Patterns of Practice of Breast Cancer Irradiation in the Department of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital 2010-2012.

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04 Feb 2021

DECLARATION

I declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been previously submitted for any degree or examination at any other University.

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ABSTRACT

Background

Globally, cancer affecting women the most is Breast cancer. Treatment may involve a combination of surgery, chemotherapy and radiotherapy. Role of Radiotherapy in breast cancer survival is often difficult to ascertain due to the number of variables prior to the patient receiving radiotherapy. However, conducting survival analysis is important for a radiation oncology department to facilitate distribution of resources to conditions that benefit most from intervention particularly for common cancers such as breast cancer. It also aids the institution in identifying potential areas for improvement.

Study Design

Records of patients receiving irradiation for breast cancer reviewed retrospectively from January 2010 to December 2012 with 5 year follow up.

Objectives

Determination of local control, overall survival and type of disease progression. To ascertain factors that affect overall survival of the local population.

Methods

Approval was obtained. 356 patient records were randomly selected out of which 95 patient files met inclusion and exclusion criteria. Staging, Pathology, type of surgery, whether neoadjuvant or adjuvant chemo received, type of irradiation and the times between surgery, chemotherapy and radiotherapy as well as patient outcomes for 5 year follow up was collected. Data was entered into SPSS and analysed using descriptive statistics, Kaplan-Meier Survival and Cox Regression for univariate analysis.

Results

Median age at diagnosis was 50 years (range 29 – 81 years), 42.1% of the study population presented with Stage I and II disease. Hormone Receptor positive, HER2 positive and Triple Negative breast cancer comprised 69.5%, 17.9% and 22.1% respectively. 84.2% had invasive ductal carcinoma, 4.2% had invasive lobular carcinoma. 78.9% had a Mastectomy, 20% had Breast Conservation Surgery.

82.2% had hypofractionated irradiation. After 5-year follow-up, Local Recurrence Rate of the entire study population was 6.4%, 20.1% had Distant Metastases while 54.7% had no progression. 5-year overall survival was 71.6%, loss-to-follow-up rate was 23.5% over the 5-year period. The mortality rate was 28.4% over 5-year follow-up. Median progression free survival was not reached. Two factors found to be significant on KM analysis: number of involved nodes (HR 3.585 CI 1.14-11.273 p=0.029) and inner quadrant tumours (HR 2.419 CI 1.062-5.511 p=0.035). 35.8% of the study population received radiotherapy within 8 weeks from preceding intervention.

Conclusion and Recommendation

Hypofractionated radiotherapy has favourable outcomes in our setting. The loss-to-follow-up rate makes analysis reliable for descriptive statistics but not reliable in survival analysis. Establishing a departmental database and regularly collecting information on patient outcomes to facilitate timely data analysis is recommended. Provision of incentives to patients for attending follow-up clinics to reduce loss-to-follow-up. Careful selection of patients to receive radiotherapy will aid in improving outcomes. Identifying patients needing radiotherapy at Multidisciplinary Team Meetings to plan scheduling ahead of time.

Abstract Word count: 441

Total word count: 12 366 (excluding abstract, tables of contents, references, tables and figures, appendices)

ACKNOWLEDGEMENTS

I would like to thank my dissertation supervisors, Dr. Faiza Mahomed, Prof. Vinay Sharma and Prof. Paul Ruff for guiding me during this process.

I would like to thank the protocol assessment committee comprising Prof. Paul Ruff, and Prof. Mboyo Di Tamba Willy Vangu for taking the time to critique my work.

I would like to thank the Human Research Ethics Committee (Wits) for their turnaround time on approval of the study.

I would also like to thank Charlotte Maxeke Johannesburg Academic Hospital CEO for their turnaround time on approval of the study.

I would like to especially thank Azwindini Maudu (Filing Clerk) in Medical Oncology for patiently retrieving patient files.

Lastly, I thank my beloved family for always being there for me – Julio, Clarisa and Daniel.

LIST OF ABBREVIATIONS

#	Fraction
ACT	Adjuvant Chemotherapy
ALND	Axillary Lymph Node Dissection
ASTRO	American Society for Radiation Oncology
BCS	Breast Conserving Surgery
BCSS	Breast Cancer Specific Survival
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CR	Complete Response
CT	Computerised Tomography
DFS	Disease Free Survival
GNI	Gross National Income per capita
HF-WBI	Hypofractionated-Whole Breast Irradiation
HJH	Helen Joseph Hospital
HR	Hazard Ratio
IDC	Invasive Ductal Carcinoma
ILC	Invasive Lobular Carcinoma
LC	Local Control
LN	Lymph Node
LRR	Loco-regional Recurrence
LTFR	Loss-to-follow-up-rate
LTFU	Lost-to-follow-up
LVSI	Lymphovascular Space Invasion
NACT	Neoadjuvant Chemotherapy
OS	Overall Survival
PNS	Perinodal Spread
PMRT	Post Mastectomy Radiation Therapy

PR	Partial Response
RCT	Randomised Controlled Trial
RT	Radiation Therapy or Radiotherapy
SA	South Africa
SANCR	South Africa National Cancer Registry
SLNB	Sentinel Lymph Node Biopsy
SP	Study Population
START	Standardisation of Breast radiotherapy
TNBC	Triple Negative Breast Cancer

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CHAPTER 1: INTRODUCTION

Breast cancer is a common form of malignant disease and is the commonest cancer affecting women in the developing and developed world. The global estimate is, that over 626 679 women worldwide died of breast cancer in 2018 (1) . In South Africa, there were 4704 deaths reported from breast cancer in 2018 (2). In 2016, the South African National Cancer Registry (SANCR) reported that Breast Cancer cases were the highest recorded cancer with a total number of 9548 females, making up 22.58% of the total cancer burden (3). The Age Standardised Incidence Rate of developing breast cancer is 35.95 per 100 000 while the Lifetime Risk in persons aged 0-74 years is 1 in 25(3).

The SANCR collects 100% information from state and private laboratory diagnosed pathology reports. It was underreported prior to 2011 as data was collected only from state laboratories following which Ministry of Health South Africa mandated that cancer is reportable and compulsory for all laboratories (4). The SANCR is a pathology based registry not a population based one, therefore patients who have not had biopsies are not included. The International Agency for Research on Cancer (IARC), the cancer wing of the WHO uses population based data to approximate the incidence of various cancers (5)

Treatment options for patients diagnosed with Breast Cancer include Surgery, Radiation therapy (RT) and Systemic therapy comprised of Chemotherapy, hormonal therapy and targeted therapies. The type of surgery varies according to the stage of disease, and ranges from breast conservation where a lumpectomy, quadrantectomy or wide local excision is conducted, to various forms of Mastectomy. Breast conservation surgery in some instances is only offered if there is a guarantee of subsequent Radiotherapy. Lymph nodes are either dissected as Sentinel nodes selected by ink drainage from tumour to draining node or by axillary dissection. Systemic therapy can be given prior to or after surgery and is dependent on several indications. RT is the treatment of cancer using X-rays, Gamma rays, Electrons and other types of radiation. In terms of sequencing of treatment, it is usually the second last treatment given and follows surgery and chemotherapy; the last treatment is hormonal therapy for Hormone receptor positive cancers. Its contribution to overall survival, local recurrence and progression free survival is therefore difficult to attribute.

The benefits of Radiation therapy include lower local recurrence rates which translates into longer disease-free survival and improved overall survival rates.

Radiation therapy services are costly, labour intensive and highly specialized. Individual patient time to receive this service is limited due to the large numbers needing the service (6). At Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), patients are referred for Radiation Therapy (RT) following Surgery and/or Chemotherapy. Patients who have inflammatory breast cancer may receive RT prior to surgery, however this group is not included in this study. They receive either Conventional fractionation (50Gy/25 (fractions)# at 2 Gy per #) or Hypofractionated Irradiation (40.05Gy/15# at 2.67 Gy per fraction) following evidence from the START B trial (2008) which showed non-inferiority as Ipsilateral breast tumour recurrences were similar between the two groups (3.3% vs. 2.2% respectively) (7) and fast forward trial. The more recent FAST FORWARD trial (2020) uses even higher hypofractionated doses and showed non-inferiority of ipsilateral breast tumour recurrence using 26 to 27Gy in 5 fractions over 1 week compared to 40Gy in 15 fractions over 3 weeks (8). The indications for Chest Wall Radiotherapy are (9):

- T3 and T4 disease or early stage disease with nodal involvement especially if ≥ 4 nodes are involved.
- Patients who have had Neoadjuvant Chemotherapy (NACT) followed by Mastectomy, with
    - a large primary tumour or
    - pathologically positive lymph nodes post chemotherapy,
    - triple negative disease with positive lymph nodes
    - clinically positive lymph nodes.

The indications for Supraclavicular Fossa radiotherapy include the following (9):

- primary surgery with ≥ 4 lymph nodes at pathological staging.
- In 1-3 positive lymph nodes, if other high-risk features such as Grade 3 or T3 tumour.
- In patients who have had NACT or hormone therapy, if patient was clinically node negative initially and after surgery assessed pathologically, supraclavicular fossa radiotherapy is not recommended.
- Supraclavicular fossa radiotherapy can be considered if patient was Clinically or biopsy proven Lymph node positive prior to NACT and is pathologically node negative after Surgery.
- Supraclavicular fossa radiotherapy is recommended if patient is found to be pathologically node positive post NACT and surgery.

- Clinically N2/N3 disease before any treatment

Patients receiving RT to the chest wall only should receive 40.05 Gy in 15 # while if axilla and the supraclavicular region is treated the fractionation is 50Gy in 25#. Reducing overall treatment time per patient is beneficial to the patient and to the facility with cost savings up to 24% (10). The aim of providing hypofractionated irradiation is to achieve local control while preserving normal tissue complications, at least to the standard fractionation schedule rate if not better.

This study aims to outline patterns of practice at CMJAH among those receiving irradiation for breast cancer.

1.1 Background Literature Analysis and Critique

1.1.1 Search Strategy

The aim of the literature review was to assess and critically analyse available literature related to breast cancer and especially pertaining to practice patterns in Africa. However, to compare with international standards and norms, the recommended text book "Perez & Brady's Principles and Practice of Radiation Oncology" Sixth Edition as well as "Handbook of Evidence-Based Radiation Oncology" 3rd Edition was read and the landmark studies such as the Danish trials and START trials were then individually looked up on EBSCO host.

The highest level of evidence in terms of systematic reviews or meta-analyses was preferred. The multisource platform EBSCO host was used using the following search terms "(breast cancer) and (South Africa or Africa)", this produced a yield of 52 512 articles, the search was then limited using years "2014 to 2019" which is for the previous 5 years to explore what current findings exist in the literature, which further reduced the yield to 21 366 articles, further limiters to "English" and "Academic journals" as well as "Africa Wide Information" further reduced yield to 52 articles. The titles of these were then individually read and the most appropriate were then selected.
Figure 1 outlines the methods used to conduct the search. In addition, factors affecting breast cancer outcome were also searched using the terms "factors affecting breast cancer outcomes", a list of common factors was produced, each factor on the list was then searched for, using for example for perinodal spread "perinodal spread radiotherapy breast survival" if addition of "systematic review or meta-analysis" produced no yield, this search term was removed and limiters such as dates for the past 5 years and "Academic journals" was used.

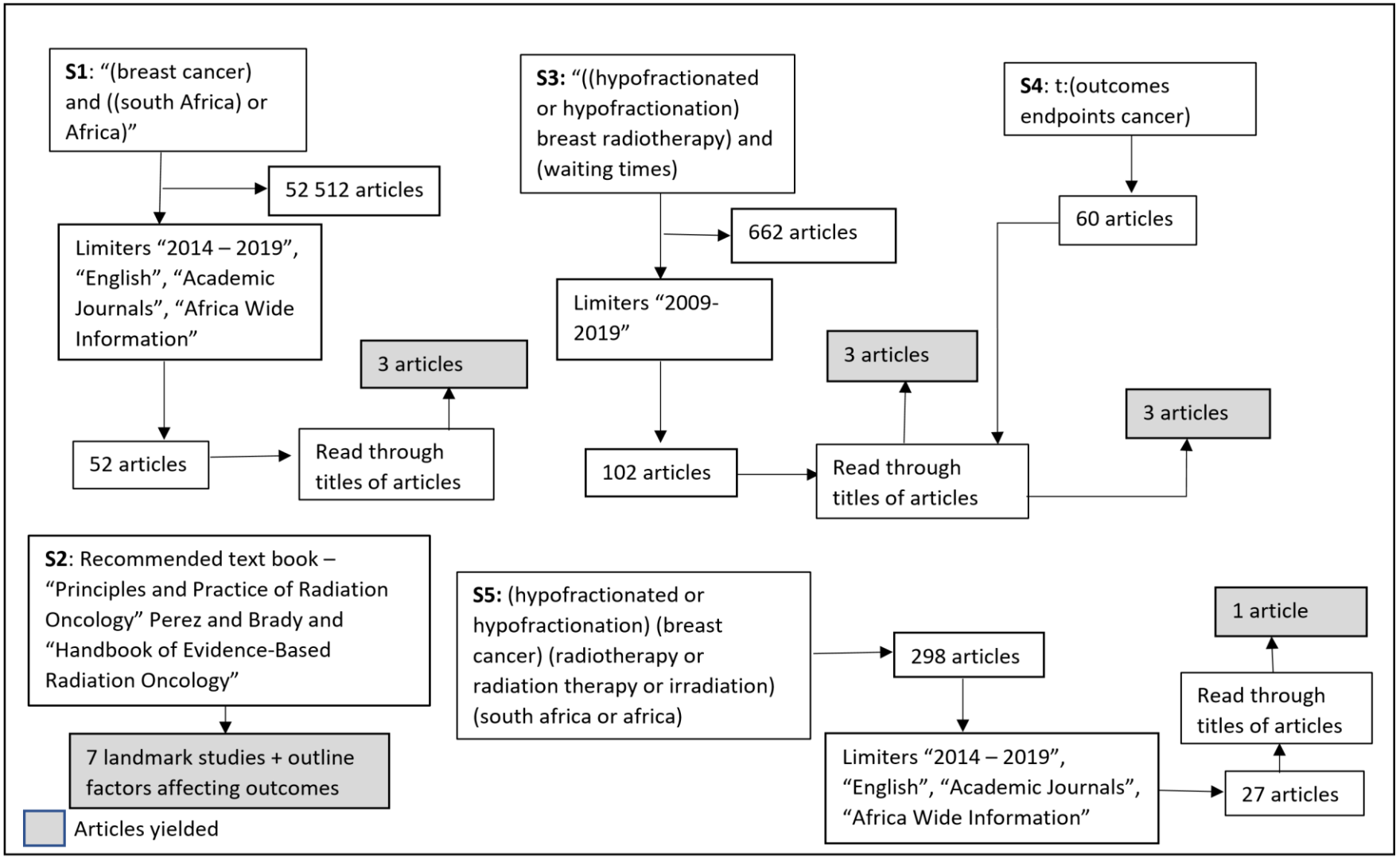

Figure 1: Search Summary

1.1.2 Literature review

Cancer treatment response needs to be measured. There are different end points that can be measured, each having their merits and limitations. Institutional patient file audits are a dependable and necessary process in determining whether an institution is achieving improvement in overall survival, local control and disease progression. Saad & Buyse (11) state that increase in overall survival does not always translate to desired patient outcomes. Despite this, it is a reflective measurable outcome on the effectiveness of treatment delivered (12). Overall survival is measured from the start of treatment or diagnosis to the timepoint a patient is either Lost-to-follow-up (LTFU) in which case the patient's data is censored or the patient has died. Robinson et al (13) state that following Phase III Trials in cancer patients, the commonest end point is progression free survival which looks at time to disease progression rather than overall survival, thereby reducing study patient follow up time. The limitation of following up patients only until they progress is lack of data on overall survival.

Treatment options for Breast Cancer

These include, total mastectomy with/without systemic therapy which includes chemotherapy and hormonal therapy with/without irradiation. In Early stage disease a patient may be offered Breast conservation therapy (BCT) which includes surgery with irradiation with/without systemic therapy (14).

Methods of administering Radiotherapy

Radiotherapy can be provided through conventional fractionation at 2Gy/fraction in 25 fractions to a total dose of 50Gy. It can also be given through hypofractionation where a higher dose per fraction such as 2.67Gy to a total dose of 40.05Gy is given. This allows for shorter overall treatment times. ASTRO (American Society for Radiation Oncology) guidelines (2011) recommended that Hypofractionated whole breast irradiation (HF-WBI) may be given to women aged $\geq$ 50 years, who have had breast conservation surgery (BCS) indicative of early breast cancer T1 – T2, node negative lesion (15). The histology is invasive cancer, margins should be free and include only those who have not received chemotherapy. The dose delivered should be uniform at the midplane (16). Boost doses ranging from 10Gy

to 16Gy are added at 2Gy per fraction for women who have undergone BCS. This is normally a smaller field directed at the tumour bed.

These guidelines have been updated in 2018.

Evidence for use of Radiotherapy

Conventional fractionation radiotherapy may be given to women receiving breast conservation surgery, and for those who have had a mastectomy for high risk disease (14). The addition of a supraclavicular field is related to nodal involvement depending on the adequacy of lymph node dissection (17). Studies done for early stage breast cancer using conventional fractionation show local tumour control rates above 83% and 10-year DFS above 62.5% (13).

Fisher et al (14) found no significant difference in disease free survival, distant-disease-free survival and overall survival in women with tumours < 4 cm, assigned to either Mastectomy, lumpectomy with irradiation and lumpectomy without irradiation. However there was a reduction in local relapse rate if irradiation was used, up to 10% (vs. 40% in lumpectomy alone) in node negative disease and 5% (vs. 50% in lumpectomy alone) in node positive disease (14).

Historically, for locally advanced disease patients underwent mastectomy, and would then receive post mastectomy radiation therapy (PMRT). In previous studies, there was increased heterogeneity in surgical techniques and there was inadequate lymph node dissection. Attributing overall survival (OS) rates to addition of irradiation was therefore difficult. Danish trials 82b and 82c (1997,1999) showed improvement in locoregional failure (LRF), disease free survival (DFS) and overall survival (OS) attributed to PMRT. A Danish trial 82b (1997) which enrolled 1708 participants was conducted in premenopausal patients who were randomised to either adjuvant chemotherapy alone or chemotherapy with Radiation therapy. This study showed reduction in locoregional failure (32% vs. 9%), improved 10-year disease free survival (34% vs. 48%) and improved overall survival (45% vs. 54%) favouring those who had received PMRT (18). A Danish trial 82c (1999) which enrolled 1406 participants was conducted in postmenopausal women and looked at the role of tamoxifen vs. tamoxifen with RT, this study also found that RT improved LRF, DFS and OS (19). A meta-analysis done by Cuzick et al in 1988 (20) showed no 10-year OS benefit

following PMRT. However, the studies that were used in this analysis were problematic due to "poor design, had several exclusion criteria, biological dissimilarity and statistical inaccuracies" (21).

Survival in women with Breast Cancer

A recent systematic review by Maajani et al in 2019 (22) showed 5 year Global Overall Survival rates of 73%, however the study did not outline what treatment if any, these patients underwent. The review also looked at regional Overall survival (OS) rates and found that in the Pan American, Western Pacific, Europe and Eastern Mediterranean regions, rates were 75%, 76%, 74% and 69% respectively while in South Eastern Asian Region and Africa, OS rates are 50% and 28% respectively. Early Stage survival ranged from 69-86% while advanced stages ranged from 32 – 51%. Those under 50 had a 5 year OS rate of 69% while those above 50 years had an OS rate of 61% (22).

Evidence for Hypofractionated Irradiation

Standardisation of Breast Radiotherapy (START) done in 2008 enrolled women who had completely resected invasive breast cancer with pT1-3a N0-1 and M0 from 35 centres around the United Kingdom (UK). START trials included women who received adjuvant chemotherapy. The Hazard Ratio (HR) for Disease Free Survival (DFS) for patients receiving 40 Gy vs those receiving 50 Gy in the UK START B trial was 0.79, this meant that DFS for 40 Gy was 21% higher than that of 50 Gy (23).

A study in Poland (2015) which is a high-income country, enrolled 667 patients into two arms, 1 (85%) underwent surgical treatment, while the other arm was treated conservatively (due to presence of DM/baseline unresectability /General Anaesthesia concerns) – the median observation time 79 months. The median time for overall disease free survival was 19.4 months while median overall survival time was 76.4 months (24). The study however did not outline whether patients enrolled in the study received any form of chemo or radiotherapy. In a South African (SA) study by Cubasch et al done in 2018 (25), disease free survival was not examined.

There are no published data on whether patients presenting at CMJAH have predominantly early or advanced stage disease. Cubasch et al (25) retrospectively looked at outcomes in a Soweto cohort, the finding was that a large proportion of women presented with advanced

breast cancer. Additionally, when examining factors affecting outcomes, the type of irradiation namely whether it was conventional or hypofractionated was not considered by Cubasch et al (25), all patients were put into one category of radiotherapy.

There are 4 landmark studies supporting the use of HF-WBI. These include, the Royal Marsden Hospital/Gloucestershire Oncology Centre (RMH/GOC) trial (26), UK based START A (27) and B trials (28) and the smaller Canadian trial (29).

The RMH/GOC trial (2005) enrolled 1410 with T1-3, N0-1, M0 invasive breast cancer into 1 of three arms, 50Gy in 25# at 2Gy per #, 39Gy/13# at 3Gy per # and 42.9/13# at 3.3Gy per # schedules. The UK START A trial (2008) enrolled 2236 women with T0-T3, N0-1, M0 into 1 of 3 arms, 50Gy in 25# at 2Gy per #, 39Gy/13# and 41.6Gy/13# at 3.2Gy per #. START B (2008) enrolled 2215 women with the same characteristics as START A trial into 2 arms, 50Gy in 25# or 40Gy/15# at 2.67Gy per #. The Canadian trial (2010) enrolled 1234 women with T stage up to T2, N0, M0 into 2 arms, 50Gy in 25# and 42.5Gy/16# at 2.67Gy per #. At CMJAH, the current regimen for hypofractionated irradiation is 40.05Gy/15# at 2.67Gy per # and is comparable with the START B trial. The data obtained in these trials included treatment of early nodal disease in the RMH/GOC trial and START A and START B trials, while the Canadian trials did not enrol women with axillary lymph node positivity. Caution needs to be practiced in using hypofractionation schedules in settings with advanced disease where supraclavicular nodal irradiation is indicated. Additionally, the studies excluded immunohistochemistry (IHC) and risk stratification as well as immediate and delayed autologous reconstruction which is increasingly being used to offer women more cosmetic outcomes.

Biological Effectiveness of Hypofractionated Irradiation

The α/β ratio of breast cancer and breast tissue is very similar. Therapeutic gain is obtained when the radiation dose to normal tissue is below the tolerance of the tissue where a fraction size has more effect on late than early effects, therefore keeping the dose below that which will cause late effects provides therapeutic gain (30). The higher dose per fraction used in the START A trial increased adverse effects such as breast oedema, telangiectasia and breast induration, while in the START B trial, there was breast shrinkage in addition to breast oedema and telangiectasia (23). Additionally, the Canadian study was the only study that

did not include Boost irradiation while the other 3 trials did, this is more reflective of a hypofractionated regimen than one that includes a Boost, adding another 5 days of standard fractionation adds to the number of days therefore the gains made in saving cost and reducing patient times are lost to a certain degree.

Outcomes of Hypofractionated Irradiation

In the 4 landmark trials, the 10-year loco-regional recurrence rate ranged from 4.3% to 9.6% (31).

1.1.2.1 Factors affecting breast cancer outcomes

Factors that can affect breast cancer treatment outcomes include inadequate surgical dissection, inadequate chemotherapy and lack of access to radiation therapy facilities (6). In patients who have access to radiotherapy, other factors may impact outcomes. These include age, stage, histology, grade of differentiation, margin status, number of excised lymph nodes and adequacy of lymph node dissection, hormone receptor status, Her-2 positivity, presence of lymphovascular space invasion, presence of perinodal extension, presence of ductal-carcinoma -in-situ (DCIS), type of surgery, waiting time for treatment and whether patient received neoadjuvant or adjuvant chemotherapy.

Loss-to-follow-up rates

The loss-to-follow-up-rates (LTFR) are largely unknown. Following up patients is important to establish effectiveness of therapy provided. It is important to know the institutional LTFR to compare with those found in the SA published study (25). This ranged from 25 to 61% from the first to 5 years (25). This can aid in determining ways in which this may be reduced in future.

Role of age on breast cancer outcomes

The age distribution of patients receiving RT is not well documented in Johannesburg. Cubasch et al (32), found about 40% of the study population (SP) was below the age of 50 and 60% above the age of 50 years. Age was not related to overall survival in the local study (25). The median age at diagnosis in a study by Phakathi et al was 57 years (33), this study was an observational cohort that aimed to "investigate the association of HIV with the clinic-pathological presentation of breast cancer" (33). Although -the Phakathi et al study (33) did

not specifically look at breast cancer treatment, it provided a good cross-section about the type of population that presents to CMJAH. One study done by Vanderpuye et al highlights a Cape Town study by Langenhoven, where patients had a median age at diagnosis of 56 years (6). These are in contrast to studies done in other Low to Lower-Middle Income African countries (Kenya, Nigeria, Tanzania, Morocco) where median age ranged from 42.7-46.9 years. South Africa is considered an Upper-Middle Income country (34) which has a GNI (Gross National Income per capita) of $3 956 to $12 475. In the UK START A and B the mean age was 57.2 and 57.4 years respectively (27,28). South Africa's age distribution follows that of the UK age distribution rather than that of the Low to Lower-Middle Income African countries. It is important to consider age as a factor affecting breast cancer outcomes as younger and older age groups are associated with worse disease free and overall survival rates (18,25).

Role of stage on breast cancer outcomes

Cubasch et al (25) had 3 year survival rates of 84% for early stage breast cancer and 56% for late stage breast cancer. The global 5 year survival rates for early breast cancer range from 69-86% while advanced breast cancer survival rates are 32-51% (22). This demonstrates that Johannesburg rates are in line with global rates however Johannesburg rates were reported for a 3-year survival period which when examined over a 5-year period, may be lower. In general, patients referred for breast cancer surgery differ slightly due to stage differences as outlined previously, it is therefore important to have a cross-section of the stage groupings that RT is being used to treat in our setting.

Role of number of axillary nodes excised on breast cancer outcomes

The number of axillary lymph nodes (LN's) excised has reduced over the years due to the complication rate of lymphoedema. In the 2015 St. Gallen Consensus, a number of <8 axillary LN's excised in a patient with pN0 disease needs Radiotherapy to the axillary LN's (14). Ebner et al (35) found that the removal of > 10 axillary LN's did not result in significant survival benefit even in High Risk PN+ breast cancer. In another multicentre study involving >9000 patients by Ebner et al (36) , age and Intrinsic subtypes were found to be significant for Overall Survival but not the number of LN's excised. There is no local publication on the outcomes of RT to patients who have had < 8 or ≥8 LN's excised.

Role of involved nodes on breast cancer outcomes

The number of involved nodes is a factor that can influence the overall survival of patients who have undergone Post Mastectomy Radiotherapy (PMRT). In the Christchurch study by Ko et al (37), which explored survival outcomes in 133 PMRT patients who had undergone hypofractionated irradiation, 15.8% had no involved nodes, while 35.3% had 1-3 involved nodes and 49.8% had ≥4 lymph nodes, the 5-year overall survival was 74.7%. This study did not compare survival outcomes of the various lymph node groups.

Role of Hormone Receptor status on breast cancer outcomes

The hormone receptor status as well as the Her2 status of a breast cancer population was explored by Cubasch et al (25), however no comparison was made on HR/Her 2 status in relation to RT. The outcomes of Hormone Receptor positive cancers are generally better if Ki-67 (mitotic rate) is low. Cubasch et al (25) found 62.5% of the population were ER positive. 53.5% were PR positive. 24.2% were Her2 positive. The Triple negative breast cancers (TNBC) made up 21.7%. In a study reported from Cape Town,the patients had tumours with ER+ 64%, PR+ 51%, Her2 + 36% and TNBC 16% respectively (6).

ER- cancer had a higher HR for death at 4 years amounting to a 2.5 fold increase, while TNBC had a 3 fold increase in the HR for death at 4 years of follow up (25). The effect of Radiotherapy on HR receptor and Her2 status was explored in a retrospective study by Brollo et al (38) which found that Luminal B/Her2/PR negative tumours have a higher LRR. This study compared a total of 466 pT1-2 Her2+ patients who received trastuzumab and had had a quadrantectomy and radiotherapy with those who had had a mastectomy without radiotherapy.

The LRR in the group that had RT was 1.5% while those who had Mastectomy without RT was 5.0%. Her-2 positive adjuvant breast cancer can be treated with 6 months of Trastuzumab which has recently become available in the SA state sector. In addition, another retrospective study conducted among 439 women with TNBC showed that LRR and BCSS were lower among women who had a mastectomy followed by RT (39). These studies

demonstrate the importance of collecting information on the Hormone Receptor and Her-2 status of women receiving RT.

Role of Tumour Grade on Breast Cancer Outcomes

The Grade of tumour provides some insight into how radiosensitive a tumour may be, those that are poorly-differentiated are more likely to have a radiosensitive tumour than those with a well-differentiated tumour. Differentiation of tumours is well to poor from Grade 1 to 3. Cubasch et al (32) found roughly 11%, 40% and 47% made up Grade 1, 2 and 3 of the SP. In the UK START trial B, the SP tumour grades were Grade 1 – 28%, Grade 2 - 47.4%, and Grade 3 – 23%. Breast cancer outcomes related to Grade were explored in the Cubasch et al (25) study and found not to have a significant impact on survival as p values were above 0.05. Cubasch et al (25), however, did not specifically look at the tumour grade and outcomes in patients who had received RT. The Danish study 82c in postmenopausal women, SP tumour grades were Grade 1-24%, Grade 2- 44% and Grade 3-16% (18). The Danish study in premenopausal women had incidence rates for Grade 1,2 and 3 of 21%, 41% and 21% respectively (19). In the Danish 82b study, patients with Grade 1 tumours fared better than Grade 2 or 3 tumours (10-year DFS 63% vs. 46% vs. 35% for Grade 1,2 and 3 respectively, 10-year OS of 71%, 52% and 39% for Grade 1,2 and 3 tumours respectively) in the SP that received RT (19). The Danish 82b study however did not use hypofractionated irradiation and this therefore needs to be explored.

Role of histology on breast cancer outcomes

The histology for Cubasch et al done in 2017 (32): Invasive Ductal (ID) made up 94%, Invasive Lobular (IL) comprised 4% histology, 0.7% had mixed ductal and lobular while 0.7% had other types of histology. Cubasch et al in 2018 (25) did not look at outcomes in relation to the histology of breast cancer as the numbers are predominantly ID. The UK START trial B in 2008 (28) had 77% ID and 11.5% IL, while a Danish study (1999) had 85% ID, 10% IL, and 2% Medullary (18). Survival outcomes in the UK START trial B were not explored in terms of Histology and RT received. Survival outcomes for patients in a Danish 82b (1997) trial were better for patients with Invasive Ductal as compared to Invasive Lobular cancer (10-year DFS 48% vs 36% and 10-year OS of 54 vs. 45 %) in those receiving RT. The effect of histology in the local population on outcomes therefore needs to be

explored as the Danish trial was done only in patients who had received Mastectomy and Adjuvant chemotherapy which was not anthracycline based. In addition, the Danish 82b trial provided only Conventional fractionation and in a small percentage (7.5%), patients received 250kv RT.

Role of DCIS on breast cancer outcomes

The role of Ductal-Carcinoma-in-situ (DCIS) when present with Invasive Ductal Carcinoma (IDC) seems to incur a better prognosis, and this was explored by Kole et al (40) into the National Cancer Database for > 500 000 patients among whom 66% had DCIS + IDC and 34% had IDC alone and found to have 89% 5 year OS rates with DCIS + IDC, versus 85% with IDC alone. The OS was however better when tumours were <3cm. The role of Radiotherapy in DCIS when present with IDC is not well researched. Perez and Brady (14) indicate that some studies support the presence of DCIS as a risk factor for recurrence while other studies are conflicting. It is therefore important to explore the role of DCIS when present with IDC in our population.

Role of Margin status in breast cancer outcomes

The role of radiotherapy in patients with positive margins was explored in a systematic review done by Rowell (41). Pooled data from 22 studies involving >18000 women, found involved margins in 2.5%, close margin in 8.0% and muscle or fascia invasion in 7.2% (41). Ink on tumour is considered a positive margin while a margin of ≤2 mm would be considered close. A margin of >2mm would be considered a clear or negative margin (42). The Breast Cancer Agency collected data on >10 000 women, defining close margins as <2 mm, Boost RT was used in 34.1%, 76.9%, and 79.5% negative, close and involved margins respectively. Breast Cancer Specific Survival (BCSS) was 93.9%, 91.8%, and 87.9%, respectively ($P < .001$) (43). The role of Boost RT has not been established in our local population.

Role of Perinodal spread on breast cancer outcomes

Perinodal spread is treated with ACT. If, however, it is still present after NACT, it is a poor prognosis indicator. There were no systematic reviews looking at PNS in terms of outcomes with or without RT. In a retrospective study by Drinka et al (44), conducted in 456 patients with pT1-T2 tumours with 1-3 nodes positive, 21.6% (99 patients) of the study population had Perinodal spread (PNS). Of these patients, 27 received RT vs 72 who did not. Those that received RT did not have significant difference in DFS compared to those that did not receive RT: 74.1% (no RT) vs. 52.06% (RT) p=0.13 or OS 78.89% (no RT) vs. 76.86% (RT) p=0.59, there were some limitations as several risk factors were not considered eg younger age, larger tumour size, margins, skin/nipple invasion and Lymphovascular Space Invasion (LVSI), HR receptor status when conducting multivariate analysis. This demonstrates the importance of examining as many risk factors as possible when conducting a study to determine their influence on outcomes.

Role of Lymphovascular Space Invasion on breast cancer outcomes

In a systematic review by Rowell et al (45) which looked at post mastectomy with RT outcome of LRR in Node negative patients, presence of LVSI increased risk of loco-regional recurrence (LRR). This review however excluded women who had received NACT. Notwithstanding 3 out of 7 studies found a statistically significant increased risk of LRR in patients with LVSI. HR's ranging from 1.81 to 6-fold increases, which were all statistically significant were found for increased LRR in the presence of LVSI. LRR in the presence of LVSI ranged from 13% to 19.8%, while in the absence of LVSI, LRR ranged from 1.2% to 5% which were significantly different (p=0.001). Cubasch et al (32) found LVSI was present in 38.2% of the SP and absent in 45% of the SP. Ko et al (37) reported LVSI was present in 63.2% of its SP and absent in 36.8%. This study did not compare survival outcomes of patients with/without LVSI. Our local setting has no documentation on the effect of lymphovascular invasion on LRR or OS.

Role of laterality on breast cancer outcomes

The laterality of breast cancer is important when considering the effect of Radiotherapy on survival outcomes. This is due to the effect of RT on organs at risk such as the heart. The outcomes in left-sided breast cancer are expected to be worse due to the effect on the heart. In a systematic review conducted by Boekel et al (46) which looked at patients who received

RT from 1989 to 2005, left sided irradiation following Mastectomy, BCS and internal mammary irradiation were associated with an increased risk of Cardiovascular Disease (CVD) compared with right-sided breast cancer. The study also found that women who were diagnosed before the age of 50 years were at greater risk for developing heart disease. In another study by Rutqvist & Johansson (47), of a Breast cancer registry in Sweden, the incidence of left breast cancer was equal to that of right breast cancer. Overall survival was also equal; however, the risk of myocardial infarction was higher among patients with left breast cancer. Local data on effect of RT treatment on different sides of breast cancer needs to be documented.

Role of Quadrant involved on breast cancer outcomes

There is a trend towards an increase in incidence of Upper Outer Quadrant (UOQ) breast cancer as was seen in a study done by Bright et al (48). This study examined SEER data from the US and compared it to UK cancer registry data. The study did not compare treatment that the patients had received. A study done by Gaffney et al (49) compared BCSS in over 45 000 patients using multivariate analysis. BCSS was worse when the tumour was located in the inner quadrant (49). For example, after adjusting for age, stage, grade and size of tumour, patients with inner quadrant tumours had BCSS 31% less than those with outer quadrant tumours (49). The fields of RT were however not recorded, and it is not known whether patients received internal mammary irradiation for tumours located in the inner quadrant. Therefore, the fields of radiation delivered based on the quadrant of tumour may have a role in outcomes such as LRR, OS and BCSS, this data therefore needs to be collected.

Role of Surgical Procedure on breast cancer outcomes

A Total Mastectomy was done among 79.6% of patients while BCS was conducted among 20.4% of the SP in the study by Cubasch et al (32) . This study showed that 72.5% of patients who underwent BCS and 57.3% who had Total Mastectomy received RT, however the field of RT was not explored. Heunis et al (50) found higher rates of BCS of 30.5% and lower Mastectomy rates of 69%, this was conducted from 2010 to 2014, a later time period which may demonstrate the rising trend toward BCS. A systematic review by Chen et al showed Mastectomy has a slight OS benefit when compared to BCS in early breast cancer

(51). The review comprised of studies from 1981 to 2008 and included Randomised Controlled Trials (RCTs) that compared BCS to Mastectomy with available HRs, confidence intervals and p values. This review looked at RT in terms of whether Boost RT was provided, it however did not look at Standard versus Hypofractionated Irradiation. Women who have undergone mastectomy can also receive hypofractionated irradiation. Outcomes are good, with 5-year local control rates above 97%, 5-year overall survival of 74.7 % and 5-year breast cancer survival of 77.7% (37). The local control rate, disease progression and overall survival for the population at CMJAH receiving irradiation is largely unknown. This is because most of the studies conducted do not look specifically at the population undergoing radiotherapy.

Role of chemotherapy on breast cancer outcomes

There is a role for chemotherapy in downstaging disease burden thereby allowing for better surgical outcomes as well as preventing recurrence if there is a high risk of recurrence after surgery (52). The use of Radiotherapy in improving outcomes following Neoadjuvant Chemotherapy (NACT) or Adjuvant Chemotherapy (ACT) and the times that patients wait to receive these services is not published in our setting. In a descriptive SA study done by Ruff et al (53) set in Soweto, 35.2% and 47.7% received NACT and Adjuvant chemotherapy respectively. This study did not explore outcomes, it was done to probe into the patient characteristics that influence the choice of NACT or ACT.

Role of waiting times for Radiotherapy on breast cancer outcomes

In a systematic review conducted in patients who had had BCS, waiting times for Radiotherapy showed a higher risk of death and local recurrence for every month of prolonged waiting time (54). In a study, Caponio et al (55) analysed 615 patients, and categorised timing of radiotherapy into categories of ≤ 60 days, 61-120 days and > 120 days. They did not find a correlation on the risk of local recurrence or disease progression. There is no local study done on the waiting times for radiotherapy and since the results are not conclusive, it is important to consider this when assessing outcomes and the factors that influence them.

CHAPTER 2: STUDY AIM AND OBJECTIVES

Aim: To determine patterns of practice in women receiving breast cancer irradiation at CMJAH, 2010-2012.

1. To determine local control (LC), overall survival (OS), and progression free survival of patients receiving breast cancer irradiation at CMJAH, 2010-2012.
2. To determine factors affecting breast cancer outcomes in patients receiving breast cancer irradiation at CMJAH, 2010-2012.
3. To compare outcomes from 2010 to 2012 with 5-year follow-up of patients receiving breast cancer irradiation therapy at CMJAH with international outcomes.

CHAPTER 3: METHODS

3.1 Study Design

A retrospective review of patient records starting RT from 01 January 2010 to 31 December 2012. This period allowed for a 5-year follow up of patient records to the 31st Dec 2017.

3.2 Setting

Department of Radiation Oncology, Area 348, Charlotte Maxeke Johannesburg Academic Hospital. This is one of the main referral hospital for Radiation Oncology services in the Province, patients are referred from other tertiary hospitals such as Chris Hani Baragwanath Hospital, and Helen Joseph Hospital.

3.3 Approvals

Study protocol was submitted for protocol assessment and was approved by the protocol board. Ethics clearance was applied for and obtained from the University of the Witwatersrand Human Research Ethics Committee (M180626).

Additionally, permission to conduct the study was obtained from the:

- Chief Executive Officer of CMJAH
- Departmental Head of Radiation Oncology, CMJAH
- Departmental Head of Medical Oncology, CMJAH
- Departmental Head of Anatomical Pathology National Health Laboratory Services, CMJAH.

The approval letters are attached to Appendix A.

3.4 Data Collection

Data collection commenced in October 2018. Patients are referred for Radiotherapy to Area 348 Clinic 4 Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from Helen Joseph Hospital (HJH), Chris Hani Baragwanath Academic Hospital (CHBAH), CMJAH Medical Oncology (495) or CMJAH Surgical Breast Unit and from other smaller peripheral hospitals.

Patients then proceed to Clinic 4 and make a booking to be assessed to receive Radiotherapy. The nurse at the desk ensures that patients have basic investigations available such as the histology, Chest X-ray and MUGA (Multigated Acquisition) scan (to assess baseline cardiac function). This occurs every Wednesday. On Wednesdays, the registrars in the unit clerk patients and then present them to the Unit Consultant who decides on whether patient is for RT and the type of RT needed. The patient is then booked for Simulation. After Simulation, patient waits about 2 weeks and then commences RT. After completion of RT, patient's file is returned to reception for filing and is retrieved at follow-up visit.

It was noted that approximately 500 breast cancer patients are attended yearly. As the study period was over 3 years, examining the files consecutively was not going to be possible in the time required to complete the project. A required sample size was calculated.

STATA's sample size calculator was used. This was provided by University of Witwatersrand appointed biostatisticians. From previous data, from 3 studies the range having Conventional fractionation is 68% to 88%, while those having hypofractionated irradiation is 12% to 34.8% (56–58). Therefore, a ratio of 65% for those having conventional fractionation to 35% for those undergoing hypofractionated irradiation was used. The significance was set at 0.05 and the power at 80%.

The required sample size was 95 patients. The calculation conducted on STATA is available in Appendix D.

As the patients involved in the study were from 2010 to 2012, the researcher proceeded to go physically to the filing room and identified files for breast cancer patients as these are marked with a colour coded tape. The filing cabinets are arranged to accommodate files for an entire year. To identify 95 patient files that adhered to the inclusion and exclusion, 356

breast cancer files were randomly selected from the filing cabinets spread out over the 3-year period. Each file was examined to see if it met the inclusion and exclusion criteria. It was then returned to the filing cabinet if it did not meet the criteria. The data collection sheet was then completed for the 95 patient files. Patients who were lost to follow up were searched on the hospital database and information obtained as to whether patients were still alive or not, their date of death was however not recorded in the database.

The following flow chart Figure 2 outlines the methods used to identify patients and collect data:

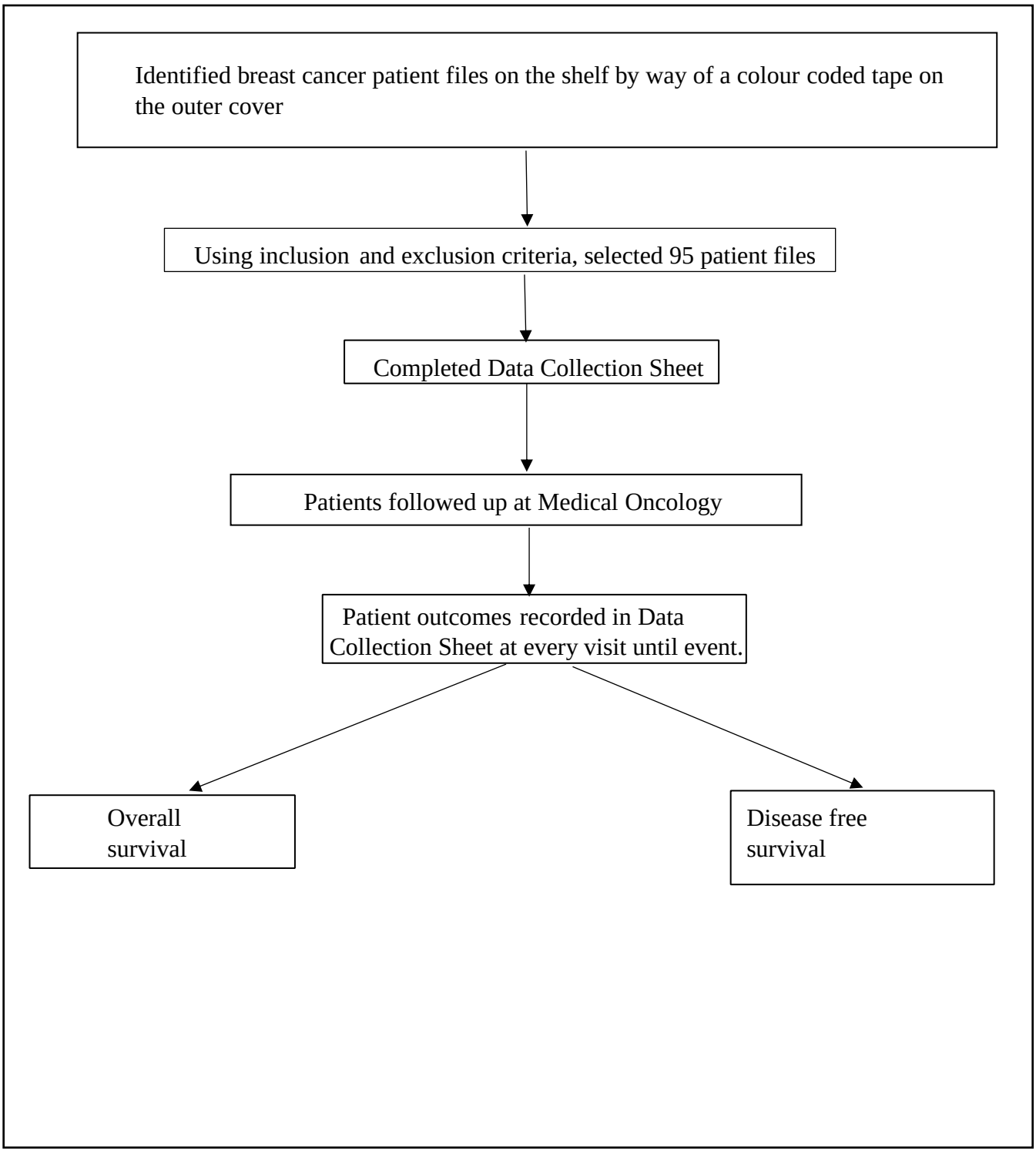

Figure 2: Summary of Methods

Patients were selected using the following inclusion and exclusion criteria shown in Table 1.

Table 1: Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Confirmed histology, invasive carcinoma.	Carcinoma-in-situ
Adjuvant and Neoadjuvant Therapy	Palliative Therapy
Any T stage	
Nodal disease present or absent.	
Bone only metastases.	Visceral metastases.
Patient positioned in the supine position	Patients positioned in the prone position.
Unilateral, unifocal breast disease.	Bilateral breast involvement.
No previous Radiation Therapy to the chest wall.	Patients who have undergone previous irradiation to the chest wall following mastectomy.

Data collected for local factors included:

1. Age
2. Stage
3. Histology
4. Grade
5. Margin status
6. Number of axillary nodes dissected
7. Number of axillary nodes involved
8. Hormone Receptor status
9. Her-2 expression
10. Perinodal spread
11. Lymphovascular Space Invasion
12. Tumour laterality
13. Quadrant involved
14. Presence of DCIS
15. Type of surgery
16. Chemotherapy whether neoadjuvant or adjuvant
17. Waiting time for Radiotherapy

3.4 Data Analysis

Data was analysed using SPSS v.25. Data was inputted into the software program after setting up variables under the following headings in Table 2, Ki-67 was not available at the time:

Table 2:Variables analysed

1. Age at time of diagnosis	11. Margins
2. T-stage (determined either clinically or mammographically or pathologically)	12. Perinodal Spread
3. N-stage	13. Lymphovascular Invasion
4. M-stage	14. Laterality
5. Number of excised nodes	15. Quadrant
6. Number of involved nodes	16. Surgery – whether Breast Conserving or Mastectomy
7. Hormone Receptor and Her-2 status	17. Chemotherapy – whether Neoadjuvant or Adjuvant
8. Grade	18. Radiation Field – whether it was to chest only or to nodes as well.
9. Histology	19. Radiation dose – whether Hypofractionated or Standard Fractionation
10. In-situ component	20. Radiation Boost – whether given or not.

Descriptive Statistics

Descriptive statistics conducted for each variable using the "Descriptive Statistics" option in SPSS v25 and then opting for "Frequencies" tab. These were then tabulated with the Valid percent.

To answer Objective 1 of this report where there are three parts namely:

- Local Control (LC)
- Overall Survival (OS)

- Progression Free Survival

For the objective LC, data was analysed using descriptive statistics and frequencies presented in Table 4-1 respectively.

To assess OS, patients were split into two groups, those who were alive and those who had died within the 5-year follow up period. Data for those who were alive but were lost-to-follow-up was right censored.

These were then assessed using Kaplan-Meier Survival Analysis. The overall time of follow-up was used as the time variable, the "status" element was the "treatment outcome" categorical variable. Univariate Survival Analysis was carried out using "Time to Event" as the Time Variable, "Treatment Outcome" as the Status variable with the event defined as those who had died. Patients that were LTFU were right-censored.

The outcome "progression free survival" was analysed using Kaplan-Meier survival analysis. The time variable was – time to event, the status was "Treatment Outcome" and the event was defined as those that were "Alive, progressed at some time point and were LTFU", "Alive, progressed at some time point and were not LTFU" and those who had "Died, unknown whether due to illness or other cause". The data for those who were "Alive without progression" and those who were "LTFU" was censored. The factor variable was "Type of progression" which was recoded into whether the patient had "No progression" or had developed "Local or distant metastases" and for those where "No documentation" was present. Those who had died were allocated to one group only as it was not possible to know from the records cause of patients' death.

The variables were categorized as shown in Appendix C

CHAPTER 4: RESULTS

Objective 1 of the study is exploring the rates of local control, overall survival and progression free survival of patients who are undergoing radiotherapy at CMJAH. Objective 2 is looking at the factors that may influence the outcomes of patients receiving breast cancer irradiation. This chapter presents the findings of data that were collected. It does so analytically in an attempt to uncover any factors that influence any differences that exist.

4.1 Descriptive Statistics

The required sample size was 95. The baseline characteristics of this population are tabulated in Tables 3 to 7 . All missing data was also recorded. All the patients were female.

Data showing referral hospitals

Figure 3 shows the referral centres that are in the catchment for CMJAH.

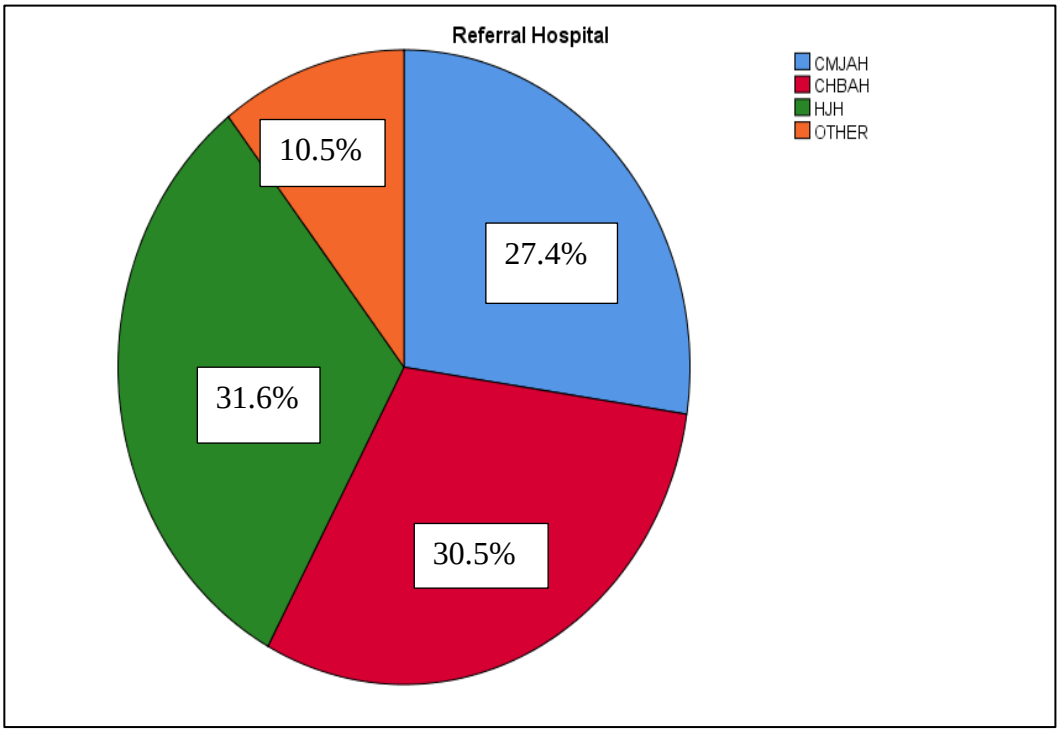

Figure 3: Pie Chart of Referral Hospital

Loss-to-follow-up rate

The cumulative LTFR for the total SP was 1.1%, 4.8%, 11.8%, 20.8%, 23.5% in the 1st, 2nd, 3rd, 4th and 5th years respectively. A total of 16 patients were LTFU. The LTFR was calculated by excluding the patients who had died, therefore the initial denominator was 94 as 1 patient died in the first year, the denominator was then 83, 76, 72 and 68 in the 2nd, 3rd, 4th and 5th years.

Distribution of Age

Data for age at diagnosis was collected as a continuous variable, it is however presented here categorically – see Figure 4. Measures of central tendency were applied to this variable. The mean age was 51.55 years and the range extended from 29 to 81 years spanning 52 years. The median age was 50 years.

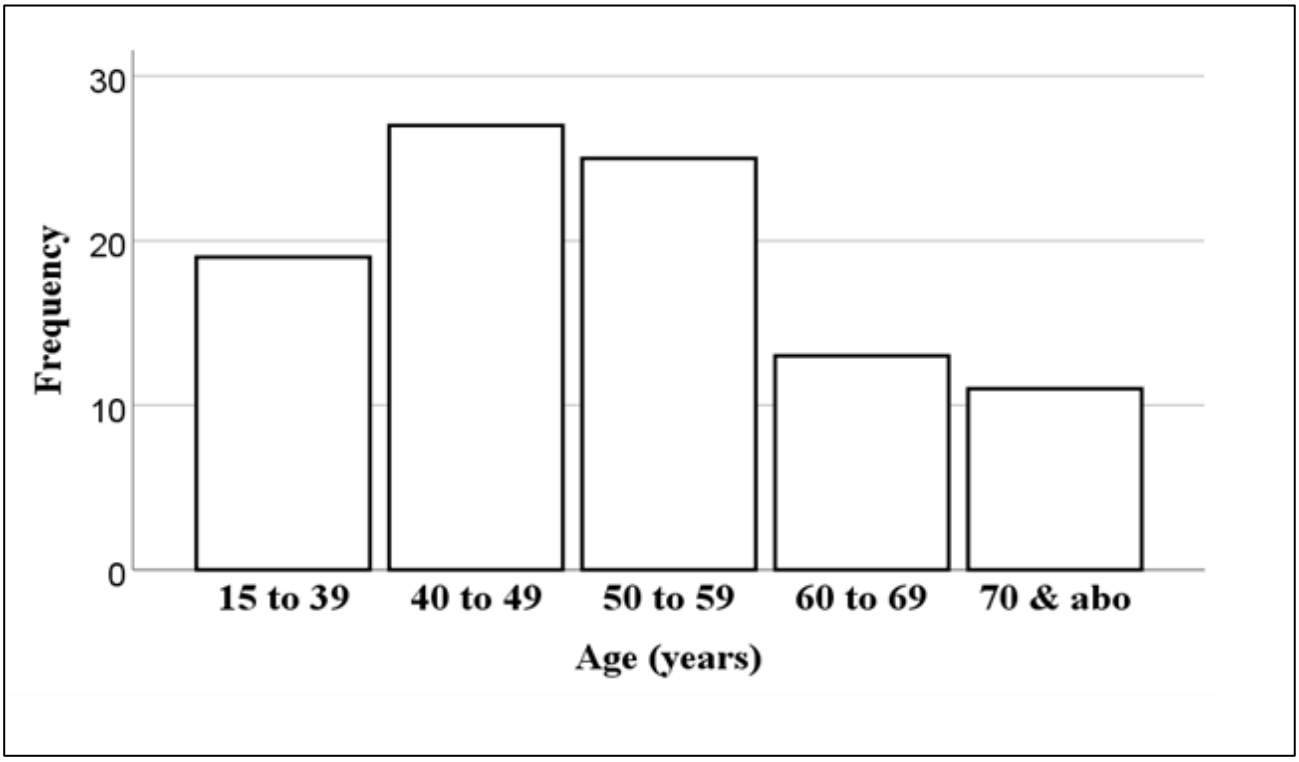

Figure 4: Bar Graph of Age Categories

Distribution of Stage

The T-stage was recorded from pathology reports if patients underwent surgery first. Those who underwent neoadjuvant chemotherapy had mammographic data which collected information on the size of the initial tumour.

Table 3: Descriptive Statistics on T,N,M stage and Stage grouping

Parameter	Categories	Value(%)
T-stage	Tx	1 (1.1%)
	T0	2 (2.1)
	T1	5 (5.3%)
	T2	37 (38.9%)
	T3	22 (23.2%)
	T4	28 (29.5%)
	Missing	0 (0%)
	Total	95 (100%)
N-stage	Nx	3 (3.2%)
	N0	30 (31.6%)
	N1	36 (37.9%)
	N2	19 (20%)
	N3	4 (4.2%)
	Missing	3 (3.2%)
	Total	95 (100%)
M stage	Mx	81 (85.3%)
	M0	11 (11.6%)
	M1	2 (2.1%)
	Missing	1 (1.1%)
	Total	95 (100%)
Stage grouping	Stage 1	1 (1.1%)
	Stage 2	39 (41%)
	Stage 3	53 (55.8%)
	Stage 4	2 (2.1%)
	Total	95 (100%)

Table 4: Descriptive Statistics on Grade, Histology, Margins, Nodal dissection

Parameter	Categories	Value(%)
Grade	1	4 (4.2%)
	2	45 (47.4%)
	3	40 (42.1%)
	Unknown	2 (2.1%)
	Missing	4 (4.2%)
	Total	95 (100%)
Histology	Invasive Ductal	80 (84.2%)
	Invasive Lobular	4 (4.2%)
	Other	10 (10.5%)
	Missing	1 (1.1%)
	Total	95 (100%)
Margins	Clear (≥ 2 mm or no ink on tumour)	51 (53.7%)
	Close (< 2 mm)	27 (28.4%)
	Involved	12 (12.6%)
	No primary tumour	3 (3.2%)
	Missing	2 (2.1%)
	Total	95 (100%)
Type of Lymph Node dissection	SLNB	14 (14.7%)
	ALND	79 (83.1%)
	Nil	2 (2.1%)
	Total	95 (100%)
Number of nodes excised (ALND)	< 8 nodes	27 (33.3%)
	≥ 8 nodes	52 (64.2%)
	Total	79 (100%)
Number of involved nodes	Nil	31 (32.6)
	1-3 nodes	34 (35.8%)
	≥ 4 nodes	28 (29.5%)
	Missing	2 (2.1%)
	Total	95 (100%)

Table 5: Descriptive Statistics on Hormone Receptor Status, LVSI, PNS, DCIS

Parameter	Categories	Value(%)
Hormone Receptor Status	ER+/PR+/Her2-	43 (45.3%)
	ER+/PR-/Her2-	11 (11.6%)
	ER-/PR+/Her2-	2 (2.1%)
	ER+/PR+/Her2+	9 (9.5%)
	ER-/PR-/Her2-	21 (22.1%)
	ER-/PR-/Her2+	1 (1.1%)
	Missing	1 (1.1%)
	Total	95 (100%)
Lymphovascular Invasion	Present	32 (33.7%)
	Absent	44 (46.3%)
	Not stated	19 (20%)
	Total	95 (100%)
Perinodal Spread	Present	38 (40%)
	Absent	39 (41.1%)
	Not stated	18 (18.9%)
	Total	95 (100%)
DCIS component	Present	57 (60%)
	Absent	38 (40%)
	Total	95 (100%)

Table 6: Descriptive Statistics on Quadrant involved, Laterality, Surgery, Chemotherapy

Parameter	Categories	Value(%)
Quadrant involved	Upper Outer	34(35.8%)
	Lower Outer	9(9.5%)
	Upper inner	13(13.7%)
	Lower inner	7(7.4%)
	Upper Mid	5(5.3%)
	Lower Mid	0(0.0%)
	Outer Mid	6(6.3%)
	Inner mid	3(3.2%)
	Retroareolar	13(13.7%)
	Missing	5(5.3%)
	Total	95(100%)
Laterality	Right	49 (51.6%)
	Left	46 (48.4%)
	Total	95 (100%)
Surgery	Mastectomy	75 (78.9%)
	Breast Conservation	19 (20%)
	Nil	1 (1.1%)
	Total	95 (100%)
Chemotherapy	Neoadjuvant	41 (43%)
	Adjuvant	46 (48.4%)
	Nil	7 (7.4%)
	Total	95 (100%)

Table 7: Descriptive Statistics on Rad. Field, Rad. Dose, Boost

Parameter	Categories	Value(%)
Radiation Field	Chest Wall only	13 (13.7%)
	Chest wall, axilla and supraclav nodes	82 (86.3%)
	Total	95 (100%)
Radiation Dose	40.05 Gy	77 (81.1%)
	42.75Gy	1 (1.1%)
	50 Gy	17 (17.9%)
	Total	95 (100%)
Boost given	Yes	55 (57.9%)
	No	40 (42.1%)
	Total	95 (100%)

Radiation Fields

The Radiation field was summarised into Chest Wall and Chest wall with Supraclavicular nodes, the following Table 8 displays the breakdown of all the fields that were delivered at CMJAH.

Table 8: Radiation Fields

Radiation Field	Frequency	Percent
1. Tans & Boost	7	7.4%
2. Tans & Drain Site	2	2.1%
3. Tans & Drain Site & Boost	3	3.2%
4. Tans & Scar & Drain Site & Boost	3	3.2%
5. Tans & Supraclavicular Nodes	29	30.5%
6. Tans & Boost & Supraclavicular Nodes	24	25.3%
7. Tans & Drain Site & Supraclavicular Nodes	5	5.3%
8. Tans & Drain Site & Boost & Supraclavicular Nodes	6	6.3%
9. Tans & Scar & Supraclavicular Nodes	2	2.1%
10. Tans & Scar & Boost & Supraclavicular Nodes	5	5.3%
11. Tans & Scar & Drain Site & Supraclavicular Nodes	2	2.1%
12. Tans & Scar & Drain Site & Boost & Supraclavicular Nodes	1	1.1%
13. Tans & Supraclavicular Nodes & Posterior Axilla	3	3.2%
14. Tans & Boost & Supraclavicular Nodes & Posterior Axilla	2	2.1%
15. Tans & Supraclavicular Nodes & Internal Mammary & Boost	1	1.1%
Total	95	100%

Tangential fields were treated using a photon beam, the energy of which varied based on the separation of the patient. The scar and drain sites also received the same dose as the Tangential fields, it was however delivered with 6 MeV electrons. The boost dose was 8.01 Gy given with 6Mev electrons in 3 fractions. Supraclavicular lymph nodes were treated with the same dose as the Tangential field. A posterior axillary field was given to 5 patients, 1 early stage without nodal involvement and 4 advanced breast cancer with nodal involvement. An internal mammary field was given in 1 patient with 6 MeV electrons. The majority of patients received Supraclavicular irradiation.

When looking at the subgroup that received Radiotherapy to the Chest wall only, this is outlined in Table 9.

Table 9: Descriptive statistics for RT Chest Wall Subgroup

	RT to Chest Wall only (15 patients)
Surgery first subsequent adjuvant chemo	11 (73%)
Surgery subsequent adjuvant RT	3(20%)
Early stage disease, no nodal involvement	10 (67%)
Early stage disease, nodal involvement	3(20%)
Advanced stage disease, no nodal involvement	2(13%)

In the subgroup of the SP that received Radiotherapy to the Chest Wall and Nodes (80 patients), 15(19%) that received Neoadjuvant chemo, had initial N0 disease and were node negative but still had Supraclavicular Fossa radiotherapy. 30 patients (38%) had N1 disease but were pathologically ypN0- post NACT and still received Supraclavicular fossa radiotherapy. In the subgroup that had received adjuvant chemotherapy, had 1-3 nodes positive with or without high-risk features such as T3 tumour or grade 3 tumour, radiotherapy was given to the supraclavicular fossa in 11% of the subpopulation.

The Radiation Field when providing HF-WBI was extended to nodal fields. 19 patients in the SP had undergone BCS. 69.2% of them received Radiotherapy to the Chest Wall and nodes. Only 1 patient in the SP had not received any chemo, 1 received NACT and 7 had received ACT. This is shown in Table 10.

Table 10: Radiation Field cross tabulated with Radiation Dose received for Whole Breast Irradiation

		Radiation Dose			
		40.05Gy	**50Gy**	**42.75Gy**	**Total**
Categorized Radiation Field	Chest Wall & Nodes	69.2%	23.1%	7.7%	100%
	Chest Wall only	100%	0%	0%	100%

The times taken into consideration included:

1. Time from biopsy to initial treatment.
2. Waiting time for Radiotherapy.
3. Overall treatment time.

1. Time from biopsy to initial treatment

Table 11: Time from biopsy to initial treatment

Categories	**Frequency/Percentage**
Up to 3 months	64 (67.4%)
> 3 months	16 (16.8%)
Missing data	15 (15.8%)
Total	95 (100%)

Initial treatment was either surgery or chemotherapy and very rarely radiotherapy, when surgery was the initial treatment, the initial treatment time of up to 3 months was met in about 77% of patients, and when Neoadjuvant Chemotherapy (NACT) was the first treatment, 56.1% of patients received their Chemotherapy within 3 months of diagnosis. When Surgery was the initial treatment, 69.2% of patients then received chemotherapy within 3 months. When NACT was the initial treatment, 52% of patients received surgery within 3 months.

2. Waiting time for Radiotherapy

Table 12: Waiting time for Radiotherapy

Categories	**Frequency/Percentage**
Up to 1 month	5 (5.3%)
1-2 months	29 (30.5%)
2-3 months	25 (26.3%)
> 3 months	31 (32.6%)
Missing data	5 (5.3%)
Total	95 (100%)

These results show that 35.8% of the SP received their Radiotherapy (RT) by 8 weeks As There is missing data of 5.3%. 4.2% of SP received RT after 6 months ie. 28.4% received RT between 3-6 months.

3. Overall treatment time from biopsy to end of RT.

Table 13: Overall treatment time

Categories	**Frequency/Percentage**
Up to 9 months	11(11.6%)
9-12 months	49 (51.6%)
> 12 months	30 (31.6%)
Missing data	5 (5.1%)
Total	95 (100%)

A large proportion of patients (63.2%) received their overall treatment over a 1-year period. About 31.6% of the SP received their overall treatment exceeding 1 year. 5.1% of data was missing.

4.2 Local control

Documented local recurrence over 5 years was 6.4%, missing data consisted 18.9% of the study population that were either lost-to-follow-up or had died with no documentation on whether metastases were local or distant.

Table 14:Type of Local Progression during follow up period for breast cancer

	Frequency	**Percent**
No progression	52	54.7
Not documented	18	18.9
Local recurrence	5	5.3
Local Recurrence with Bone metastases	1	1.1

Looking at the population that had local recurrence i.e. the 6 patients who had local recurrence:

Characteristics of patients		**Frequency**
Age:	Below 50	3
	Above 50	3
Stage:	1	1
	2	1
	3	4
First treatment:	NACT	5
	Surgery	1
Surgery:	BCS	1
	Mastectomy	5
	Re-excision	1
Radiation dose received:	40.05 Gy	5
	50 Gy	1
Radiation Field:	Chest Wall only	2
	Chest Wall & Nodes	4

Characteristics of patients		Frequency
Hormone Receptor status:	TNBC	2
	HR positive	4
	Her 2 positive	0
Margins:	Clear	4
	Close	1
	Involved	1
PNS:	Present	2
	Absent	3
	Not stated	1
LVSI:	Present	3
	Absent	0
	Not stated	3
Nodal Involvement:	Present	4
	Absent	2

It is not known if the local recurrence was within the field of radiation or outside the field of radiation. These numbers are too small to provide meaningful statistical evaluation and to draw any conclusions.

4.3 Distant Metastases

Table 15: Type of Distant Progression during follow-up period for breast cancer

	Frequency	Percent
No progression	52	54.7
Not documented	18	18.9
Distant metastases - Bone only	7	7.4
Distant metastases - Visceral	11	11.6

4.4 Development of a new primary

1 patient had development of a contralateral metastases more than 6 months after completion of treatment.

4.5 Overall Survival

Overall survival, which is defined in this study as the time from diagnosis to death or in the instance where the initial date of diagnosis was not available, the first treatment (meaning surgery, chemo or radiotherapy whichever was first) to the date to death. This was 71.6%. It includes patients who were LTFU with right censoring of this group. This is depicted in Figure 5 below. The median OS has not been reached.

Table 16: Overall survival

Treatment outcome	**Frequency**	**Percent**
Alive	68	71.6%
Died	27	28.4%
Total	95	100%

Patients who were alive were either followed up for the entire 5 year period, were LTFU or had progressed at some time point.

Table 17: Category breakdown of all outcomes

Treatment Outcome	**Frequency**	**Percent**
Alive, no progression for 5 years	47	69
LTFU at some point	13	19
Alive, progressed at some time point then LTFU	3	4.5
Alive, progressed at some time point, no LTFU	5	7.5
Total	68	100

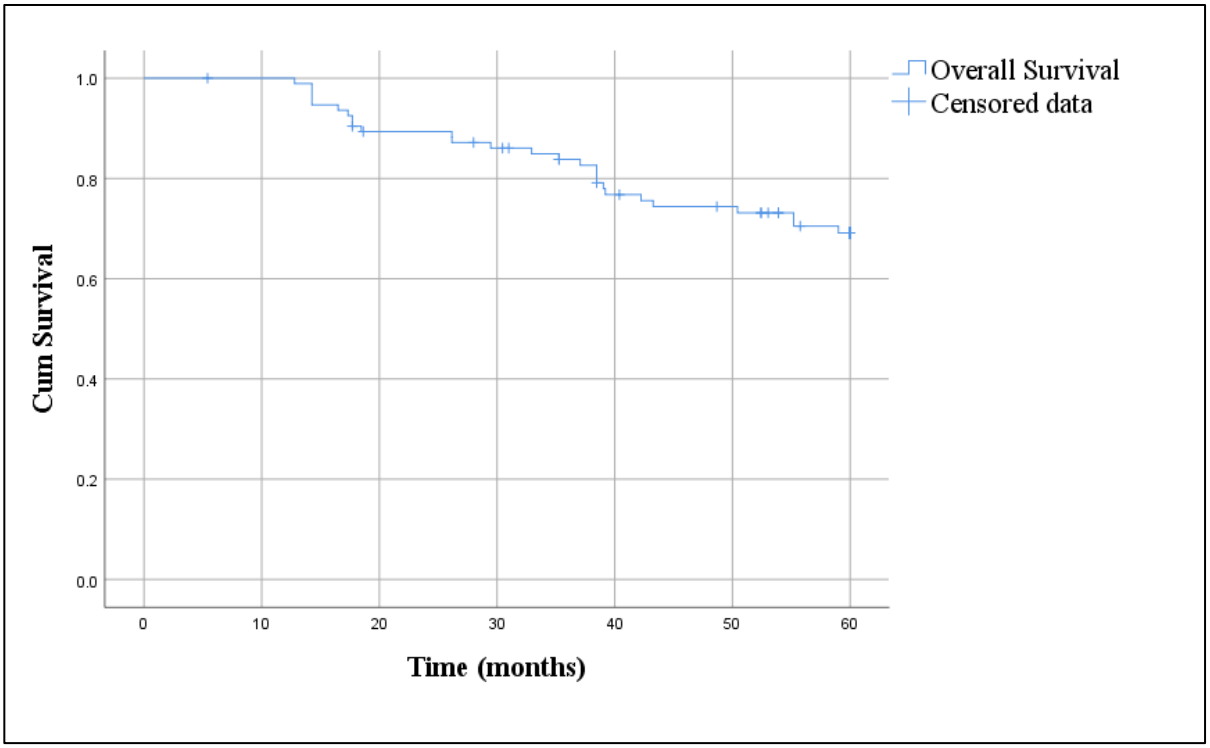

Figure 5: Overall Survival of study population

4.6 Progression Free Survival

The overall progression free survival for the entire group is depicted in Figure 6. The median progression free survival for the study population has not been reached. The stage grouping of those who had progressed compared to those who had not progressed was compared using Chi-squared test, this was not found to be significant (p=0.09) and is represented in the following Bar Graph - Figure 7. "Not documented" refers to the last visit where the attending clinician did not indicate whether there was any clinical or radiological evidence of progression.

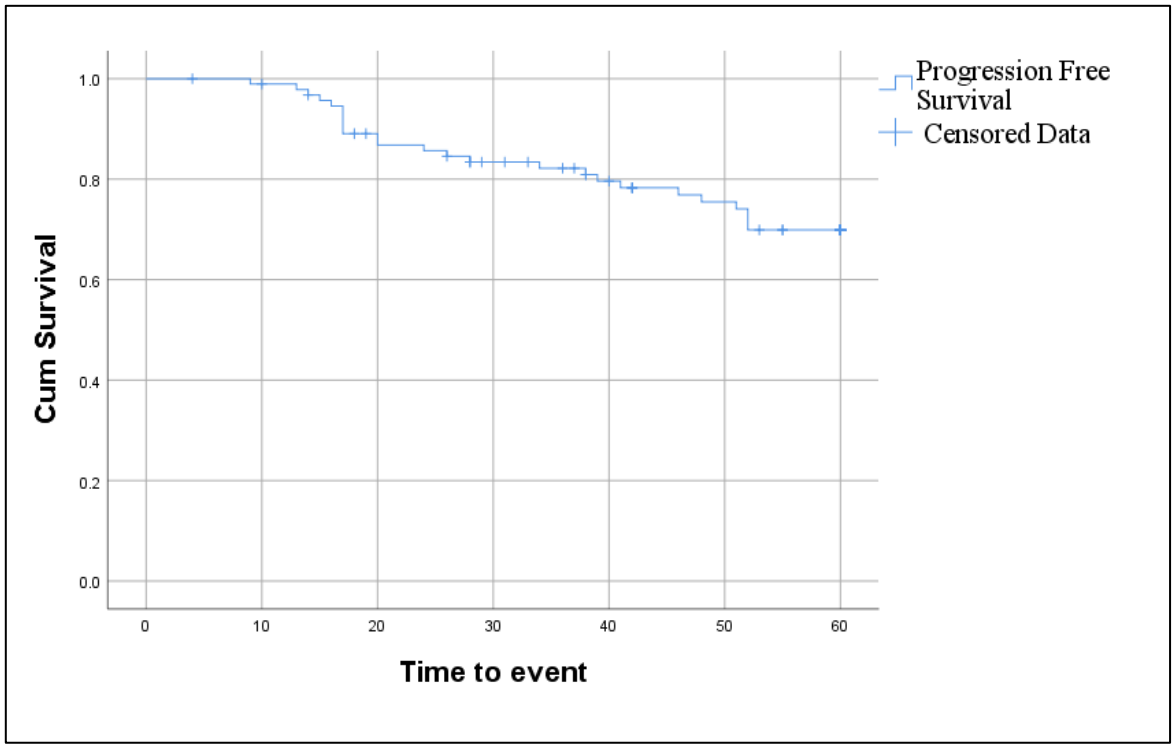

Figure 6: Progression free survival of study group.

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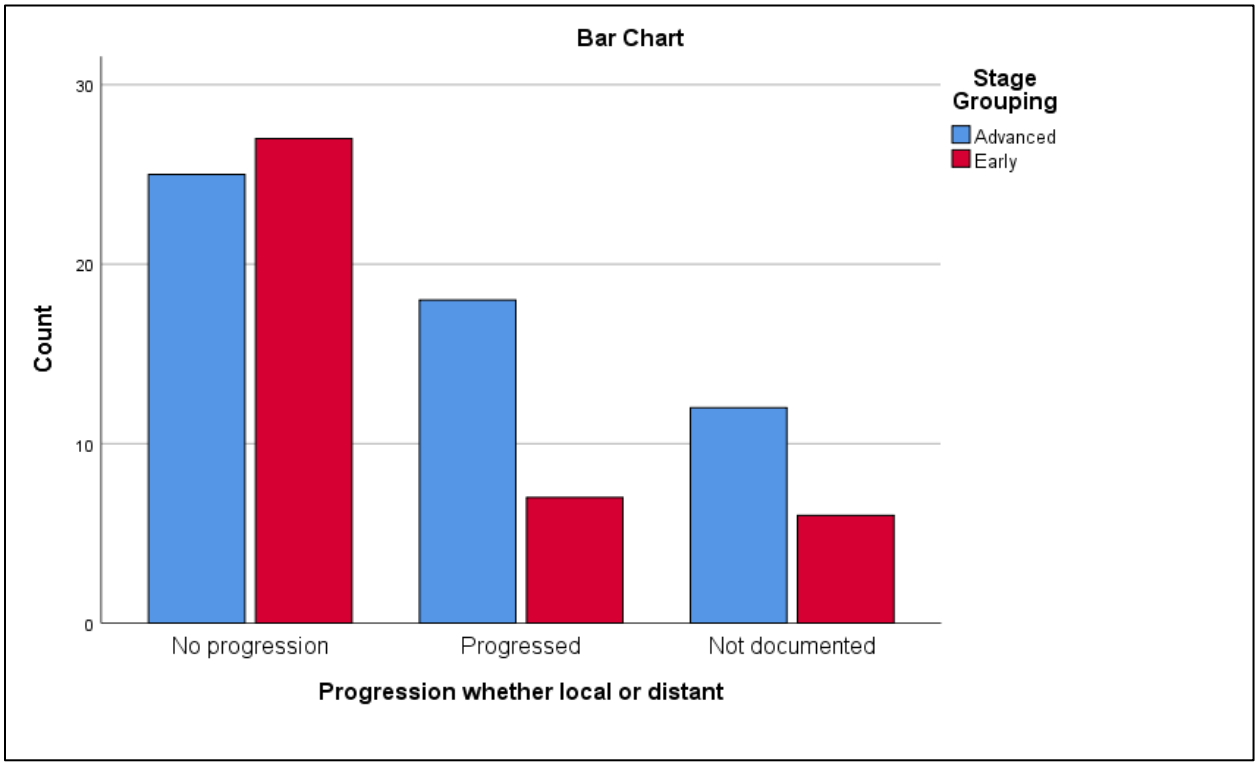

Figure 7: Progression Free Survival categories of study group.

4.7 Factors affecting breast cancer outcomes

Kaplan-Meier and Cox Proportional Hazard analysis

The overall survival (OS) for each of the factors affecting outcomes was considered. The data being presented considers patients that were lost to follow up. This data was right-censored. This means that data for patients who were LTFU is still considered even though it is incomplete. The Median Survival is not reached as only 27 patients are confirmed dead for the 5-year time period.

Two significant findings were the number of involved nodes and quadrant involved. "Number of involved nodes" group had 3 categories, each category was compared to the other and the significant finding was between "No involved nodes" and "≥ 4 nodes" with a p-value of 0.029 HR 3.585 (95% CI 1.14 to 11.273). The reference group is "No involved nodes" and the Hazard ratio for this group is 1. This means that patients with ≥ 4 nodes have a 3.585 times risk of dying than those who do not have involved lymph nodes. This is a significant finding as the p-value is less than 0.05 and the confidence interval lower limit does not go below 1.

Overall Survival of early stage breast cancer had a trend towards improved overall survival than that of advanced stage breast cancer as HR was 1.419, however, this was not statistically significant as the confidence interval spans across 1 and p=0.1. The OS for each of the T-stage, N-stage and M-stage was not done as some of the groups have few numbers (less than 10) thereby skewing the results, with confidence intervals reaching infinity and p-values of 0.000. 5-year OS Early breast cancer survival was 77.9% while Advanced breast cancer survival was 62.9%. At 3 years, in this SP 92.5% overall survival for early stage breast cancer and 78.2% for advanced breast cancer.

The overall survival of patients who had had ALND was analyzed for adequacy of lymph node dissection.

The OS of those who had PNS was not significant as the p-value was equal to 0.057 and it should be less than 0.05 for it to be significant.

The median OS for all the factors analyzed is represented in Table 18.

The survival plot for involved nodes and quadrant involved is shown in Fig. 8 & 9 respectively.

Table 18: Median Survival and Cox Proportional Hazard Regression Analysis

Parameter	*Categories*	*Median survival (months)*	*Hazard Ratio*	*Confidence Interval*	*P-value*
Age at diagnosis	15 – 39	Not reached	1		
	40-49		0.545	0.175-1.696	0.527
	50-59		1.045	0.372-2.938	0.933
	60-69		1.119	0.763-3.202	0.853
	>70 yrs		0.237	0.028-1.968	0.182
Stage grouping	Advanced	Not reached	1		
	Early		0.498	0.216-1.147	0.101
	Metastatic	17.7	1.686	0.225-12.645	0.612
Histology	Invasive Ductal	Not reached	1		
	Invasive Lobular		1.019	0.594-1.749	0.945
	Other				
Grade	1	Not reached	1		
	2				
	3		1.295	0.711-2.358	0.395
Margins	Clear (≥ 2mm or no ink on tumour)	Not reached	1		
	Close (< 2mm)		0.887	0.542-1.452	0.634
	Involved				
Number of nodes excised ALND	< 8 nodes	Not reached	1		
	≥ 8 nodes		0.993	0.646-1.525	0.977
Number of involved nodes	0 nodes	Not reached	1		
	1-3 nodes		2.115	0.722-6.192	0.172
	≥ 4 nodes		**3.585**	**1.14-11.273**	**0.029**
Receptor Status	HR negative	Not reached	1		
	HR positive		0.837	0.364-1.928	0.677
	Her 2 negative	Not reached	1		
	Her 2 positive		1.181	0.407-3.329	0.759
	Triple negative	Not reached	1		
	Non-triple neg		0.712	0.301-1.686	0.440
DCIS component	Present	Not reached	1		
	Absent		0.878	0.601-1.284	0.503

Significant findings are in bold.

Parameter	Categories	Median Survival (months)	Hazard Ratio	Conf. Interval	P-value
Lymphovascular Invasion	Present	Not reached	1		
	Absent		0.905	0.420-1.953	0.800
	Not stated				
Perinodal Spread	Present	Not reached	1		
	Absent		0.438	0.187-1.024	0.057
	Not stated				
Laterality	Right	Not reached	1		
	Left		0.958	0.450-2.040	0.912
Quadrant involved	Outer	Not reached	1		
	Inner		**2.419**	**1.062-5.511**	**0.035**
	Mid		0	0	
	Retroareolar		1.102	0.311-3.906	0.880
	Upper		1		
	Lower		1.248	0.492-3.166	0.641
	Mid		0	0	-
	Retroareolar		0.811	0.238-2.768	0.738
Surgery	Mastectomy	Not reached	1		
	Breast Conservation		0.784	0.461-1.334	0.370
Chemotherapy	Neoadjuvant	Not reached	1		
	Adjuvant		0.805	0.361-1.794	0.596
Radiation Field	Chest Wall only	Not reached	1		
	Chest wall and supraclav nodes		1.327	0.728-2.419	0.355
Radiation Dose	40.05 Gy	Not reached	1		
	50 Gy		1.484	0.599-3.679	0.394
Boost given	Yes	Not reached	1		
	No		1.088	0.744-1.590	0.665
Time from biopsy to initial treatment	Up to 3 months	Not reached	1		
	> 3 months		1.115	0.675-1.842	0.972
Waiting time for Radiotherapy	> 6 months	Not reached	1		
	3-6 months		1.216	0.301-4.903	0.784
	Up to 3 months		1.153	0.368-3.611	0.807
Overall treatment time	< 9 months	Not reached	1		
	9-12 mnths		1.127	0.626-2.030	0.690
	> 1 year		1.088	0.487-2.429	0.837

Significant findings are in bold.

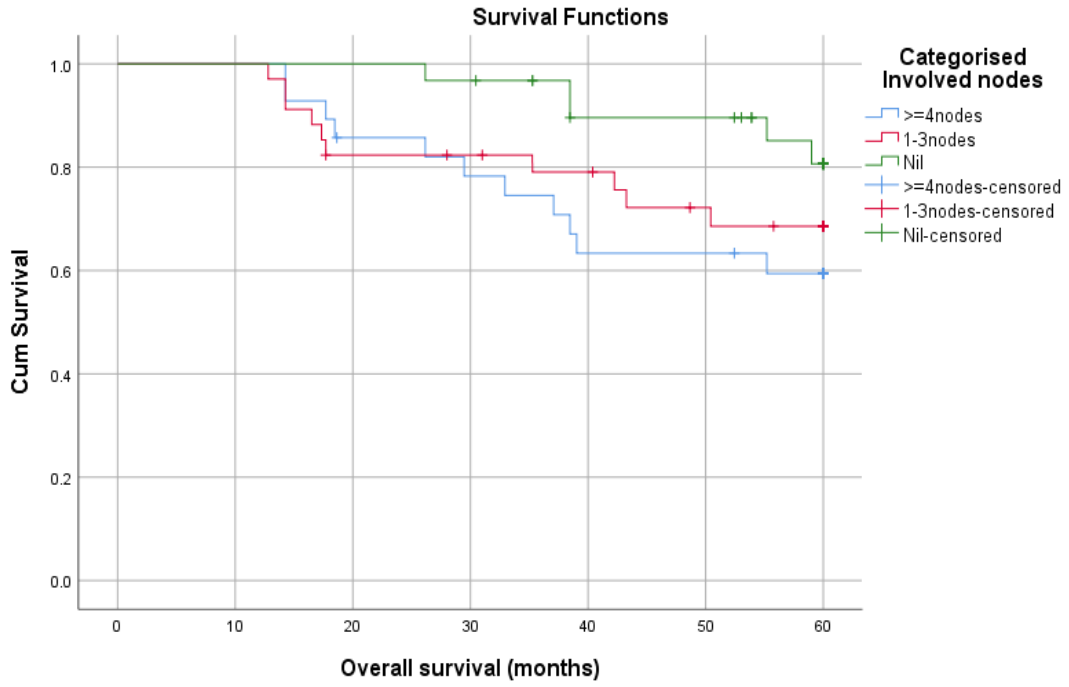

Figure 8: Kaplan-Meier analysis of survival by categorisation of involved nodes

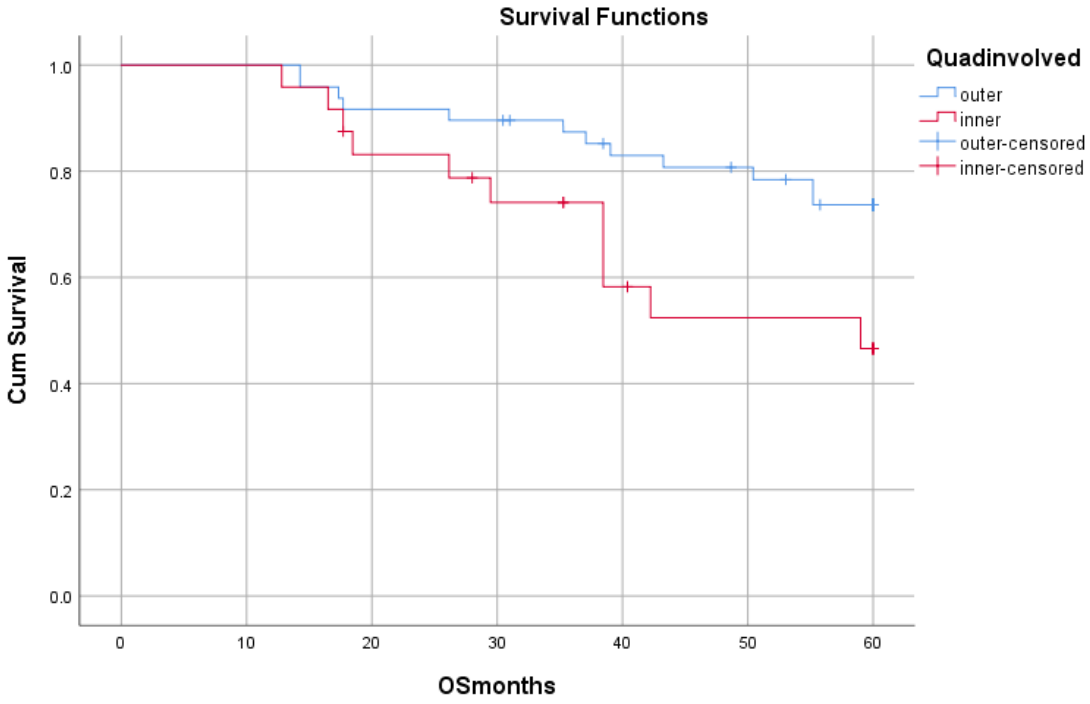

Figure 9: Kaplan-Meier analysis of survival by Quadrant Involved

CHAPTER 5: DISCUSSION

This chapter discusses the findings presented in the results section compared with local and international findings where literature was available.

Referral Hospital

Most of the patients attended in the Department of Radiation Oncology at CMJAH are from CMJAH, Helen Joseph Hospital which is located about 8 km away, and CHBAH which is 22km away. The percentage of patients from other hospitals is far less possibly due to the distance from CMJAH, e.g. Thelle Megoerane is almost 40km away.

Age

This is in keeping with previous data, Cubasch et al (32) had 48% of the study population (SP) below the age of 50 and 52% above the age of 50 years. The median age at diagnosis was 50 years, this is slightly lower than Phakathi et al where Median age was 54 years (33). The SP in the study by Phakathi et al enrolled 1050 patients from both CHBAH and CMJAH and is more representative of the Johannesburg population. Studies done in other Low to Lower-Middle Income African countries (Kenya, Nigeria, Tanzania, Morocco) ranged from 42.7- 46.9 years, except for 1 study done in Cape Town where Median Age was 56 years (6) the methodology of these studies was not reported in the review by Vanderpuye et al, it is therefore difficult to draw conclusions if the SP in this study has a higher median age attributed to Socioeconomic status, as South Africa is considered an Upper-Middle Income country (34).

The Mean age in this SP was lower than that in the UK START A and B (51.6 yrs vs.57.2 and 57.4 years respectively (27,28)), the UK is an Upper Income Country. The START trials had different populations where patients had early stage breast cancer while in this SP the patients were heterogenous with early, advanced and metastatic breast cancer. The findings in this SP appear as if patients referred for Radiotherapy at CMJAH are slightly older than in other Low to Lower-Middle Income African countries but younger than patients referred for Breast Surgery in Soweto and Cape Town and in other first world countries, however as previously mentioned, it is difficult to draw conclusions due to the small population size and the different methodologies used in obtaining data.

In this SP, younger age was not a factor associated with worse prognosis as is seen in other studies (25). It was not possible to collect information on whether the deaths observed were due to breast cancer or another cause, Cubasch et al (25) collected information on deaths from ambient data and hospital records, therefore they also could not attribute mortality to breast cancer alone. It is possible that women aged above 60 for example died due to other causes and not from breast cancer. Life expectancy using Global Life Expectancy Tables for South African females by WHO at that age would need to be considered before making any assumptions. Additionally, in this SP patients with TNBC had similar survival rates compared to non-TNBC which in the literature is associated with higher mortality (6,25).

Stage

A greater proportion of patients in this SP have advanced disease while Cubasch et al (32), found 66.1 % have early breast cancer and 33.9% have advanced breast cancer. The difference in stage presentation maybe because early breast cancer in some instances is not referred for RT. Cubasch et al (32) followed-up patients from Diagnosis while the SP referred for RT is further downstream in terms of treatment. Patients with T1 or T2 lesions without nodal disease or without high risk features such as Age ≤ 40 years, Tumour size ≤ 5 cm, Lymphovascular Invasion who have had a Mastectomy are not referred for Radiotherapy, this may be an explanation for the observed differences. Additionally, Cubasch et al (32) did not include patients with T4 disease.

Cubasch et al (25) reported 3 year survival rates of 84% for early stage breast cancer and 56% for late stage breast cancer. The 5 year survival rates for early breast cancer in this SP rates are comparable to global rates, while advanced breast cancer survival rates are better than global averages (22), however it is not known whether the patients in the global study received Surgery, Systemic therapy and Radiotherapy.

Adequacy of nodal dissection

The rate of adequacy of lymph node dissection was higher than the Danish 82c (18) study which had 40% of the population with ≥ 8 lymph nodes dissected while 60 % had <8 lymph nodes dissected. The Danish study was conducted in the 1980's. This possibly demonstrates the difficulties that surgeons face in dissecting adequate numbers of axillary

nodes, and coupled with high rates of lymphoedema post operatively was likely the impetus for SLNB (59).

In this SP, the number of axillary nodes excised was not a significant factor in the overall survival of patients. This compares to findings in the 2 Ebner et al studies (35,36) where removal of > 10 axillary lymph nodes did not result in a significant survival benefit or in recurrence free survival. Ebner et al (35), looked at a database with 2992 women included in the study, about half of the patients did not adhere to recommended guidelines which included systemic therapy and radiotherapy, however, there is no indication as to which part of the guideline the patients were not adherent to. Additionally, the mean age in the Ebner studies was 62 years, T1 made up 38.2%, T2 made up 52.6% and T3/4 made up 9.2%. Almost 60% of the population had 1-3 positive LN's, 24.5% had more than 4 but less than 10 positive lymph nodes and 16.4% had more than 10 positive LN's. The differences in the stage of the population in the Ebner study makes comparison difficult (36).

Number of Involved Lymph Nodes

Ko et al in New Zealand (2015) (37) enrolled 133 patients and had patients up to Stage III disease which is comparable to this SP however they had almost half of the patients with ≥ 4 lymph nodes while this SP had up to one third. This could be because of better pathology services where the pick up rate is higher. The Royal Marsden study which enrolled 1410 women looked at early breast cancer and therefore had higher percentages of N0 (67.3%), 1-3 nodes in 24.1% and 8.6% of SP having ≥ 4 LN's (26). In the SP, OS for the number of nodes involved showed statistical significance as the Hazard ratio for the group with ≥ 4 involved nodes was greater, this is expected and is comparable to current scientific knowledge that lymph node involvement has a worse prognosis. In a systematic review by Headon et al (60), in women with 1–3 positive lymph nodes, post-mastectomy radiotherapy (PMRT) significantly reduced the risk of loco-regional recurrence and improved overall survival by 3% compared to those in whom PMRT was omitted. The overall survival in the SP corresponds to the expected survival of more than 5 years in the literature review for those who have 3 or less involved lymph nodes. However, this finding was for postmenopausal women who had Stage II or III breast cancer in the Danish 82c study (18). Data on menopausal status was not collected in

patient files making it difficult to look at overall survival in this particular group of patients, unless an assumption is made that patients above 50 years are postmenopausal.

Hormone Receptor Status

Oestrogen receptor positivity is comparable to the Cubasch et al (32) study, 62% of SP were ER positive.and another study done in Cape town, 64% were ER positive. TNBC is also comparable to the Cape Town study that had 16% (6). Mullooly et al in Ireland, 2017 (61) looked at over 22000 people with breast cancer, 82% were ER positive. This is higher than in our population which could be due to genetic differences..

Hormone Receptor status was not assessed in the START A & B trials and in the Danish trials (18,19,27,28). Her2 positivity is comparable to Mullooly et al which comprised 18% of the population (61) but in contrast to the Cape Town study where Her 2+ cancers comprised 3 times the number in this SP.

Regarding the influence of the Hormone Receptor status on Overall Survival, when comparing with the local study by Cubasch et al (25), the profiles that had a significant finding on HR were the ER- status with a HR of 2.5X that of ER+ tumours and TNBC with a 3 fold increase in HR compared to ER+ cancers. In this SP, the HR for non-TNBC was found to be less than TNBC, however the findings were not statistically significant.

Grade of Tumour

Grade of tumour was very similar to the Cubasch et al (25) study, where 49.2% of the SP had Grade 2 tumours, approximately 40% had Grade 3 tumours, while roughly 11% had Grade 1 tumours. This was in contrast to the UK START trial B (28), the SP tumour grades were Grade 1 – 28%, Grade 2 - 47.4%, and Grade 3 – 23%. Also in contrast to the Danish study 82c in post-menopausal women, the distribution of SP tumour grades were Grade 1-24%, Grade 2- 44% and Grade 3-16% (18). The Danish study in premenopausal women had incidence rates for Grade 1,2 and 3 of 21%, 41% and 21% respectively.

Therefore, the two Danish studies had a different distribution of tumour grade to both this SP and that of Cubasch et al (25). The Grade of the tumour did not impact the OS as the number in the Grade 1 group was small. The findings were not statistically significant. The Danish studies showed a statistically significant result for the effect of tumour grade and overall survival as well as disease free survival (18,19). The Cubasch study did not

show statistically significant results after 4 years with adjusted HR as p-value was >0.05 (25). These findings could again be reflective of the pathology services that attend to a large population thereby spending less time looking at each specimen.

Histology

Histology of the SP comprising the ID and IL components were comparable to Cubasch et al study (32), however the other histologies made up a higher percentage in this SP as these included Medullary, Mucinous, Invasive Papillary, Squamous Cell Carcinoma, Malignant Mesenchymoma, Mixed Ductal and Lobular vs. 0.7% had mixed ductal and lobular while 0.7% had other types of histology in the Cubasch study (32).

The UK START trial B (28) had 3 times the percentage of Invasive Lobularas did the Danish study (18). The lower incidence of lobular cancer in both studies done in Johannesburg may be reflective of the pathology services in our setting.

In this SP, Invasive lobular cancer seemed to have a better prognosis than Invasive Ductal Cancer, however the findings were not statistically significant (46). In the Danish studies, OS was better with IDC than ILC in Premenopausal women however, it was also not statistically significant. In post-menopausal women, findings were that OS was better in ILC than IDC. In this SP, the number of patients with ILC was 4, therefore drawing conclusions from this small sample size is not appropriate.

In-situ component

In this SP, the findings with IDC in the presence of DCIS showed no statistically significant difference in Overall Survival when compared to IDC without DCIS. DCIS when present with IDC was significantly associated with a better prognosis as was seen in a study by Kole et al in Alabama, USA in 2017(40) . Kole et al reported findings from a retrospective study done of a National Cancer Database in USA that included 515 044 women. 66% had IDC with DCIS while 34% had IDC alone. 5-year OS was 89% in the DCIS + IDC group versus 85% in the IDC alone group ($p<0.001$ HR 0.73 95% CI 0.72-0.74).

Margin status

In this SP and in the Department of Radiation Oncology at CMJAH, involved margin was considered to be “Ink on tumour” or tumour seen at surgical margin. A close margin was deemed as < 2 mm, while ≥ 2 mm would be considered a clear margin. This contrasts

with studies reported in the literature, Cubasch et al (32) reported their findings using >1mm, ≥1mm & ≤5mm and 5-10 mm. However, a study done by Rubio et al from Spain, 2016 (42) considered "Ink on tumour" as involved margin and a close margin as ≤ 2mm and clear margin of > 2mm as 10 year local recurrence did not detect any difference in women with early breast cancer undergoing BCS.

Margin status is more of a risk when breast cancer is inflammatory as was seen in a meta-analysis conducted by Rowell et al from Kent, UK in 2010(41), information about inflammatory breast cancer was not collected in the present SP.

When compared to a review and a study done by Tyler et al (42,43), margins in the local SP are comparable. The same thresholds were used to determine what are close and what are clear margins, making comparison reliable. In this SP, there was no significant difference observed in the OS of patients who had involved, close or clear margins. In the study done by Tyler et al involved, close and clear margins had 10-year Breast Cancer Specific Survival (BCSS) of 93.9%, 91.8%, and 87.9%, respectively (P <0.001) (43), comparison is difficult because the local SP included patients who had Mastectomy and BCS while the Tyler study only looked at patients who had had BCS. In the local SP, there is no difference in the 5-year OS while the study done by Tyler et al shows decreased 10 year survival BCSS when margins are either involved or close.

Perinodal spread

In a 2015 Texas study by Drinka et al (44) done in patients with pT1 tumours with 1-3 nodes positive, 21.6% of patients had Perinodal spread (PNS). In this SP, overall PNS was low compared to the Drinka study as our SP had only 5.3% with T1 disease and this group did not have PNS, the group is too small to draw conclusions that patients in this SP are not prone to PNS. Drinka et al (44) also found that both disease free survival and overall survival were reduced, however on multivariate analysis this was true only before the year 2000, post 2000, Perinodal spread influence on OS had diminished over time, which could be reflective of the influence of neoadjuvant chemotherapy on breast cancer outcomes.

Lymphovascular Space Invasion

LVSI was comparable to Cubasch et al study (32) where LVSI was present in 38.2% of the SP and absent in 45% of the SP. In New Zealand, a study found LVSI of 63.2% in its SP and absent in 36.8 (37). Most of the other comparative studies did not report this on their SP's. It is interesting that although 32.6% of the SP had no involved nodes, LVSI was absent in 46.3% of SP. For the 65.3% who had involved nodes, LVSI was present in only 33.7% of the population. There was no statistically significant difference in the OS in patients who had LVSI compared to those that did not. This is in contrast to the systematic review done by Rowell et al (41) where the HR's showed between 1.81 to 6 fold increases in the risk of death when LVSI was present. A larger sample size may have produced different results. Further analysis into premenopausal or postmenopausal factors may also have an impact in the findings.

Laterality

In this SP, the percentage of right versus left breast was almost 50%. This is comparable to a study done of patients in the Swedish breast cancer registry (47). The OS of patients with left breast cancer vs those with right breast cancer was the same. This is in comparison to the findings in the literature where although risk of cardiovascular disease was greater among patients with left breast cancer, the overall survival remained the same (46,47).

Quadrant involved

The clinical relevance for looking at the quadrant involved is mostly to determine if there is any benefit from irradiation of Internal Mammary nodes for tumours that are located in the inner quadrants. Upper Outer quadrant incidence in this SP is comparable to a UK study (48). The OS for outer quadrant tumours was 53 months versus 46 months for inner quadrant, and was statistically significant. These finding are comparable to SEER data where inner quadrant tumours had statistically significant worse OS outcomes HR 1.11(95% CI 1.03-1.19 p=0.004) (49).

Type of Surgery

The types of surgery that patients in this SP underwent, is similar to the local study conducted by Cubasch et al (32). The time periods for the 2 studies overlap. Another study done in Cape town showed higher rates of BCS of 30.5% and Mastectomy rates of

69%. This study was conducted from 2010 to 2014, during a later time period which may demonstrate the rising trend toward BCS (50). In this SP the Univariate analysis shows no statistical significance when comparing OS of Mastectomy vs BCS, a matched analysis of early stage cancer was also not statistically significant. This is in contrast to a systematic review conducted that showed that Mastectomy has an OS benefit when compared to BCS in early breast cancer (51).

Role of Chemotherapy - whether Neoadjuvant or Adjuvant

Concerning the chemotherapy that was received, this is similar to results from a local study done by Ruff et al (53). The percentage of those receiving neoadjuvant chemotherapy corresponds to the precentage of patients with advanced disease. This is in keeping with recommendations to down size a tumour to make it more operable. The percentage of those receiving Adjuvant chemotherapy was half and reflects that those with early disease had other indications for receiving adjuvant chemotherapy such as a tumour size above 1cm, positive lymph nodes detected after surgery, or Oestrogen receptor negative disease.

Radiation Field

The Radiation Field had a significant proportion receiving Chest wall and Regional Nodal Irradiation reflective of the more advanced disease presentation. In the Ko et al (37) study with different patient characteristics predominantly early stage disease , the percentage of Chest wall and Supraclavicular nodes was 39.8%, Chest wall only was 38.3%, Chest wall, supraclavicular and axillary nodal regions was 21.8%.

The indications in our SP for Chest wall only Radiotherapy included Positive margins despite reexcision being done as well as Triple Negative disease which is slightly different to the standard guidelines therefore it is difficult to compare. In this SP, Supraclavicular fossa Radiotherapy could have been avoided in about 18% of the subgroup that had NACT and then surgery, were clinically Node negative at presentation and ypN0 post-surgery. Of the subgroup that had received adjuvant chemotherapy following surgery and adjuvant radiotherapy following ACT, 11% of patients who had 1-3 nodes, were initially N0 and did not have high risk features such as T3 tumour or Grade 3, received supraclavicular fossa radiotherapy and this could have been avoided.

It was difficult to make out the indications for a Posterior axillary field as there were only 5 patients who received this and there were inconsistencies in that early stage patients without nodal involvement received this as well as advanced stage patients with nodal involvement.

Radiation Dose

The Radiation Dose included 82% with a hypofractionated regimen and 18% with a standard fractionation. The initial calculation for sample size was done using 35% for hypofractionated regimen and 65% for standard fractionation, however the uptake for hypofractionation was excellent following publication of the UK START trials in 2008 (23,28). Therefore, most of the patients included had undergone hypofractionation. Ideally, the sample collected should have been greater to account for this gap, however due to time constraints, this was not possible.

ASTRO guidelines (2011) recommended HF-WBI to patients who had BCS, were early T1-T2 tumours without nodal involvement, had not received previous chemotherapy In our SP, 69% of patients who had BCS received nodal irradiation using hypofractionation, however updated ASTRO guidelines (2018) which compare with 2011 guidelines still recommend that HF-WBI is given to the chest wall only (15).

Radiation Boost

A boost was given to both groups of patients receiving Mastectomy or Breast Conserving Surgery (BCS) using electron field. It was however done more frequently in patients with Advanced breast cancer rather than early breast cancer. It was done 90% of the time in those who had BCS. This is in contrast to START B patient characteristics, where Boost was conducted in 42.6% of patients who had received BCS (28). The local recurrence rate was 5.3% in this SP, while in the START B trial it was 2.2% which is similar and a low incidence.

Waiting Times

Departmental waiting times showed that 61% of the SP had received Radiotherapy by 3 months. A survival analysis comparing the OS of those who had received Radiotherapy between 1-2 months and those who had received it between 2-3 months showed no significant difference. This is in contrast to the findings in the systematic review done by Gupta et al (54) where the relative risk of death increased by 0.99 per month of delay

in radiotherapy. A larger sample size would have been better positioned to detect any differences as there are several other factors that may have had a role to play.

Local Control

The documented 5-year Local recurrence rate is similar to that found in the 4 landmark trials in Hypofractionated Breast Irradiation which ranged from 4.3% to 9.6% over 10 years (27). However, 23.2% of the study population had documentation lacking on the presence of progression making this comparison unreliable.

Overall Survival

The 5-year overall survival is better than that found in the African Region with rates as low as 28% (22). This rate is influenced by the loss-to-follow-up-rate (LTFR), which is approximately 23.5% and is similar to LTFR's found in retrospective studies done in The Gambia, Nigeria, South Africa and Uganda where the ranges for LTFU were 22%-42% and lower than the Cubasch et al study (25) where there were 42% overall LTFU over 3 years. The difference between the present study and Cubasch study could be explained by the losses that Cubasch attributed to patients who were LTFU without receiving treatment, in the first 30 days, 53% of those who were LTFU had not received any treatment at all (25).

Progression Free Survival

The median progression free survival has not been reached. The median time for disease free survival in a study in Poland which is a high income country was 19.4 months while median overall survival time was 76.4 months (24). In Cubasch et al (25), disease free survival was not examined. Median overall survival seems to be longer than 5 years even in our setting with locally advanced breast cancer making up more than half the study population. However due to significant missing data, it is not possible to definitively say that median overall survival is longer than 5 years.

5.1 Conclusion

The study findings appear reliable as 11 out of 20 variables examined had comparable results to local and international studies. The exceptions were adequacy of nodal dissection, DCIS, margins, PNS, Rdiation Fields, Boost irradiation, waiting times, local control, overall survival and PFS. Hypofractionated radiotherapy has favourable outcomes in our setting at least equivalent to other low-middle income countries. The loss-to-follow-up rate makes analysis reliable in descriptive statistics but not reliable in survival analysis. Patients with a higher number of nodal involvement are likely to have worse outcomes. Patients with inner quadrant tumours also have a lower overall survival indicating the need to explore further on inclusion of internal mammary lymph nodes in the Radiation Field.

5.2 Recommendations

Establishing a departmental database and regularly collecting information on patient outcomes to facilitate timely data analysis is recommended. A larger scale study should be done to enable meaningful conclusions. Study should be repeated over another era to enable comparisons on outcomes in order to offer recommendations. A quantitative/qualitative study is recommended into reasons why women have difficulties attending follow up. It may be necessary to provide an incentive to patients to attend follow-up clinics to reduce loss-to-follow-up. Careful selection of patients to receive the correct type of radiotherapy will aid in improving outcomes. Identifying patients needing radiotherapy at Multidisciplinary Team Meetings to plan scheduling ahead of time may be useful.

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APPENDICES

Appendix A Approval Letters

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr AMG Bunga

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180626

NAME: (Principal Investigator)	Dr AMG Bunga
DEPARTMENT:	School of Clinical Medicine Department of Radiation Sciences Division of Radiation Oncology Medical School University
PROJECT TITLE:	Patterns of practice of breast cancer irradiation in the Department of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital 2010-2012
DATE CONSIDERED:	29/06/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor V Sharma
APPROVED BY:	CB Penny Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/08/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature — Date: 24 August 2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Tell: (011): 488-4812
Email: Nolwazi.Mzila@gauteng.gov.za
5th October 2018

GP_201808_031

Dear Dr. Antonia M. Gonzalez Bunga

STUDY TITLE: Patterns of Practice Breast Cancer Irradiation in the Department of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital 2010 -2012

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 9/10/2018

Approved/~~not approved~~

Ms. G. Bogoshi
Chief Executive Officer
Date: 10/10/2018

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

26 June 2018
Person No: 1064863
PAG

Dr AMG Bunga
P O Box 150240
0000
Botswana

Dear Dr Bunga

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Patterns of practice of breast cancer irradiation in the Department of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital 2010-2012* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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10 October 2018

Dear Dr Bunga,

RE: PERMISSION TO CONDUCT STUDY OF PATIENT FILES

As discussed you may collect data for your MMed study in the Medical Oncology Clinic, Area 495.

Please make sure that I am kept informed as to the progress of your study.

Sincerely yours

PROFESSOR PAUL RUFF
PROFESSOR AND HEAD
DIVISION OF MEDICAL ONCOLOGY

11th January 2019

The Head of Anatomical Pathology (NHLS)

Charlotte Maxeke Johannesburg Academic Hospital

Dear Sir / Madam,

My name is Dr AMG Bunga, a senior registrar in the Department of Radiation Oncology. I am completing an MMed entitled "Patterns of practice of breast cancer irradiation in the Department of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital". This study is a retrospective record review using hospital files, on patients that had undergone radiation therapy. We have obtained the necessary clearances, including Ethics (M180626) and permission from the Hospital CEO, to undertake this study, however upon reviewing the patient files we noticed that some records (histological examination results) were incomplete. We therefore request your assistance in this regard, to please access some of the histological findings (± 5 patients).

A letter of amendment to the protocol for this request will be submitted to the ethics committee as soon as your assistance and permission to access the results is granted.

In anticipation of a favourable outcome I thank you for your assistance.

Permission granted
P.J. SWART
(Acting HOD)
11/1/2019

Kind regards

Dr AMG Bunga

Senior Registrar
Department of Radiation Oncology
1064863@students.wits.ac.za

Appendix B Data Collection Sheet

Identification

Study Identification number

Sex

☐ Male ☐ Female

Ethnicity

☐ Black ☐ White ☐ Indian ☐ Mixed Race

☐ Chinese ☐ Other

Age at diagnosis _____

Clinical details

Date first diagnosed _____

☐ Wide local excision (partial mastectomy, quadrantectomy or segmentectomy)

☐ Re-excision

☐ Mastectomy

☐ Mastectomy post neoadjuvant therapy

☐ SLNB ☐ ALND

Initial investigation to rule out mets

☐ CXR ☐ CT scan ☐ MRI ☐ Bone scan

☐ USS ☐ Blood Tests

Initial tumour site and size

☐ Right ☐ Left

☐ Upper quadrant ☐ Lower quadrant

☐ Outer quadrant ☐ Inner quadrant

Size: _____mm

Biopsy

Tumour size _____mm X_____ mm X mm

Initial nodal involvement

Location _____

No. of involved nodes _____

Total number of nodes excised _____

☐ Extracap extension

PROCEDURE DONE AND TIME LAPSE BETWEEN PROCEDURES

Procedure SURGERY	Order it was done	Time in months between procedures	Date conducted
CHEMOTHERAPY HORMONAL THERAPY			
RADIATION THERAPY			

Histologic grade (Bloom & Richardson)

☐ Grade 1 ☐ Grade 2 ☐ Grade 3

Invasive carcinoma subtype

☐ DCIS

☐ Invasive Carcinoma of No Special Type (Ductal)

☐ Invasive lobular carcinoma

☐ Other

State type: _____

Initial clinical stage
T _____ N _____ M _____

Initial pathological stage
T _____ N _____ M _____

Differentiation

☐ Poor ☐ Mod ☐ Well

☐ Not stipulated

Adjuvant treatment

☐ Yes ☐ No ☐ Not stipulated

Chemotherapy _____

Dates _____

Hormonal _____

Dates _____

Neo - Adjuvant treatment given

☐ Yes ☐ No ☐ Not stipulated

Regimen chemotherapy_____

_____

No. of cycles _____

Response?

☐ Partial ☐ Complete ☐ Nil

Assessed using: _____

Hormone Receptor Status

ER ☐ Pos ☐ Neg

PR ☐ Pos ☐ Neg

Her 2 ☐ 1+ ☐ 2+ ☐ 3+

Ki-67% _____

☐ LVI ☐ PNI

Treatment delivered

Prescribed dose: _____

Number of fractions: _____

Boost given: _____

Overall treatment time:

_____

Stated reasons for missed doses:

Treatment outcome														
	1st year				2nd year			3rd year			4th year		5th year	
	6/52	4/12	8/12	1yr	4/12	8/12	1yr	4/12	8/12	1yr	6/12	1yr	6/12	1yr
Alive, no local recurrence														
Alive, disease progressed														
LTFU														
Died due to primary disease														
Died from other causes														

Appendix C Variable Coding on SPSS

Variable	Categories	Values	Types of variable	Recoding
Age	Open	Numerical	Continuous/Input	Categorised 15-39 years 60-69 years 40-49 years ≥70 years 50-59 years
Initial T-stage	Open	Tx,T0,T1,T2,T3,T4	Categorical/Input	Nil
Initial N-stage	Open	Nx,N0,N1,N2,N3	Categorical/Input	Nil
Initial M-stage	Open	Mx,M0,M1	Categorical/Input	Nil
Stage grouping	Stage 1,2,3 or 4	Stage 1,2,3 or 4	Categorical/Input	1 & 2 – Early 4 - Metastatic 3 - Advanced
Number of excised nodes	Open	Numerical	Continuous	Categorised < 8 nodes ≥ 8 nodes
Number of involved nodes	Open	Numerical	Continuous	Categorised 1-3 nodes ≥ 4 nodes
Hormone Receptor Status	ER+/PR+/Her2- ER+/PR+/Her2+ ER+/PR-/Her2- ER-/PR-/Her2- ER-/PR-/Her2+ ER-/PR+/Her2-	ER+/PR+/Her2- ER+/PR+/Her2+ ER+/PR-/Her2- ER-/PR-/Her2- ER-/PR-/Her2+ ER-/PR+/Her2-	Categorical	HR positive / HR negative Her 2-positive / Her 2-negative Triple negative / Non-triple neg
Grade	Grade 1,2,3	Grade 1,2,3,	Categorical/Input	Nil
Histology	Invasive Ductal, Invasive Lobular, Paget's Other	Invasive Ductal, Invasive Lobular, Paget's Other	Categorical/Input	Nil
Histology – in-situ component	DCIS, LCIS	DCIS, DCIS-Solid, DCIS – Cribriform, DCIS – Comedo, DCIS-Medullary, DCIS – Papillary, LCIS, Nil	Categorical/Input	DCIS Present DCIS Absent

Variable	Categories	Values	Types of variable	Recoding
Margins	Involved Clear Close No primary tumour	Involved Clear Close No primary tumour	Categorical/Input	Nil
Perinodal Spread	Present Absent	Present Absent	Categorical/Input	Nil
Lymphovascular Invasion	Present Absent	Present Absent	Categorical/Input	Nil
Laterality	Right Left	Right Left	Categorical/Input	Nil
Quadrant Involved	Upper, Inner, Mid, Retroareoalar,	Upper, Inner, Mid, Retroareoalar,	Categorical/Input	Outer Retroareolar Inner
Quadrant Involved	Outer,Inner,Mid	Outer,Inner,Mid	Categorical/Input	
Surgery	Wide Local Excision, Mastectomy, Mastectomy after Neoadjuvant Chemotherapy, Re-excision.	Wide Local Excision, Mastectomy, Mastectomy after Neoadjuvant Chemotherapy, Re-excision.	Categorical/Input	Breast Conserving Surgery Mastectomy
Chemotherapy	Adjuvant Neoadjuvant	Adjuvant Neoadjuvant	Categorical/Input	Nil
Radiation Field	Tans & Boost, Tans & Drain Site, Tans & Drain Site & Boost, Tans & Scar & Drain Site & Boost, Tans & Supraclavicular Nodes, Tans & Boost & Supraclavicular Nodes, Tans & Drain Site & Supraclavicular Nodes, Tans & Drain Site & Boost & Supraclavicular Nodes, Tans & Scar & Supraclavicular Nodes, Tans & Scar & Boost & Supraclavicular Nodes, Tans & Scar & Drain Site & Supraclavicular Nodes, Tans & Scar & Drain Site & Boost & Supraclavicular Nodes, Tans & Supraclavicular Nodes & Posterior Axilla, Tans & Boost & Supraclavicular Nodes & Posterior Axilla, Tans & Supraclavicular Nodes & Internal Mammary & Boost	String	Categorical/Input	Chest Wall Chest Wall & Nodes
Radiation Dose	Open	Numerical	Continuous/Input	40.05Gy 50Gy

Radiation Boost	Open	Numerical	Continuous/Input	Given Not given
Time to event	Open	Numerical	Continuous/Output	Nil
Variable	Categories	Values	Types of variable	Recoding
Type of Progression	Nil, Local Recurrence, Distant mets – lung, distant mets – brain, distant mets – bone, distant mets – bone, lung, brain, Progressive disease-not documented what type of recurrence, local recurrence with bone mets, Contralateral breast	Nil, Local Recurrence, Distant mets – lung, distant mets – brain, distant mets – bone, distant mets – bone, lung, brain Progressive disease-not documented what type of recurrence, local recurrence with bone mets, Contralateral breast	Categorical/Output	0 - Nil 1 - Present
Treatment Outcome	Alive Died	Alive, no progression for 5 years Alive, progressed at some time point then LTFU Alive, progressed at some time point, no LTFU LTFU at some point Died, unknown if due to primary disease or other cause	Categorical/Output	Nil

Appendix D Sample Size Calculation

power two proportions 0.65 0.35, test(chi2) nratio(2) nfractional Performing iteration ...

Estimated sample sizes for a two-sample proportions test

Pearson's chi-squared test

Ho: p2 = p1 versus Ha: p2 != p1 Study parameters: alpha =

0.0500 power = 0.8000 delta = -0.3000 (difference) p1 =

0.6500 p2 = 0.3500

N2/N1 = 2.0000

Estimated sample sizes:

N = 94.7372 rounded off = 95

N1 = 31.5791 rounded off = 32

N2 = 63.1581 rounded off = 63

Appendix E Turnitin Report

Turnitin Originality Report

Processed on: 01-Oct-2020 9:49 PM SAST
ID: 1402597693
Word Count: 17922
Submitted: 1

1064863:1064863_Bunga_Antonia.docx By Antonia Bunga