipsilateral lung volume receiving at least 20 Gy
ILV35Gy:	Ipsilateral lung volume receiving at least 35 Gy
ILV40Gy:	Ipsilateral lung volume receiving at least 40 Gy

LINAC:	Linear accelerator
MHD:	Mean Heart Dose
MLD:	Mean Lung Dose
MUHAS:	Muhimbili University of Health and Allied Sciences
OAR:	Organ at Risk
ORCI:	Ocean Road Cancer Institute
PR:	Progesterone receptor
PS:	Performance status
PTV:	Planning Target Volume
QUANTEC:	Quantitative Analyses of Normal Tissue Effects in the Clinic
RTOG:	Radiation Therapy Oncology Group
SPSS:	Statistical Package for Social Sciences
TNM:	Tumour, Node, Metastasis classification system
UK:	United Kingdom

DEFINITIONS OF KEY TERMS

Breast cancer: A malignant disease of the breast tissue that may involve the ducts, lobules or connective tissue, characterised by fast growing cells unresponsive to normal growth regulation.

Radiotherapy: Treatment of cancer using ionizing radiation

Fractionation: Refers to division of the total radiation dose into several smaller doses over a period of days, with the aim of minimizing the toxic effects on healthy cells while at the same time maximising the effect of radiation on the tumour/cancer.

Standard fractionation: Refers to the delivery of radiation in 1.8 to 2 Gy daily fractions typically over a period of 5-6 weeks

Hypo-fractionation: Refers to the use of use of higher than standard doses per fraction, while at the same time reducing the total dose, with the aim of minimizing late radiation effects on normal tissue, while at the same time maximising tumour cell kill

Acute radiation toxicity (also early radiation effects): Refers to normal tissue reactions that occur within 90 days after onset of the radiation exposure. They occur due to impairment of cell production in tissues that have a high turnover, such as skin and gastrointestinal epithelial cells. The latent time is largely independent of dose and is defined by tissue biology (turn-over time). Usually, complete healing of early reactions is observed.

Late radiation toxicity (also late radiation effects): Refers to normal tissue effects that can occur after symptom-free latent times of months to many years following radiation exposure, with an inverse dependence of latency on dose. They occur due to a complex interaction of damage on various slow growing cell populations (organ parenchyma, connective tissue, capillaries), with a contribution from macrophages. Late normal tissue changes are progressive and usually irreversible. Late effects are sensitive to a reduction in dose rate.

Dosimetric parameters: Information obtained after radiotherapy planning that provides objective information on the radiation doses received by the treatment targets and the organs considered at risk.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background information

According to the Global Cancer Observatory (GLOBOCAN) 2018 data, female breast cancer is the second leading cause of cancer deaths in both males and females globally. Amongst females, it is the most commonly diagnosed cancer and the leading cause of cancer deaths. In 2018, 2.1 million new cases were reported of which 0.9 million died (1).

In Tanzania, just as in most other sub-Saharan countries, this number is only second to cervical cancer. While data regarding the actual epidemiological distribution of breast cancer in Tanzania is unknown, published studies suggest that most breast cancer patients present with locally advanced disease(2,3).

The management of breast cancer has evolved steadily over the years, but a constant facet in management has been radiotherapy. Early studies demonstrated the beneficial role of radiotherapy in reducing the recurrence and mortality risks, a principle that is solidly grounded as the justification for radiotherapy in breast cancer(4–6).

Radiotherapy has traditionally been delivered in 2Gy daily fractions over 5-6 weeks, based on previous early assumptions that breast cancers, like many other human cancers were relatively insensitive to fraction sizes, as compared to late responding normal tissues(7–9). However, revolution of radiobiological knowledge generated data demonstrating that breast cancer was just as sensitive to fraction size as the late reacting and dose limiting normal tissues of the breast and the underlying ribcage(10–12). This therefore implied that small fractions of 2 Gy or lower had no therapeutic advantage and that shorter regimens of fewer fractions greater than 2 Gy would be effective while at the same time significantly reducing adverse effects(11,13). Indeed several landmark trials were conducted and proved this premise to be true, leading to a new era of hypofractionation in breast cancer, a practice that has been embraced in many centres worldwide(11,14).

The implications of hypofractionation are vast, ranging amongst others, shortening the treatment durations thus allowing treatment of more patients, at less cost to both the patient and the health system(8,15). Breast cancer, being second only to cervical cancer, forms a

significant volume of radiotherapy workload at Ocean Road Cancer Institute, and therefore hypofractionation would be of prime benefit to both patient waiting times and to institutional management costs. At the moment no local or regional data regarding the dosimetric outcomes and radiation toxicities with this already tested regimen, as compared to the conventional fractionation employed.

1.2 Literature Review

1.2.1 Demographic patterns of breast cancer

Female breast cancer is the second most commonly diagnosed cancer globally, and also the most commonly diagnosed and leading cause of cancer deaths in over 100 countries globally, while only second to cervical cancer in Sub-Saharan Africa (SSA) (1). Over the past few decades, rapid increases in incidence rates have been noted in countries in Africa, South America and Asia, a trend that is likely reflective of social and economic development including postponement of childbearing, having fewer children, greater levels of obesity, physical inactivity and increased breast cancer screening and awareness (1,16). While hereditary and genetic factors have been demonstrated to account for 5% to 10% of breast cancer cases, comparisons of low-risk populations migrating to high-risk areas reveal increasing incidences rise in successive generations, illustrating that non- hereditary factors are the major drivers of breast cancer incidence (1,17).

Available evidence shows an increasing incidence of breast cancer in Africa, with North Africa registries reporting slightly higher incidences than other Sub-Saharan Africa registries (18,19).

Published data on breast cancer in Tanzania show that most cases are locally advanced (3). Breast cancer in the second leading cause of cancer mortality among women in Tanzania The lifetime risk for developing breast cancer in Tanzania is approximately 1 in 20, and approximately half of all women diagnosed with breast cancer in Tanzania will die of the disease (20) It is projected that the number of new breast cancers will increase to 4,961 cases in 2030, up from 2,732 in 2012, an increase of 82%, with a similar 80 % increase in breast cancer deaths by 2030 (20).

Survival from breast cancer in Africa is generally poor, and this is attributable to late presentations, inadequate health infrastructure and funding, socioeconomic inequities and other competing health needs (18,21,22). Thus late presentations and advanced stages at diagnosis are prevalent, possibly explaining the high mortality rates (22). It is projected that with an increasing population, ageing and adoption of affluent lifestyles, breast cancer will likely continue to increase, particularly in the absence of adequate policies and interventions (1,18,23).

Against this backdrop, it is therefore prudent to adopt safe and cost-effective breast cancer treatment strategies in a bid to reduce the associated mortality rates, whose highest estimates are unfortunately high within SSA(1).

1.2.3 Clinical-pathological characteristics and management of breast cancer patients.

Breast cancer is a histological diagnosis made through standardized pathological criteria. Globally the most common breast cancer histology is invasive ductal carcinoma (50-75% of patients), with invasive lobular accounting for 5-15% of patients and the remainder being mixed ductal and lobular carcinomas and other rare histology (24). Breast cancer can further be classified into 3 histological categories based on the presence or absence of molecular markers for estrogen (ER) and progesterone (PR) receptors, and human epidermal growth factor 2 (HER 2): hormone receptor positive/HER negative, HER2 positive, and triple negative (lacking all 3 standard markers). Respectively, they account for 70%, 15-20% and 15% of breast cancers (24,25)

In developed countries, more than 90 per cent are diagnosed at early stages (1,24). In contrast, most breast cancer cases are diagnosed at advanced stages (22). Studies conducted in Tanzania have shown that most breast cancer patients are diagnosed at advanced stages, with the proportion of ER positive (ER+) tumours diagnosed in Tanzania ranging from 33% to 48% (2,3,26,27)

A retrospective study on pathological features of breast cancer patients revealed that 64% were diagnosed at clinical stage III (specifically IIIB), and 70.4% had lymph node metastasis at the time of diagnosis. Only 4.3% of the patients were in clinical stage I at the time of diagnosis. Invasive ductal carcinoma was the leading histology (91.5%) followed by mucinous carcinoma (5.2%), Invasive lobular carcinoma (3%) and in situ ductal carcinoma (0.3%), with (56.4%) demonstrating grade 3 disease (27)

In patients with non-metastatic disease, treatment goals are tumour eradication and prevention of recurrence. The 5-year breast cancer–specific survival for stage I triple-negative tumours is 85% contrasted against 94%to 99% for hormone receptor positive and HER 2 positive tumours (24). Recurrence is more likely with triple-negative breast cancer as compare with the other 2 subtypes (28).

Therefore systemic therapy for non-metastatic breast cancer is determined by subtype: patients with hormone receptor–positive tumours receive endocrine therapy, and a minority receive chemotherapy as well; patients with HER2 positive tumours receive HER2 targeted therapy combined with chemotherapy; and patients with triple-negative tumors receive chemotherapy alone (24,25). Local therapy for all patients with non-metastatic breast cancer consists of surgical resection, with addition of postoperative radiation as guided by the nature of surgical intervention, resection status, and nodal status (24). Some systemic therapy may be delivered preoperatively (neoadjuvant) to improve resection margin status (24). Radiotherapy may be delivered to the whole breast after lumpectomy, or to the chest wall following post mastectomy (4,25)

Metastatic breast cancer is treated according to subtype, with goals of prolonging life and palliating symptoms. Median overall survival for metastatic triple-negative breast cancer is approximately 1 year in contrast with approximately 5 years for the other 2 subtypes (24,28)

Traditionally, the management of breast cancer has employed a multi-disciplinary approach(4). Radiotherapy has been shown to improve loco regional control and survival in early breast cancer treated with breast conserving surgery and in high risk disease treated with mastectomy(5). Multiple landmark studies have been extensively quoted as providing the foundation for the use of adjuvant radiotherapy for breast cancer.

A meta-analysis of patient data from 17 randomised trials of radiotherapy vs. no radiotherapy after breast conserving surgery, conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), revealed that overall, radiotherapy reduced the 10 year risk of any first recurrence from 35% to 19.3%, and reduced the 15 year risk of breast cancer death from 25.2 to 21.4%, both findings being considered statistically significant (29)

Data from the 20 year follow up of patients in the widely quoted British Columbia Trial demonstrated that chemotherapy and radiation therapy compared with chemotherapy alone yielded statistically significant improvement in all the endpoints studied, including the survival free period from isolated loco regional recurrences (30). A more recent meta-analysis by the EBCTCG demonstrated that after mastectomy and axillary dissection,

radiotherapy reduced both the recurrence and breast cancer death in women with one to three positive lymph nodes, even in the presence of systemic treatment (6)

In Africa, optimal breast cancer care is hampered by amongst other factors, limited availability of breast conserving therapies and limited availability of skilled specialists (31,32). Coupled with poor access to radiation therapy and surgeons' preferences, this therefore implies that mastectomy rates are high in Africa (2,17,31,33,34). This is in stark contrast with the lower rates of mastectomy and the rising rates of breast conserving surgery in the developed countries (16,31,35). As already stated above, most breast cancer patients in Tanzania present with locally advanced disease(3), and therefore radiotherapy will more often than not, be delivered in the post-mastectomy setting.

1.2.4 Dosimetric parameters and acute toxicities in post mastectomy patients undergoing radiotherapy with standard fractionation vs. hypofractionation

The choice of a radiotherapy regimen is guided by the relationship between fraction size and both normal and tumour tissue responses, as quantified by the α/ β (alpha/beta) ratio (12). It is established that normal tissues and tumours have different responses to radiotherapy fraction size, a principle termed fraction sensitivity; these distinct responses are explained by an empirical model in which sensitivity to fractionation size is represented by the α/ β ratio (11). Low α/ β values signify greater sensitivity to fraction size than higher α/ β values (5,36). In human squamous cell cancers, for instance, an α/ β value of ≥ 10 is estimated, indicating low sensitivity to fraction sizes, and the use of small fractions ($\leq$ 2Gy) to a high total dose spares normal tissues relative to tumour tissue. On the other hand late reacting normal tissues have relatively lower α/ β values ($\leq$5Gy), and thus small changes in fractionation yield large changes in normal tissue complications (9,11,12).

Traditionally, breast radiotherapy has been delivered in 2 Gray (Gy) daily fractions over 5 to 6 weeks, in what is referred to as standard or conventional fractionation (7,8). The use of this fractionation schedule is based on the premise that a high total dose delivered in small fractions of 2 Gy minimises normal tissue damage while maximising tumour control (9). This practice appears to have arisen from previous radiobiological assumptions that breast cancers, like other human cancers, were relatively insensitive to fraction sizes

compared to late responding normal tissues (37,38). However this notion would later be challenged by radiobiological experiments that generated data suggesting that breast cancer was as sensitive to fraction size as the late reacting and dose limiting normal tissues of the breast and the underlying ribcage (10–12). The implication of this new perception was that small fractions of 2 Gy or lower offered no therapeutic advantage and that a shorter regimen of fewer fractions greater than 2 Gy would be effective while at the same time significantly reducing adverse effects (11,13).

A phase III randomized trial in the UK, conducted between 1996 and 1998 was the first major trial to demonstrate that the breast α/β was close to that for normal tissue (around 3 Gy) (12). The primary endpoint of the study was late change in breast appearance, while the secondary endpoints were breast in duration and ipsilateral tumour recurrence, with a minimum 5 year follow up. One thousand four hundred and ten (1410) women with T1-3, N0, M0 invasive breast cancer were randomized into one of three radiotherapy regimens: 50 Gy in 25 fractions, and 39 or 42.9 Gy in 13 fractions. An α/β value of around 3 Gy was ultimately demonstrated (11,12). Two points are noteworthy; first, the trial aimed at estimating the breast α/β value based on primary and secondary endpoints, and secondly all three regimens were delivered over 5 weeks.

Subsequently, the UK Standardization of Breast Radiotherapy (START) Trial B, randomly assigned 2215 women with T1-3a N0-1 M0 to after surgery to receive 50 Gy in 25 fractions of 2.0 Gy over 5 weeks or 40 Gy in 15 fractions of 2.67 over 3 weeks, with the principal endpoints of loco-regional tumour relapse, late normal tissue effects and quality of life (9). The findings demonstrated that the hypofractionation regimen (40 Gy in 15 fractions) offered rates of loco-regional tumour relapse and late normal tissue effects as comparable and favourable as the conventional/standard regimen (50 Gy in 25 fractions) with the added benefit of a shortened treatment duration for the former (9,14).

Concerns regarding the extension of hypofractionation to post mastectomy patients are premised partly on the fact that the UK START Trials were conducted on women with early breast cancer majority of whom had undergone breast conserving procedures (36). Of the 4451 women enrolled in both START A and B trials, 513 had undergone mastectomy, and an analysis of hazard ratios for the endpoints reveals comparable results, irrespective

of whether the primary surgery was breast conserving or mastectomy. Furthermore, 470 patients received lymphatic radiotherapy in the START Trials, most commonly to the supraclavicular fossa and extending to the upper axillary levels in a smaller minority, with the implication that variable volumes of level I/II nodes would have been included in the treatment field. Nonetheless retrospective analyses of patient reported outcomes have demonstrated no enhanced arm or shoulder dysfunction as a consequence of hypofractionation (36,39).

Data supporting hypofractionation in the post mastectomy setting has been on the increase. A five year (2003-2008) retrospective review of early breast cancer patients treated with post mastectomy hypofractionation (40 Gy in 16 fractions) demonstrated high local control rates survival rates, with mostly grade 1 skin toxicity rates of about 10% and no grade 3 skin toxicities, although lacking a control group treated conventionally (7). Comparative prospective studies, mostly single-institutional based have been published comparing hypofractionation and conventional fractionation, with consistent reports of comparability with respect to local control, survival rates and acute and late normal toxicity profiles (4,15,40–42). While this data reflects the experience in high income and a few LMIC countries such as Egypt and India, no data exists regarding hypofractionation in Tanzania and indeed the East African region.

The practice changing study, of immediate relevance to Tanzania and most African countries, supporting post mastectomy radiotherapy for high risk breast cancer would undoubtedly have to be a phase III trial conducted in China and published in the Lancet Journal in 2019. In this randomised non inferiority open label trial, 820 patients were randomly assigned to conventional (50 Gy in 25 fractions over 5 weeks) or hypofractionation (43.5 in 15 fractions over 3 weeks), with a primary endpoint of 5 year loco regional recurrence (43). Eligible patients had to have undergone mastectomy with either ≥4 positive axillary nodes, or primary tumour stage T3-T4. At a median follow up of 58.5 months, the trial demonstrated that hypo fractionated radiotherapy was non inferior and had similar toxicities to conventionally fractionated radiotherapy in patients with high risk breast cancer. It is noteworthy that patients in this study are reflective of the patient profile seen at ORCI, just as in most African countries (3,19,33).

Concerns regarding survival outcomes toxicity profiles due to hypofractionation have not only been dispelled by phase III trials, but also addressed at the molecular level through radiobiological experiments and reviews (5,14,44). Furthermore, modern computer based treatment planning systems allow for review of dosimetric and other planning parameters, which can then be compared with published risk prediction models, and thus allowing for comparisons of virtually any dosing regimen and radiotherapy technique (45,46).

Target volume and organs at risk can be evaluated for dose hotspots and measures of homogeneity, all of which have established roles in determining the quality of radiotherapy plans and prediction of radiotherapy toxicities (47–49). Toxicity risks usually graded by the RTOG/EORTC criteria, and predicted by the widely utilised QUANTEC model (46,50). Based on these radiobiological principles and clinical data, it has been demonstrated that hypofractionation using various regimens of approximately 2.6 Gy and total doses between 40-42.6 Gy over 3 weeks is as effective and as safe as conventional hypofractionation (5).

During radiotherapy planning for breast cancer, the PTV is often under dosed in an effort to minimize the dose to the lungs, heart and the contralateral breast. Compared to conventional fractionation, the lower prescribed dose associated with hypofractionation has been shown to allow improved target coverage, as evaluated using the V95% coverage (51). Concerns regarding the slightly higher dose per fraction have been dispelled by long term follow up of patients treated with commonly utilised breast hypofractionation regimens, which demonstrate no increased risk of late organ-at-risk effects (36). Furthermore, it has been extensively demonstrated that with the moderate hypofractionation regimens, the equivalent dose in 2 Gy daily fractions (EQD2) and biologically effective dose (BED), are lower with hypofractionation than conventional fractionation, assuming using an alpha beta ratio of about 4 for late lung effects and about 1.5 for late cardiac effects (5,52,53). This implies that any reduction in OAR doses could result in at the very least comparable, if not better sparing to these critical dose limiting structures (5,36,51).

Despite this equivalent local control, and non-inferior late effects, hypofractionation remains underutilized globally (54,55). Possible reasons include individual physician preferences and physician reimbursement models that favour longer patient treatment time, and thus conventional fractionation (55). In countries where government funding is the mainstay of healthcare funding, it is noteworthy that hypofractionation would be immensely beneficial, given the demonstration of significant cost reduction and the potential channelling of scarce resources to other aspects of the health system (56–59). In Tanzania, the recent introduction of linear accelerators at Ocean Road Cancer Institute has already paved way for the utilization of hypofractionation in breast cancer at the facility. Nonetheless no data has been generated comparing the dosimetric patterns of hypofractionation and standard fractionation at the facility.

In conclusion, given the established local control and survival outcomes between hypofractionation and conventional fractionation, shorter treatment durations associated with hypofractionation have added advantages of increasing the level of treatment compliance owing to shorter treatment times and the resultant possibility of treating more patients in a given duration (8,15).This is especially crucial for Tanzania, given that like other African countries, female breast cancer, especially locally advanced disease, is already recognised as a commonly managed condition in most radiotherapy centres on the continent (2,3,60), and thus shorter treatment times would allow higher patient turnover, thus reducing the operational costs on institutions, not to mention the reduction in the costs for individual patients travelling from far flung areas (8,15,60).

1.3 Problem Statement

Hypofractionated radiotherapy can significantly reduce the waiting time for radiotherapy, working load on machines, patient visits to radiotherapy departments and medical costs. Standard or conventional adjuvant fractionation schemes consist of a total dose of 50 Gy delivered at 1.8 to 2Gy daily, in 25 fractions delivered over 5 weeks. Hypofractionation schemes include a variety of lower total doses such as 42.5 or 40 Gy, delivered at higher than conventional daily doses, in fewer fractions over a shorter total duration, typically 3 weeks. Although the standard fractionation scheme has for a long time been utilised after both breast conserving surgery and mastectomy, radiobiological experiments and phase III trials have demonstrated that hypofractionated schemes are equally effective with reduction in treatment durations and no added adverse risk (9,12). Single institutional prospective studies and a recently published phase III trial have generated evidence that hypofractionation in patients with locally advanced disease after mastectomy is just as effective and safe as in the breast conserving setting (61). The utilization of fractions greater than 2 Gy while reducing the total doses is now established to have greater tumour effect, while significantly reducing adverse effects on normal tissue such as the skin, blood, heart and lungs during radiotherapy (11,13). Additionally, in contrast with standard fractionation, hypofractionation, due to the associated shorter treatment duration, offers advantages of increasing treatment compliance and allowing more patients to be treated within a given duration and thus greater economic benefits to radiotherapy departments (8,13).

Hypofractionation in the post mastectomy setting is slowly gaining popularity across the world in countries such as the UK (62–64), India (15,51), Egypt (65) and China (61) due to dosimetric advantages in terms of infrequent incidence of radiotherapy related early effects and improved survival rate as well as reduction of machine load. Although unpublished, majority of breast cancer patients, and indeed cancer patients in general, receive radiotherapy as part of their treatment, a service that is delivered using only 2 linear accelerators (Linacs) and 2 Cobalt 60 units. However, in Tanzania, despite the on-going progressive shift from standard fractionation to hypofractionation, there is no study that provides evidence on the dosimetric, toxicity and patient load reduction advantage of hypofractionation over standard fractionation scheme.

Therefore, this study aims at comparing standard fractionation and hypofractionation among breast cancer patient treated at ORCI in with a focus on dosimetric parameters and related acute effects.

1.4 Conceptual Framework

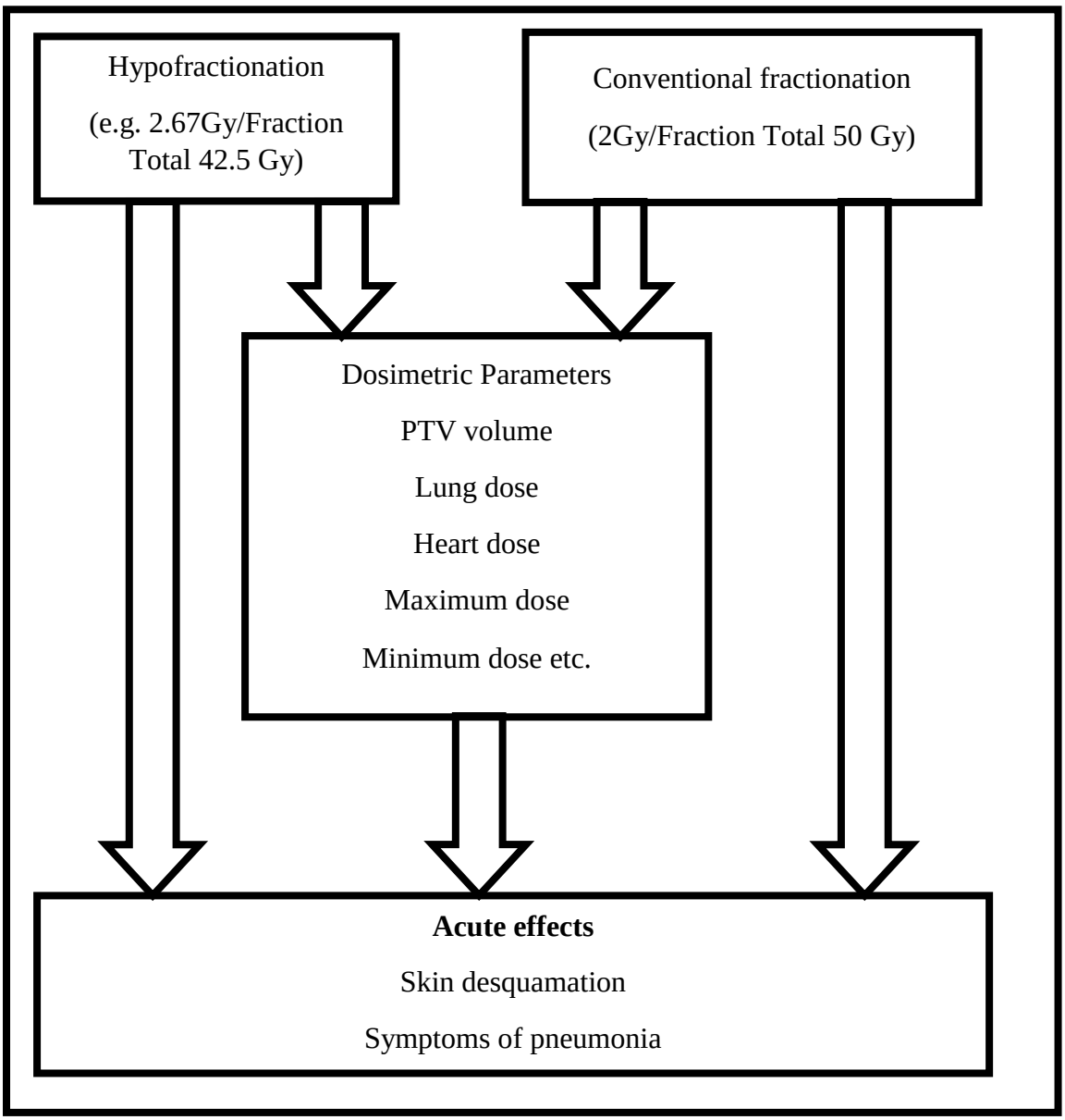


Figure 1: Conceptual frame work

Description of conceptual framework

Both hypofractionation and conventional hypofractionation have inherent predisposition to the development of acute radiation effects.

During radiation planning, it is possible to deduce the plan parameters such as the doses to the various organs at risk and to the intended target regions. These parameters can predict for the occurrence of radiotherapy effects.

It is expected that due to the different fraction sizes and total doses that these parameters will be different for the two schedules, thus allowing for their comparison.

1.5 Rationale

This study aims to generate a body of comparative data on the dosimetric parameters regarding target volume coverage and doses to the organs at risk (OAR's) of concern (heart and lung), and acute toxicities arising from the utilization of either conventional or hypofractionation in the management of breast cancer patients at ORCI. Data thus generated would help in determining if the former regimen is adaptable to the local setting given that no such study and subsequently such information is available within Tanzania and indeed the East African Region.

1.6 Research Questions and hypothesis

Research question	**Hypothesis**	**Null Hypothesis**
What are the clinico-histopathologic and treatment characteristics of breast cancer patients undergoing radiotherapy at ORCI?		
Are there any differences in the dosimetric plans generated from plans utilizing either hypofractionation or conventional fractionation in breast cancer radiotherapy at ORCI?	There is a difference in the mean values of dosimetric parameters between conventional and hypofractionated breast radiotherapy.	There is no difference in the mean values of dosimetric parameters between conventional and hypofractionated breast radiotherapy.
Are there any differences in the acute skin toxicity patterns/profiles amongst breast cancer patients treated with either hypofractionation or conventional fractionation?	There is a difference in acute skin toxicity profile among breast cancer patients treated with hypofractionation and conventional fractionation	There is no difference in acute skin toxicity profile among breast cancer patients treated with hypofractionation and conventional fractionation

1.7 Study objectives

1.7.1 Broad Objective

Determination of the clinical-pathological characteristics and comparison of dosimetric parameters and acute skin toxicities in post mastectomy patients treated with either hypofractionation or conventional fractionation at Ocean Road Cancer Institute from December to March 2020.

1.7.2 Specific Objectives

i. To determine the demographic and clinical-pathologic characteristics of breast cancer patients undergoing post-mastectomy radiotherapy at ORCI from December 2109 to March 2020.
ii. To compare the dosimetric parameters in post-mastectomy patients undergoing radiotherapy with standard fractionation vs. Hypofractionation from December 2109 to March 2020.
iii. To compare the acute skin toxicity profiles in post-mastectomy patients undergoing radiotherapy with standard fractionation vs. Hypofractionation from December 2109 to March 2020.

CHAPTER TWO

2.0 MATERIAL AND METHODS

2.1 Study Design

The study was a comparative prospective three month study of locally advanced breast cancer patients treated using the conventional fractionation and the hypofractionation regimens from December 2019 to March 2020.

2.2 Study Population

The population of this study was all post mastectomy breast cancer patients at ORCI scheduled to undergo radiotherapy between December 2019 and March 2020

The target population was all breast cancer patients who met minimum eligibility criteria.

2.3 Study setting

This study was conducted at ORCI. Located along the Indian Ocean, ORCI is the only specialized public tertiary hospital for cancer treatment in Tanzania. The hospital was the only cancer facility for both private and public in Tanzania before the emergence of other centres such as Bugando Medical Centre in recent years. It was established by Germany colonial government in 1895. It previously functioned under Muhimbili National Hospital as the paediatric wing, but in early June 1996, the Parliament of United Republic of Tanzania declared it an autonomous institute under the ministry of health. Currently, ORCI has 15 consultant clinical oncologists 37 radiotherapists, 27 oncology nurses and 6 medical physicists. Annually, hospital records show that ORCI receives around 540 breast cancer patients, with a monthly average of 40-50 cases. Nearly 97% receive post-operative radiotherapy. Prior to the introduction of the Linear Accelerator (Linac), manufactured by VARIAN at late months of 2018, all patients were treated with standard radiotherapy at the Cobalt 60 (Co-60), Teletherapy machine. The latter machines are currently used predominantly for palliative radiation services. The introduction of the Linac machines has facilitated the adoption of hypofractionation.

2.4 Eligibility criteria

2.4.1 Inclusion criteria

Patients with histologically confirmed infiltrating ductal carcinoma of the breast without evidence of distant metastases or second malignancy, and with normal baseline cardiac, renal and pulmonary function, with an Eastern Cooperative Oncology Group (ECOG) performance scale 0-2 and all patients age above 18 years. It was estimated that in one month, about 50 patients would meet this criteria.

2.4.2 Exclusion criteria

Patients with inconsistent treatment plan parameters would excluded from the study.

Seriously ill and mentally unstable patients were also excluded.

2.5 Sample Size

The sample size calculations are obtained from the power method (66,67).

Formula for a continuous outcome and equal sample sizes in both groups (hypofractionation and conventional group), assuming: alpha = 0.05 and power = 0.90 (beta = 1.28.)

n = the sample size in each of the groups

μ1 = population mean in treatment Group 1

μ2 = population mean in treatment Group 2

μ1 − μ2 = the difference at σ2 = population variance (SD) a = conventional multiplier for alpha = 0.05 β = conventional multiplier for power = 0.90

$$n=\frac{2[(\alpha+\beta)^2\delta^2]}{(\mu_1+\mu_2)^2}$$

$$n=\frac{2[(1.96+1.28)^2 3.5^2]}{2^2}=64$$

Therefore the number of sample for each group would be 64, and since two groups are included in this study, hence 64x2=128.

The projected sample size for this study will be 128 breast cancer patients.

2.6 Study variables

Dependent variables of this study were dosimetric parameters and treatment toxicities.

Skin toxicity was the primary dependent variable

Dependent Variable	**Independent Variable**
Dosimetric parameters -95% PTV coverage -Heterogeneity index -Lung V20, Mean Lung Dose	Fractionation schedule -Conventional fractionation -Hypofractionation
Acute toxicities -Skin toxicity	Fractionation schedule -Conventional fractionation -Hypofractionation

2.7 Data Collection

2.7.1 Baseline evaluation.

All patients were assigned unique study numbers and information documented in individualised forms that were used at baseline and upon completion of treatment. Data regarding patient demographics, tumour related information and management were obtained and documented in the forms (Appendix 1)

Demographic data that collected were age, sex, address/residence, weight, height, BMI and history of comorbid conditions

Tumour related information included, histology and grade, hormonal receptor (ER, PR and HER 2) status, anatomic side, quadrant of the breast, T, N& M stage and AJCC stage, involved.

Management related information included type of surgery, chemotherapy (neoadjuvant and adjuvant) regimens and cycle

Radiation-site skin examinations were conducted immediately after completion of radiotherapy and at one subsequent visit within 90 days post treatment, and graded as per the RTOG/EORTC acute toxicity system(50). (Appendix 2)

2.7.2 Radiotherapy protocol

Recruited patients with indications for post-mastectomy radiotherapy were simulated and had their radiotherapy planning as per the ORCI protocol (Appendix 3).

Prescription was at the discretion of the responsible oncologist as per institutional practice, and no intervention was made by the PI. Patients received one of two regimens, either conventional fractionation (CFRT) given at a total dose of 50 Gy in 25 fractions at 2.0 Gy per fraction, one fraction per day, over 5 weeks, or hypofractionation (HFRT) given at a total dose of 40 Gy in 15 fractions, at 2.67 Gy per fraction, one fraction per day, over 3 weeks.

2.7.3 Dosimetric Analysis

All patient treatment plans were evaluated for their dose volume histogram (DVH) data regarding coverage of target volumes and OAR's following the ORCI protocol (Appendix 3)

Dosimetric parameters about target volume coverage included the chest wall PTV receiving 90% and 95% of the prescribed dose (the V90% and V95% respectively), the dose delivered to 90% of the PTV (D90), and the hottest point in the plan.

The doses to 1%, 2%,5%, 95% and 99% of the target volume (D1%, D2%, D95% and D95% respectively) were used to determine the Homogeneity Index (HI) as defined by RTOG(47).

Planning dose volume histograms (DVH's) were evaluated for doses received as defined by the QUANTEC guidelines namely ipsilateral lung V20% and mean dose, heart V25% and mean dose and mean contralateral breast dose.

2.8 Investigation tools, Validity and Reliability

Suitability of the data abstraction forms and their ease of use were pre-tested prior to the start of the study.

2.9 Data analysis

Data was analysed using SPSS version 23.

Continuous variables were summarized using measures of central tendencies that is mean/standard deviation or median/ranges.

Categorical variables were summarized using frequencies and percentages then presented in tables and figures.

Mean values of the various dosimetric parameters were obtained and SPSS tools used to seek differences between the two treatment fractionation regimens.

Table 1: Data analysis plan per specific objective

S/N	Specific objective	Analysis plan
i.	To determine the demographic and clinical-pathologic characteristics of breast cancer patients undergoing post-mastectomy radiotherapy at ORCI	Frequency/Percentage
ii.	To compare the dosimetric parameters in post-mastectomy patients undergoing radiotherapy with standard fractionation vs. hypofractionation	Student's t-test statistics p value less than 0.05 will be considered significant.
iii.	To compare the acute toxicity profiles in post-mastectomy patients undergoing radiotherapy with standard fractionation vs. hypofractionation	Cross tabulation Chi-square, p value at 0.05 were considered statistically significant

2.10 Ethical Issues

Clearance to conduct the study was sought in writing to both ORCI and MUHAS Research Ethics Committees.

All patients involved in the study were informed of the aims of the study and their roles in it, and their willingness following this communication expressed in the form of a signed consent form by themselves or their minder.

All patients and patient data were anonymised, and all data collected for the purpose of the study stored on secured computers only accessible to the investigator, supervisor and administration of the oncology department.

Any patients developing treatment related toxicities will be provided the best standard of care as per the institutional management protocols. The study did not involve any invasive procedure and sought to compare radiotherapy interventions that are the part of the institution’s treatment for breast cancer, hence it imposes minimal risk.

CHAPTER THREE

3.0 RESULTS

This study recruited 74 post mastectomy breast cancer patients who were on treatment at Ocean Road Cancer Institute between December 2019 and March 2020. Both HFRT and CFRT were allocated 37 patients each, with fairly equal distribution of social demographic and clinical features. The mean participant age was 51±12 years, with the majority within the age range 41-50. The mean BSA and BMI were 1.7±0.2 and 24.8±7.6 respectively. Most of the patients had no pre-existing condition, with the most commonly encountered condition being hypertension, accounting for 5.41% and 18.92% in the CFRT and HFRT arms respectively. [Table2]

All participants had a diagnosis of invasive ductal carcinoma. The most commonly encountered stage was IIIB (27%) and IIIA (29.7%) in the CFRT and HFRT arms respectively. A predominance of left sided tumours was noted generally (56.76%), most of whom were treated in the HFRT arm, as contrasted with right sided tumours in the CFRT arm. Generally, most patient records lacked information regarding tumour grade and LVSI. Amongst the documented reports, the most encountered grade was III (18.9%) and II (18.9%) in CFRT and HFRT respectively. 33% of all participants' patients had ER positive tumours, while ER-, PR+, HER2+ and HER2- status was documented in 40%, 26%, 23% and 51% respectively. Most of ER positive patients were treated within the CFRT arm, whereas most of ER negative were treated within HFRT. Distribution within both arms was even for PR+/- and HER2+/- tumours. [Table4]

Majority of the participants in both arms had surgical margin status documented as negative (54.1% CFRT and 59.5% HFRT). Nonetheless 22 (29.73%) of the participants lacked information on margin status. The mean number of dissected lymph nodes was 8 in both groups (SD ±5 and ±3 in CFRT and HFRT respectively). In general, 20.27% of the participants had a positive ratio of ≥50% of dissected nodes at pathological evaluation. All patients received chemotherapy, with most receiving it adjuvantly (75.7% in CFRT and 78.4% in HFRT). An anthracycline, cyclophosphamide and taxanes based regimen was the most commonly encountered regimen (71.6%), with variation in terms of addition HER2+ directed therapy, number of cycles and choice of anthracycline. [Table 3]

All patients had two planned volumes, for the chest wall (CW) and supraclavicular fossa (SC). The maximum dose to the chest wall PTV, as indicated by D2%, was higher with CFRT (mean=55.20 Gy) than with HFRT (mean=47.15Gy). The minimum dose to the chest wall PTV, as indicated by the D98% was lower with HFRT (mean=37.61Gy) than with CFRT (39.94%). This trend was similarly noted for the separately planned supraclavicular PTV. The mean V95% of the chest wall PTV was 90.19%, (range= 76-100%) in CFRT, and higher (92.58%) in HFRT (range= 84-99) %, a difference that was statistically significant (p=0.001). No statistically significant difference was noted between the mean V105% and the V107% of the 2 groups. [Table 5]

There was a statistically significant difference in the objective dose constraints for the lung, and spinal cord dose, with HFRT noted to result in lower doses compared to CFRT. No statistically significant difference was noted with respect to the dose constraints for the heart between the two fractionation arms. [Table 6]. Overall, left sided tumours resulted in higher values of the dose constraints for the heart, while right sided tumours had higher values of the dose constraints for the spinal cord. [Figure 2].

No statistically significant difference was noted in the acute skin toxicities between CFRT and HFRT. Grade 0 and 1 toxicities were the most commonly encountered toxicities immediately at the end of treatment (51.4% vs 48.6% for CFRT and 48.6 vs 51.4% for HFRT). Toxicity grade appeared to change at subsequent follow up within 90 days of treatment, with grade 2 and 3 toxicities being noted, respectively, in 43.25% and 10.8% of patients in CFRT, and 45.9% and 8.1% of patients in HFRT [Table 7-8]

Table 2: Base line information of the study participants

Clinical Variables		**RT regimen**	
		CFRT	HFRT
		n (%)	n (%)
Age	<30	0(.0)	2(5.4)
	31-40	5(13.5)	7(18.9)
	41-50	14(37.8)	13(35.1)
	51-60	8(21.6)	5(13.5)
	61+	10(27.0)	10(27.0)
Residency	Upcountry	19(51.4)	21(56.8)
	Coast	18(48.6)	16(43.2)
BMI	18.5	4(11.1)	7(18.9)
	18.5-24.9	20(55.6)	12(32.4)
	25-29.9	9(25.0)	11(29.7)
	30-34.9	3(8.3)	4(10.8)
	35+	0(.0)	3(8.1)
BSA	<2.05	37(100.0)	34(91.9)
	2.06-2.57	0(.0)	3(8.1)
Comorbidity	Asthma	0	1
	DM	1	0
	Hypertension	2	7
HIV status	Positive	1(2.7)	2(5.4)
	Negative	36(97.3)	35(94.6)
ART	Yes	1(100.0)	2(100.0)

The mean ± standard deviation age of the study participants was 51±12. Majority of the study participants were at the age of 41-50 years. The mean participants BMI was 24.8 and standard deviation was 7.6. Majority of the participants had BMI 18.5-25. The mean BSA was 1.7 and standard deviation was0.2. One patient had asthma and one had diabetes while nine patients had hypertension. However, three patients were HIV positive and were all on ART.

Table 3: Treatment information of the study participants

		RT regimen	
		CFRT	HFRT
		n (%)	n (%)
Surgical margins	Positive	3(8.1)	3(8.1)
	Negative	20(54.1)	22(59.5)
	Close	3(8.1)	1(2.7)
	Not reported	11(29.7)	11(29.7)
LN removed	Mean (SD)	8±5	8±3
	Range (Min-Max)	3-21	4-17
LN +ve %	<50	32(86.5)	27(73.0)
	>50	5(13.5)	10(27.0)
Chemo	Neo adjuvant	6(16.2)	6(16.2)
	Adjuvant	28(75.7)	29(78.4)
	Both	3(8.1)	2(5.4)
Chemo regimen	1FEC-3T	0	1
	3FEC-3T	0	3
	3FEC-3TH	0	1
	4AC-4T	12	8
	4AC-4TH	2	8
	4AC-8T	0	1
	4AC-9T	2	2
	4EC-4T	8	4
	4EC-4TH	1	4
	4EC-9TH	0	1
	4TAC	0	1
	4TC	1	0
	6FEC	3	1
	6TAC	8	2

Almost all patients underwent surgery, chemotherapy and radiotherapy. Six patients (8.1%) had positive surgical margins and 22(29.7%) had no surgical margin report. Thirty six (48.6%) had undergone lymph node dissection. All patients received, with the majority receiving it in the adjuvant setting 57(77.02%). The most prominent regimen was 4AC-4T, 4EC-4T and 6TAC. (A=Doxorubicin, C=Cyclophosphamide, E=Epirubicin, F=5-Fluorouracil, T=Taxane, H=Trastuzumab)

Table 4: Clinical and tumour characteristics of the study participants

Pathological Variables		**RT regimen**	
		CFRT	HFRT
		n (%)	n (%)
Histology	Invasive ductal	37(100.0)	37(100.0)
Grade			
	Grade 1	1(2.7)	0(.0)
	Grade 2	6(16.2)	7(18.9)
	Grade 3	7(18.9)	6(16.2)
	Not Reported	23(62.2)	24(64.9)
LVSI	Present	11(29.7)	9(24.3)
	Absent	2(5.4)	0(.0)
	Not reported	24(64.9)	28(75.7)
ER	Positive	22(59.5)	12(32.4)
	Negative	15(40.5)	25(67.6)
PR	Positive	12(32.4)	14(37.8)
	Negative	25(67.6)	23(62.2)
HER2	Positive	9(24.3)	14(37.8)
	Negative	28(75.7)	23(62.2)
Laterality	Right	19(51.4)	13(35.1)
	Left	18(48.6)	24(64.9)
Stage	IIA	2(5.4)	1(2.7)
	IIB	6(16.2)	7(18.9)
	IIIA	7(18.9)	11(29.7)
	IIIB	10(27.0)	10(27.0)
	IIIC	4(10.8)	5(13.5)
	Not Available	8(21.6)	3(8.1)

All patients were histologically confirmed invasive ductal carcinoma. Majority of the patients had grade three tumours, although most patients lacked grading information. LVSI was present in 20 participants while over half of the participants had no LVSI report. ER, PR and HER2 positive tumours were 34, 26 and 23 respectively. Majority of the patients had a left sided tumour. However, most of ER positive patients were treated with conventional dose whereas most of ER negative was Hypofractionated. Both PR and HER2 were fairly evenly distributed between both groups.

Table 5: Comparison of the mean target volume dosimetric parameters of post mastectomy breast cancer patient treated at ORCI from December 2019 to March 2020

Dosimetric Parameter	CFRT Mean(±SD)	HFRT Mean(±SD)	t (p value)
PTV_{CW}	812.83(352)	726.83(341)	1.068(0.289)
PTV_{SC}	181.95(74)	197.36(185)	0.471(0.639)
$D_{2\%}$ CW	55.20(1)	47.15(1)	26.017(0.000)
$D_{2\%}$ SC	55.79(2)	47.24(2)	20.551(0.000)
$D_{5\%}$ CW	54.33(2)	46.76(1)	18.165(0.000)
$D_{5\%}$ SC	55.19(2)	46.83(2)	19.507(0.000)
$D_{95\%}$ CW	43.96(6)	39.76(2)	4.072(0.000)
$D_{95\%}$ SC	45.49(3)	39.36(2)	10.770(0.000)
$D_{98\%}$ CW	39.94(9)	37.61(4)	1.449(0.152)
$D_{98\%}$ SC	41.62(6)	36.36(4)	4.799(0.000)
$V_{95\%}$ CW	90.19(6)	94.20(4)	3.318(0.001)
$V_{95\%}$ SC	91.51(5)	92.58(3)	1.076(0.286)
$V_{98\%}$ CW	79.46(8)	84.68(5)	3.425(0.001)
$V_{98\%}$ SC	83.99(7)	85.78(5)	1.258(0.213)
$V_{105\%}$ CW	30.84(12)	31.09(16)	0.075(0.941)
$V_{105\%}$ SC	43.35(16)	38.65(17)	1.237(0.220)
$V_{107\%}$ CW	16.45(10)	16.78(12)	0.134(0.894)
$V_{107\%}$ SC	29.5(14)	23.13(18)	1.715(0.091)

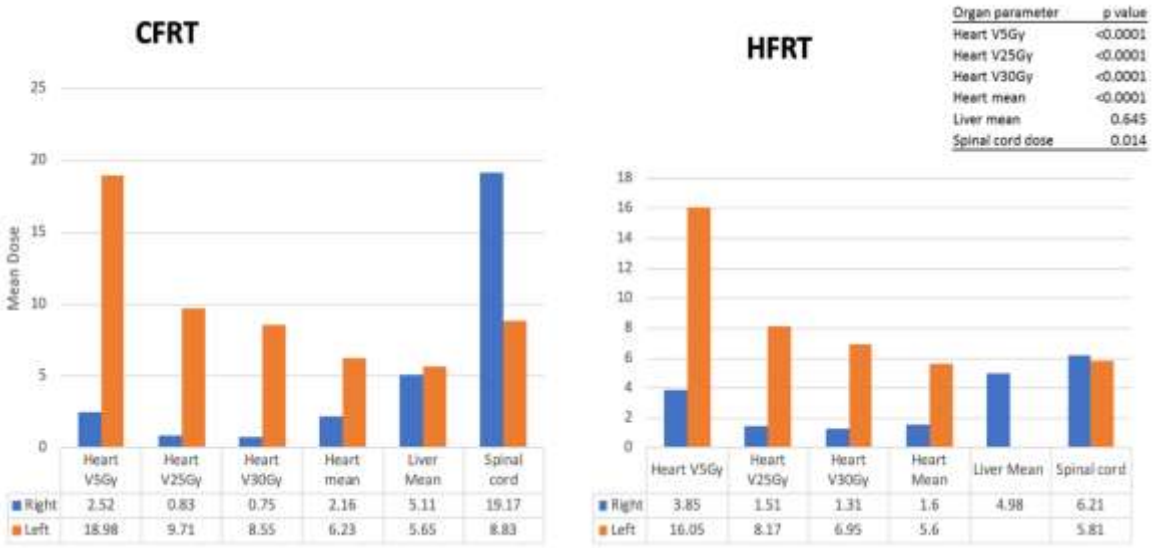
An independent-samples t-test was conducted to compare conventional and hypofractionation radiotherapy. Hypofractionation resulted in significantly lower mean D2% CW, D2% SC, D5% CW, D5% SC, D95% CW, D95% SC, D98% SC, V95% and V98% CW.

Table 6: Comparison of the mean organ-at-risk dosimetric parameters

Dose Parameter	CFRT Mean(±SD)	HFRT Mean(±SD)	t (p value)
IL_{V20Gy}	28.99(3.8)	27.27(3.8)	1.953(0.055)
IL_{V35Gy}	21.81(5.3)	17.94(3.3)	3.767(0.0001)
IL_{40Gy}	19.64(3.8)	7.48(4.4)	12.693(0.0001)
$IL_{\text{Mean dose}}$	14.63(2.2)	12.80(1.5)	4.205(0.0001)
$CL_{\text{Max dose}}$	3.28(4.0)	2.02(2.4)	1.636(0.106)
$CL_{\text{Mean dose}}$	0.68(2.4)	0.21(0.1)	1.185(0.240)
$Heart_{V5Gy}$	10.53(11.6)	11.76(9.3)	0.505(0.615)
$Heart_{V25Gy}$	5.15(6.6)	5.83(5.0)	0.497(0.621)
$Heart_{V30Gy}$	4.55(5.9)	4.97(4.4)	0.349(0.728)
Mean Heart Dose	4.14(4.1)	4.19(2.8)	0.061(0.952)
Mean Liver Dose	5.19(2.2)	4.98(1.2)	0.250(0.805)
Spinal Cord Max Dose	14.14(13.1)	5.95(9.0)	3.143(0.002)

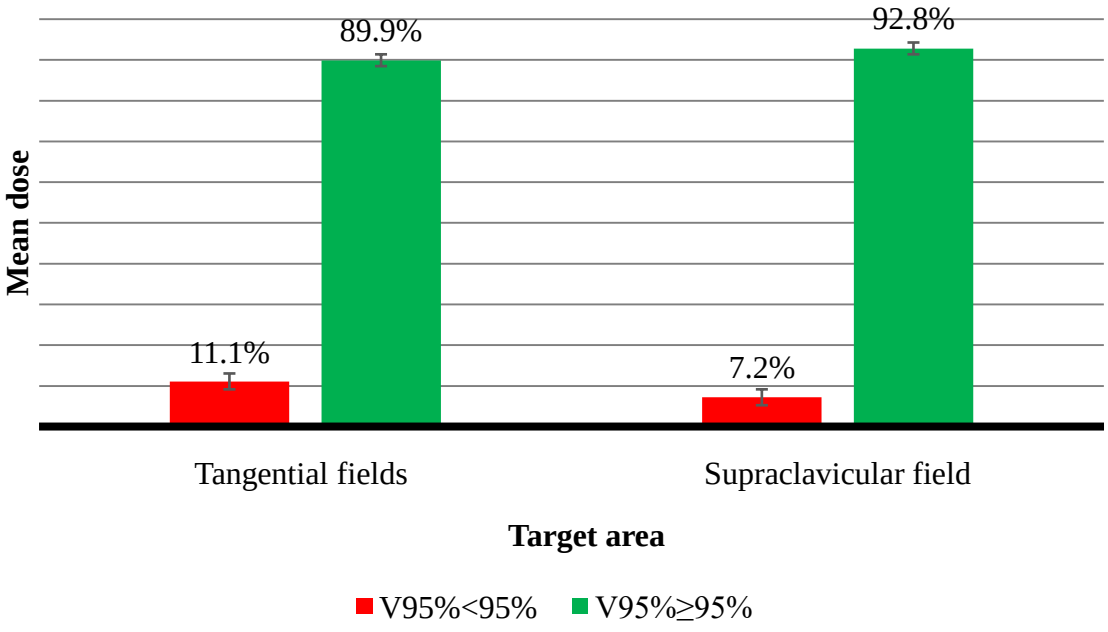
An independent-samples t-test was conducted to compare conventional and hypofractionation radiotherapy. There was significant difference in mean parameters of organ at risk such as ILV35Gy, IL_{40Gy}, $IL_{\text{mean dose}}$, and Spinal cord dose. This suggests that when hypofractionated radiotherapy was used ipsilateral lung and spinal cord received relatively less dose compared to conventional.

Figure 2: Comparison of Dosimetric Parameters by Tumour Laterality



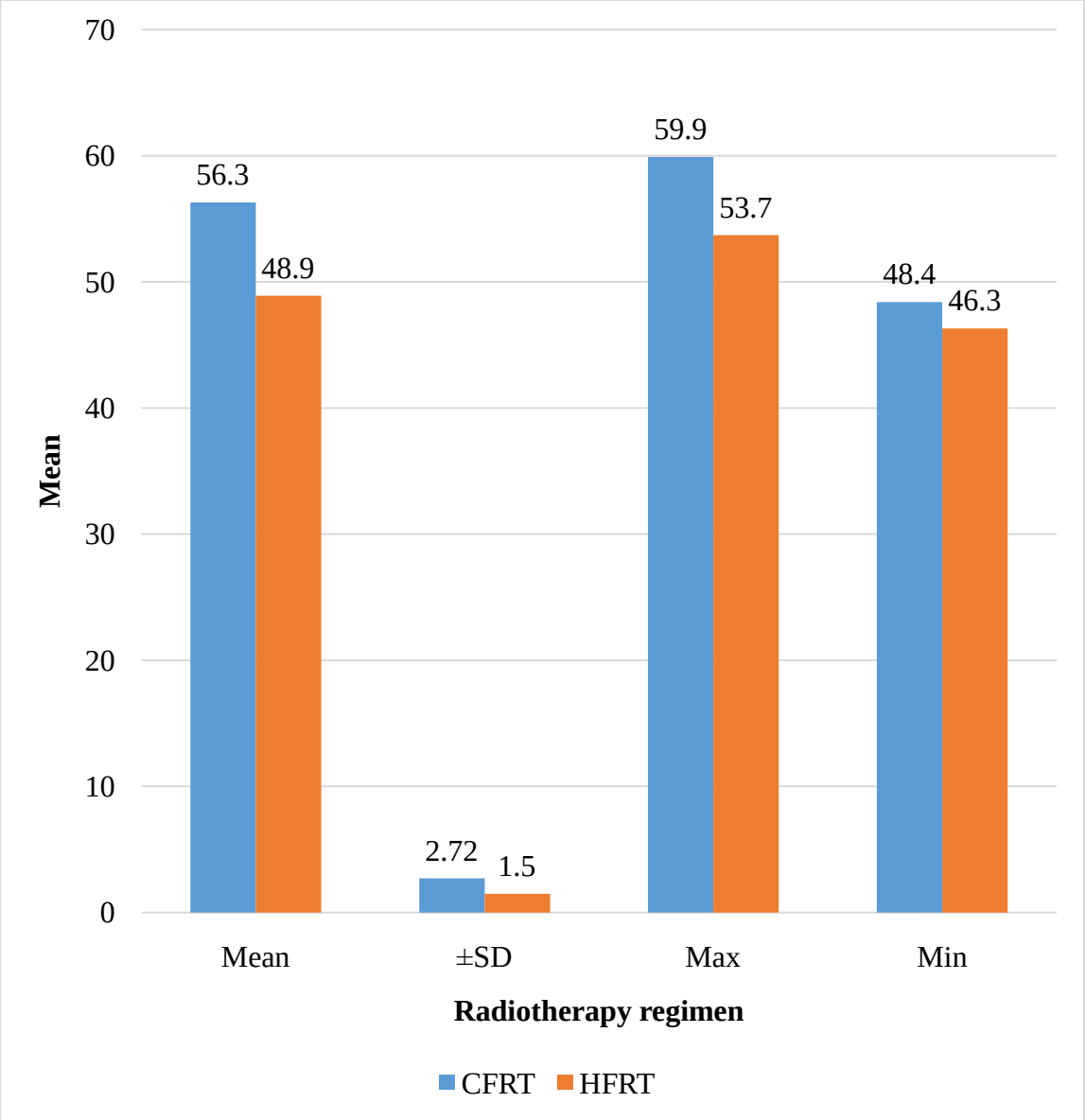
For patients with left sided tumours, hypofractionation resulted in a statistically significant lower average dose to the heart, and the spinal cord using the evaluation constraints.

Figure 3: Comparison of the mean $V_{95\%}$ tangential and supraclavicular dosimetric parameters



Most plans had an adequate V95% coverage, with only 11.1% and 7.2% of the tangential and supraclavicular plans respectively not meeting this threshold.

Figure 4: Comparison of the mean and range of maximum plan dose between CFRT and HFRT



The mean maximum plan dose was higher (56.3%) with CFRT than HFRT (48.9%), with corresponding trends in the maximum value. The minimum plan dose was expectedly lower with HFRT (46.3%).

Table 7: Distribution of the skin acute toxicities with respect to radiotherapy regimens offered

		RT regimen				
		CFRT		HFRT		P value
		n	%	n	%	
Skin toxicity at end of treatment	0	19	(51.4)	18	(48.6)	0.816
	1	18	(48.6)	19	(51.4)	
Skin toxicity 1-3 months post treatment	1	17	(45.9)	17	(45.9)	0.917
	2	16	(43.2)	17	(45.9)	
	3	4	(10.8)	3	(8.1)	

There was no statistical difference in the occurrence of acute skin toxicities between conventional and hypofractionation radiotherapy. Assessment of acute skin toxicities immediately after the treatment recorded RTOG grade 0 and 1. However, one month post treatment the grades appeared to progress to grade 2 and 3 with relatively similar changes in both CFRT and HFRT.

Table 8: Comparison between skin toxicity immediately after treatment and 1-3 months post radiotherapy

Toxicity immediately after treatment	Toxicity 1-3 months post treatment				P value
	Grade 0	Grade 1	Grade 2	Grade 3	
	n (%)	n (%)	n (%)	n (%)	0.0001
Grade 0	0(.0)	32(86.5)	5(13.5)	0(.0)	
Grade 1	0(.0)	2(5.4)	28(75.7)	7(18.9)	

Assessment immediately post radiotherapy revealed only grade only grade 0 and 1 toxicities in general. However, at subsequent follow up (at 1-3 months), 86.5% had progressed from grade 0 to grade 1. Similarly, majority of those with grade 1 toxicity immediately post treatment had progressed to grade 2 (75.7%). Grade 3 toxicity was only noted in those with documented grade 1 toxicity immediately post treatment. The chi square test showed that these changes were statistically significant $p<0.05$.

Table 9: Skin toxicity in relation to dosimetric parameters

	RTOG Skin Toxicity1 Grade		
	0	1	t (p value)
	Mean± SD	Mean± SD	
V105% CW	33.52(16.53)	28.41(10.99)	1.567(.122)
V105% SC	40.44(14.95)	41.57(17.89)	0.295(.769)
V107% CW	17.45(11.74)	15.78(9.61)	0.670(.505)
V107% SC	24.34(15.41)	28.33(17.07)	1.056(.295)
Plan hotspot	52.18(4.36)	52.96(4.28)	0.776(.440)

The independent t test was run and showed no statistically significant difference in the means of various dosimetric parameters with skin toxicity across grade 0 and 1.

Table 10: Skin toxicity in relation to dosimetric parameters

Skin toxicity 1-3 months post treatment				
	1	2	3	t(P value)
	Mean± SD	Mean± SD	Mean± SD	
V105% CW	32.00(16.30)	30.74(12.88)	27.00(8.59)	0.350(0.727)
V105% SC	40.21(16.05)	42.04(16.16)	39.97(21.06)	0.467(0.642)
V107% CW	16.21(11.15)	17.25(11.14)	15.62(6.30)	0.382(0.703)
V107% SC	24.24(16.43)	28.55(15.26)	26.00(21.06)	1.112(0.270)
Plan hotspot	51.98(4.42)	52.90(4.09)	53.95(4.98)	0.888(0.378)

An independent t test was run and showed no statistically significant difference in the means of various dosimetric parameters and skin toxicity across grade1, 2 and 3, assessed 1-3 months post treatment.

CHAPTER FOUR

4.0 DISCUSSION

The use of radiotherapy is a key facet in breast cancer management, with various landmark studies showing its crucial role in improving local control and survival in early breast cancer and in high risk patients treated with mastectomy (4,6,29). For post-mastectomy patients, radiotherapy reduces both recurrence and death, even in the presence of systemic treatment (6). Breast radiotherapy is typically administered conventionally, utilizing 2 Gy daily fractions over 5 to 6 weeks, on the basis that this schedule minimises normal tissue damage while maximizing tumour control (8,9). However, radiobiological experiments have led to a shift in this view point, given the strong evidence that small fractions of 2 Gy or lower offer no therapeutic advantage, and that in fact a shorter regimen of fewer fractions greater than 2 Gy would be equally effective and safe (37,38,62).

Post mastectomy hypofractionation, and particularly in the patients with locally advanced breast cancer is a relatively new practice, with the first non-inferiority, open label phase three trial in this context having been conducted and published recently. This trial demonstrated that hypofractionation (43.5Gy in 15 fractions over 3 weeks), was non inferior to and had similar toxicities with conventionally fractionated radiotherapy in patients with high risk breast cancer (43). Prior to this, a few single institutional studies comparing the two regimens in the post mastectomy context had demonstrated similar findings (4,15,41,60).

At Ocean Road Cancer Institute, annual hospital records show that over 550 breast cancer patients are seen annually, with a monthly average of 40-50 cases. Majority of these patients receive post-operative radiotherapy, following mastectomy for locally advanced disease. ORCI is the main public facility for radiotherapy services, and therefore, shortening treatment time whilst ensuring safety would be a more cost-effective use of the radiotherapy resources. Skin toxicity following breast radiotherapy may lead to pain, systemic infection, scarring and may result in temporary or permanent cessation of treatment with detrimental tumour control outcomes, and a poor quality of life. As such a detailed understanding of dosimetric parameters that may be related to acute skin toxicity is a crucial in improving radiotherapy outcomes for breast cancer patients (68). Therefore

establishing how hypofractionation compares to conventional fractionation through evaluation of dosimetric parameters and acute toxicities will be crucial in further advising decision making on its utilization in Tanzania.

In this study, 74 patients were recruited equally into either of the two study groups, HFRT and CFRT, with a fairly uniform distribution of social demographic and clinical-pathological features. It is noteworthy that the regimen utilized in the HFRT arm was 42.5 Gy in 2.67 Gy daily fractions, similar to that used in the landmark Ontario study (69). The dose per fraction used at ORCI for hypofractionation falls within the range of 2.67-3.3 Gy that have been studied and yielded an α/β of 3 Gy for breast tissue (62). This low α/β value implies hypofractionation offers a better chance at breast tumour control than conventional fractionation, as pointed out by several authors (12,70).

In this study, the mean ipsilateral lung V20 was below 30%, a threshold that has been demonstrated as vital in keeping symptomatic pneumonitis rates at less than 20% (46) . No difference was noted with this parameter in both CFRT and HFRT.

The mean lung dose was slightly higher in CFRT than in HFRT (14.62 Gy vs 12.84 Gy respectively). According to the QUANTEC paper, a mean dose of 13 Gy is associated with a 10% risk of symptomatic pneumonitis, suggesting that this risk may be lower in HFRT than in CFRT(46). To further evaluate this risk, this study evaluated the V40, which at $\leq$25% is associated with a low risk of symptomatic radiation pneumonitis in patients undergoing radiotherapy to the breast and regional nodes (71). A significantly lower mean V40 of 7.75Gy was noted in the HFRT than in the CFRT arm (19.65 Gy), and thus suggesting a greater reduction in the risk of radiation induced pneumonitis with the former.

There was no statistically significant difference in the heart constraints between CFRT and HFRT within this study. The QUANTEC paper recommends a V25 threshold of <10% in required in order to keep the risk of long term cardiac mortality at <1% (46). This study established a safe V25 value of 5.15% and 5.83% in CFRT and HFRT respectively. This fits well with what has already been established in larger studies, where no unfavourable cardiac outcomes were noted with the use of HFRT (9,64).

Interestingly, it was noted that while there was no statistically significant difference in the mean heart dose (MHD) of the two arms, for the left breast in particular, this was slightly lower with HFRT than CFRT (5.60Gy vs 6.23Gy). Some authors have shown that an incremental dose of the MHD by 1 Gy increases the risk of major coronary events by 7.4% (72). At a bare minimum, this study found no significant difference in cardiovascular risk with HFRT as predicted by the V25; however, the slightly lower MHD may need further studies to establish its potential benefit in reducing coronary events.

While this study demonstrated a favourable comparisons in the lung and heart doses, it is noteworthy that safety concerns regarding the use of hypo fractionated radiotherapy often arise from the uncertainty of the late effects of the larger fraction size(5). Using an α/β of 1.5 and 4 for late cardiac and lung effects respectively, various papers have clearly demonstrated that hypofractionation in breast cancer will result in lower EQD_2 value sand generally milder late effects compared to conventional fractionation (5,62). Indeed major studies on hypofractionation in breast cancer have shown no detriment on the heart and lungs with the use of hypofractionation even after long follow-up durations(12,14)

Generally, the most commonly encountered skin toxicities immediately at the end of treatment were grade 0 and 1, with grade 2 and 3 toxicities documented at subsequent follow up, although the noted differences between the two arms were not statistically significant. When compared to other HFRT and CFRT comparative studies, more grade 2 and 3 toxicities were noted in this study. For instance, Rastogi et al reported grade 2 or higher acute dermatitis at a rate of 40% in CFRT and 42% in HFRT (42.72 Gy in 16 fractions of 2.67 Gy) (15). Similarly Bhattacharyya et al reported no grade 3 toxicities, with most patients scoring grade 0, and grade 1 being more common than grade 2 (4). Such variations in findings may be attributable to various treatment related factors discussed herein, and patient related factors like racial differences and genetic factors predisposing to radiation sensitivity as noted in literature on this subject (73). Additionally, none of the patients received prophylactic treatment for radiation induced dermatitis. Although the absence of this intervention cannot explain this variation, it has been demonstrated to reduce the occurrence of severe skin toxicities in high risk patients such as post mastectomy patients and those with predictive dosimetric parameters such high V110% values (68,73).

In this study, there was no statistically significant difference between the acute skins toxicities between patients treated with either regimen. This finding is in agreement with other authors who found no difference in the acute skin toxicity trends overall and with regard to distribution by grade (15,65). On the other hand, this is contrary to the finding by several authors who have noted that hypofractionation generally results in significantly fewer grade 2 and higher toxicities than conventional fractionation (4,44,74).

The most commonly encountered toxicities at the end of treatment were grade 0 for CFRT and 1 for HFRT and no grade 2 and 3 toxicities were documented. Upon subsequent examination, grade 2 toxicities occurred at a rate of 43.2% in CFRT and 45.9% in HFRT. Although relatively fewer, grade 3 toxicities were noted at a rate of 10.8% in CFRT and 8.1% in HFRT, and overall at a rate of 9.46%. This suggests that reliance on assessment findings immediately at the end of treatment may be misguiding for most patients in our setting as the findings are likely to change over a period of up to 3 months.

This study did not find a statistically significance difference in the mean values of dosimetric parameters across all skin toxicity grades post treatment. . Various authors have attempted to use dosimetric parameters to predict for the presence of acute skin toxicities. In their single institutional retrospective, Keenan L.G et al (75) evaluated the V95%, the maximum dose, the V105% and the V107% and their relationships with grade 2 or higher skin toxicities. It was noted that V105%, V107% and V95% did not show statistically significant association with grade 2 or higher toxicity when analysed as continuous variables. A V105% >30cc was nonetheless found to be a statistically significant predictor of grade 2 and higher skin toxicity, with an odds ratio of 5.3 On the other hand, Chen et al (68), Ciamella et al(76) and Torterelli et al (77) found statistically significant associations between V107% and skin toxicities.

CHAPTER FIVE

5.0 LIMITATIONS CONCLUSION AND RECOMMENDATION

5.1 Limitation

While the study yielded pertinent information on this set of patients, it enrolled a relatively small number of patients.

Due to the COVID-19 outbreak, it was not possible to recruit more patients owing to University closure and a national directive against further pursuance of ongoing research. These factors made it hard to extend the study period and recruit more patients. Thus, a smaller sample of patients relative to the projected was ultimately recruited.

5.2 Conclusion

This study demonstrated that hypofractionation and conventional fractionation regimens have comparable acute skin toxicity profiles, with grade 2 toxicity being the most common. Further, hypofractionation was noted to result in lower mean doses to the heart and lung as predicted by respective dose constraint thresholds, and thus a lower predicted late effect risk to these organs. Therefore, hypofractionation appears to offer a dosimetric advantage in the avoidance of late lung and heart radiation effects, and acute skin toxicity rates compare to conventional fractionation thus making its implementation in Tanzania feasible.

5.3 Recommendations

A larger sample size and a longer time are recommended to further elucidate the relationship between dosimetric factors, clinical-pathological data and acute skin toxicities. This can then provide a basis for the development of interventions to mitigate any possible toxicity in post mastectomy patients scheduled undergoing radiotherapy.

Secondly, the adoption of cardiac and pulmonary function screening prior to initiation of therapy and as part of follow up may provide a more objective assessment of risk to these organ systems, given the limitation of relying on predicted risks generated by dosimetric data.

Third, prophylactic topical therapy and the use of hypo fractionated radiotherapy should be incorporated into routine management at ORCI as part of a strategy to reduce the slightly higher rate of grade 2+ toxicity noted in this study.

Finally, while patients who have undergone post mastectomy hypofractionated radiotherapy show no difference when compared to CFRT with regard to skin toxicities, further evaluation for late skin effects and acute and late cardiac and pulmonary effects should be made, to provide certainty on the safety of this regimen in Tanzanian patients.

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APPENDICES

Appendix 1: Data collection form

(INFORMATION TO BE OBTAINED FROM PATIENT'S FILE AND TREATMENT PLANNING WORKSTATION)

SECTION A: DEMOGRAPHIC DATA

AGE	RESIDENCE	MARITAL STATUS	HIV SEROSTATUS			COMORBID CONDITIONS
			POS	ON ART	NOT ON ART	
			NEG			

SECTION B: TUMOUR RELATED INFORMATION (EXCLUDE NON INFILTRATING DUCTAL CARCINOMA (IDC) HISTOLOGY)

Histology	Grade	LVSI	ER	PR	HER 2 neu	Laterality	Stage	Wt	Ht	BSA
						Right left bilateral				

SECTION C: MANAGEMENT

SURGERY	NEO ADJUVANT CHEMO	ADJUVANT CHEMO	DATES AND INTERVAS INTERVALS	
MARGIN STATUS	Y N	Y N	NEOADJUVANT	ADJUVANT
L/NODE DISSECTION Y N IF YES: Positive/Harvested: Tick if Unreported:	IF YES Regimen: No Cycles: Preop Post op	Regimen: No Cycles	Date of 1st Cycle Date of Last Cycle Date of Surgery Date of RT	Date of Surgery Date of 1st Cycle Date of Last Cycle Date of RT

SECTION D: DOSIMETRIC PARAMETERS

TARGET VOLUME DATA				
1. Regimen	CFRT	HFRT		
2. PTV Volumes (cm3)	Chest Wall	Supraclav		
3. Dose to x% of volume	Chest Wall		Supraclav	
	Absolute (Gy)	Relative (%)	Absolute (Gy)	Relative (%)
D2%				
D5%				
D95%				
D98%				
4. Volume receiving x% of Dp	Chest Wall	Supraclav		
V95%				
V98%				
V105% (cc)			Mean	
V107% (cc)			Mean	
V110% (cc)			Mean	
5. Heterogeneity Index:				
6. Plan Hotspot:	Absolute	Relative	Volume cc	
ORGAN AT RISK DATA				
1. Ipsilateral Lung	V20Gy:	V35Gy:	V40Gy:	Mean:
2. Contralateral Lung	Max dose:	Mean:		
3. Heart	V5Gy:	V25Gy:	V30Gy:	Mean:
4. Liver (Right Sided Tumour)	Mean:			
5. Thyroid gland	Dmax (% of Dp)			
6. Cervical Oesophagus				
7. Spinal Cord	Dmax			
8. Contralateral Breast				

TREATMENT FIELDS					
	Field	Weight	Energy	Bolus	Wedge
Chest Wall	Medial Tan				
	FIF				
	Lateral Tan				
	FIF				
Supraclav	SCV Field Angle				
	AP FIF				
	PA FIF				
IMN Field					

[Dp: Prescribed dose, Dx%: Dose receiving x % of the prescribed dose, VxGy: Volume receiving xGy, HI: Heterogeneity index, Plan Hotspot: Maximum percentage dose in the plan]

Appendix 2: Adapted acute toxicity scores (RTOG/EORTC)

Fill applicable score on the 'SCORE" column below the table. ONLY ONE score is applicable.

ORGAN TISSUE	[0]	[1]	[2]	[3]	[4]
SKIN	No change over baseline	Follicular, faint or dull erythema/epilation/dry desquamation/decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate oedema	Confluent, moist desquamation other than skin folds, pitting oedema	Ulceration, haemorrhage, necrosis

END OF TREATMENT (WEEK 5 FOR CFRT, WEEK 3 FOR HFRT) Grade: ☐ Date_____

FIRST POST-TREATMENT CLINIC (1 Month): Grade: ☐ Date_____

Appendix 3: Ocean Road Cancer Radiotherapy protocols: Breast cancer section

External Beam Radiotherapy Protocols

- *In – vivo dosimetry*
  - The absorbed dose to the patient shall be estimated based on *in vivo measurements using diodes.*
  - The verification shall be performed once and *within the first 5 days of the treatment.*
  - The in vivo dosimetry results shall be within *10%* of the planned dose.
  - If Deviations of more than 10% are found, the treatment *delivery/ plan* shall be adjusted accordingly.

Quality Management

- Pre-treatment patient-specific dosimetry
  - The treatment for each new patient shall be independently verified with *independent calculations/measurements.*
  - The independent dose results shall be within *10 %* of the planned dose. Deviations of more than 10 % shall be adjusted according to the *protocol for corrective action.*
  - In case a plan is not passing the acceptance criteria, the reasons shall be further analyzed, and *replanning/change of technique* shall be considered.

Breast cancer

Patient pre-treatment preparation

- Patient identification and counseling about the procedure to be done.
- Breast board immobilization device shall be used at the angle of 15-20 degrees to ensure the sternum is parallel to the tabletop.
- If breast board unavailable/ small diameter of the CT-Scanner, chest thermoplastic shell shall be used.
- The indexing of the breast board shall be clearly documented on the day of the scan.
- Patient in the supine position with both arms elevated above the head, with neck rotation towards the contralateral side. If bilateral breast then the head should be straight but extended.
- The patient reference coordinate system shall be defined by using skin tattoos on positions corresponding to those of radiopaque makers positioned before pre-treatment imaging on the anterior and lateral points of intersection of lasers.

Pre-treatment imaging

- For structure delineation and planning, CT imaging shall be performed with CT-slice thickness of 5mm.
- The CT scanning shall be performed from the angle of the mandible to T12.
- Image sets from CT shall be transferred to TPS through DICOM.
- CT images shall be used for treatment planning calculations and must, therefore comply with the requirements of the TPS.

Specification of treatment prescription

- Volume specification
  - The recommendations made by ICRU shall be followed.
  - The volumes shall be delineated with the appropriate grey scale window center and width.
  - The **Clinical Target Volume (CTV-breast)** shall include:
    Whole breast excluding the pectoralis muscle, muscles of the chest wall and ribs.
    CTV – **boost**, where the primary disease was using clips inserted during surgery or changes, noted post surgery and seroma if present.
    -CTV-N if axillary nodes not adequately removed.
  - The **Clinical Target Volume(s) (CTV-chest wall)** shall include: CTV-chest wall
    -Chest wall including pectoralis muscle, chest wall muscles, and ribs.
    CTV-N - shall include supraclav and axillary level I, II and III nodes.
  - The **Planning Target Volume(s) (PTV)** shall include margins 1 cm from CTV 1 & 2 for set-up uncertainties.
  - Right & Left lungs, heart, spinal cord, ipsilateral head of humerus shall be delineated as Organ at risk.
  - The Planning Organ at Risk Volume of the lungs shall be delineated using a 0.5cm margin.
  - Target and organs-at-risk motion shall be taken into account by using margins
- Absorbed dose prescription
  - The prescribed absorbed dose 45Gy/18#/2.5Gys per fraction, specified as dose to ICRU reference point given in five times a week in 3.5 weeks.

Normal tissue tolerance table

Volume	Dose (Gy) or dose/volume parameters	Endpoint
Heart	V25Gy<10%	Pericarditis
Ipsilateral lung	V20Gy<20%	Pneumonitis Fibrosis
Rt/Lt heads of humerus	D100%≤52Gy	Necrosis <5%
Spinal cord	Dmax≤45Gy	Myelopathy

- **Fractionation and treatment time**
  - Radiotherapy is given daily, 5 days/week with a single daily fraction of 2.5 Gy in 18 fractions to a total dose of 45Gys.
  - The minimum time between daily fractions is 8 hours.
  - Allowed treatment days are 5days/week.
  - Boost shall be given sequentially.
  - Unintended interruptions shall be compensated within the intended overall treatment time according to EQD2/BED/modified fractionation schedule.
  - If there is a miss of ≥2days compensated.

Relation to other concomitant therapies

- **Surgery**
  - Radiotherapy is given postoperatively.
  - Adjuvant Chemotherapy followed by Radiotherapy should start 4-6 weeks post-surgery.
  - Details about the surgical treatment are stated in the surgical notes and findings on the histopathology report.
- **Drug therapy**
  - Hormonal therapy is given to patients after completion of adjuvant chemotherapy concurrently with radiotherapy.
  - Details about the chemotherapy are stated in the chemo chart.
  - The delay between chemo and RT shall be 4 weeks.

Treatment planning and delivery

- **Treatment technique**
  - The radiation treatment shall be given with photon, 6X at 600cGy/MU dose rate and3*DCRT* technique.
  - Isocentric tangential wedged beams shall be used in the breast/chest wall and single anterior beam/ opposed APPA beams in supraclavicular nodal volume.
- **Dose computation**
  - Reference (absolute) dosimetry is carried out according to IAEA TRS398 and verified through the dosimetry audit program.
  - The absorbed dose in the patient geometry shall be calculated by using Analytical Anisotropic Algorithm and presented as absorbed dose to water.
  - The calculation grid shall be 0.25cm size and resolution.

- Treatment plan evaluation
  - The choice of the final treatment plan shall be documented by *dose/volume summary and critical structure analysis*
  - The radiation oncologist shall review and approve the whole plan to assess patient details, laterality, target coverage and DVH, OAR DVH and hotspots outside PTV / unexpected cold spots.
- ***Geometric verification of treatment delivery***
  - The patient position shall be verified using *MV portal images (PIs).*
  - The verification shall be performed during the first three fractions in the first week and thereafter once weekly. The position verification results shall be within *10 mm* of the planned position.
  - Deviations of more than 10 *mm* shall be adjusted according to extended no action level protocol (eNAL) as follows: calculation of the mean deviations in all three planes shall be performed after the first three fractions. The mean deviations shall be applied as shifts for all subsequent treatment fractions. This shall be followed with once weekly imaging for the remaining fractions.
- *In – vivo dosimetry*
  - The absorbed dose to the patient shall be estimated based on *in vivo measurements.*
  - The verification shall be performed *during* the before delivery of 20% of the prescribed dose.
  - Calculations shall be done to compare measured and expected doses and comparisons made between measured and expected doses. The percentage difference between measured and expected doses shall not exceed 10%.
  - Based on the analysis the treatment *delivery/ plan* shall be adjusted accordingly.

Quality Management

- *Pre-treatment patient-specific dose verification*
  - The treatment for each new patient shall be independently verified with *independent calculations and in vivo dose measurements.*
  - The delivery shall be compared to the plan by in vivo dose measurements using diodes and analyzed by comparing delivered and expected doses. The tolerance level for the difference between delivered and expected doses shall be 10%.
  - In case a plan is not passing the acceptance criteria, the reasons shall be further analyzed, and *replanning/change of technique* shall be considered.

Appendix 4: Informed consent form

Kiambatanisho II: Idhini ya Mshiriki

Kichwa cha utafiti: Tathimini ya tofauti katika maandalizi ya tiba ya mionzi na madhara ya mionzi, kati ya wagonjwa wa saratani ya matiti wanaotibiwa kwa jumla ya wiki tano na wanaotibiwa kwa jumla ya wiki tatu, katika Taasisi ya Saratani ya Ocean Road, Tanzania

Utangulizi: Naitwa Dk. Kevin Makori. Ni mwanafuzi wa shahada ya juu ya utaalamu wamatibabu ya saratani,

Dhumuni la utafiti: Utafiti huu una lengo la kutathmini iwapo kuna tofauti kubwa katika maandalizi ya tiba ya mionzi na madhara ya mionzi, kati ya wagonjwa wa saratani ya matiti wanaotibiwa kwa jumla ya wiki tano na wanaotibiwa kwa jumla ya wiki tatu, katika idara y atiba ya mionzi, Taasisi ya Saratani ya Ocean Road Tanzania

JukumulaMshiriki: Baada ya kusaini fomu ya idhini, jukumu lako nikujibu kukubali taarifa zako zilizo kwenye faili na tarakilishi za maandalizi ya tiba ya mionzi, na kufanyiwa uchunguzi kwenye sehemu iliyopata mionzi.

Hatari na faida:

Utafiti huu unahusisha aina mbili za tiba ya mionzi, ambazo zinakubalika katika matibabu ya saratani ya matiti duniani kote. Tiba ya mionzi inafahamika kuwa na madhara mwilini. Madhara ya mionzi siku chache baada ya kuanza tiba hadi kukamilisha tiba ni: uchovu, maumivu mwilini, na mabadiliko ya ngozi, kama kubadilika rangi na vidonda kwenye sehemu inayotibiwa. Haya madhara huisha baada ya kukamilika kwa mionzi, na iwapo yatajitokeza, yanaweza kutibiwa. Madhara ya mionzi miezi michache hadi miaka mingi baada ya kukamilisha tiba ni kama ugumu wa ngozi kwenye sehemu iliyotibiwa na uvimbe wa mkono kwenye upande uliotibiwa. Madhara mengine ambayo ni nadra ni kama madhara ya moyo na mapafu, na saratani ya ngozi kwenye sehemu iliotibiwa.

Faida ya kupata tiba ya mionzi inazidi madhara haya. Iwapo yatajitokeza, utapata matibabu ama ushauri kulingana na mwongozo wa matibabu

Gharama: Hakuna gharama kwa washiriki.

Fidia: Hakuna malipo kwa washiriki.

Usiri: Hakuna jina au maelezo ya kutambulika ya washiriki yatatumika kwa madhumuni mengine Zaidi ya utafiti huu, sasa au baadaye. Taarifa zote za mshiriki ni siri baina yake na mtafiti.

Mawasiliano: Mshiriki yeyote ana haki ya kuwasiliana na mtafiti, msimamizi na mkurugenzi wa utafiti na machapisho kabla, wakati na baada ya utafiti na kuuliza maswali yoyote. Ninakuomba usaini hii fomu ya idhini.

TAMKO LA IDHINI

Mimi....., umri miaka zaidi ya 18 na nimeelewa juu ya utafiti huu ambapo nimekubali kwa hiari yangu kushiriki katika utafiti. Kusudi la utafiti limeelezewa na mtafiti na maswali yote yamejibiwa kikamilifu na nimeridhika. Nimeelezwa faida nahatari za utafiti na nina uhuru wa kujiondoa kwenye utafiti wakati wowote na hautanizuia kupata matibabu katika hospitali. Nimeridhia kuhojiwa na maelezo kutoka kwenye faili langu la matibabu yanaweza kutumiwa pia kwa madhumuni ya utafiti huu.

Saini.....Tarehe.....

Taarifa ya Mtafiti

Mimi ..... nathibitisha kwamba nimemuelezea mshiriki kusudi na asili ya utafiti huu.

Sahihi.....

Tarehe.....

Simu: 0621763444

1. Dk Bruno Sunguya: Mkurugenzi wa utafiti na uchapishaji, Chuo Kikuu cha Afya na Tiba Muhimbili P.O.BOX65001, Dar es Salaam, Tanzania. Barua pepe:

2. Msimamizi: Dk Mamsau Ngoma Idara ya Saratani Chuo Kikuu cha Afya na Tiba Muhimbili P.O.OBOX 65001 Dar es Salaam, Tanzania.