Hookwire Guided Breast Conserving Surgery at Charlotte Maxeke Johannesburg Academic Hospital Breast Unit

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Surgery.

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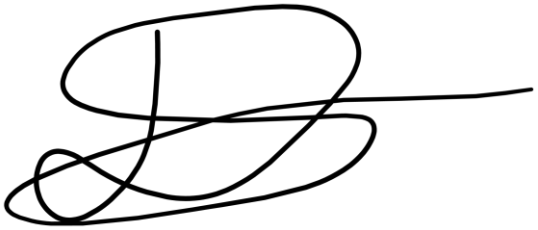
TABLE OF CONTENTS

DECLARATION

I, Danielle Simone Ferrar, declare that this research report is my own original work. It is being submitted for the degree of Master of Medicine in Surgery at the University of Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any other degree or examination at this or any other University.



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LIST OF ABBREVIATIONS

BCS: Breast Conserving Surgery

BIRADS: Breast Imaging Reporting and Data System

CHBAH: Chris Hani Baragwanath Academic Hospital

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

DCIS: Ductal Carcinoma in Situ

ER: Estrogen Receptor

HOD: Head of Department

HREC: Human Research Ethics Committee

IQR: Inter Quartile Range

LN: Lymph Node

NAC: Neo Adjuvant Chemotherapy

NHLS: National Health Laboratory Service

NIHR: National Institute for Health Research

RECIST: Response Evaluation Criteria in Solid Tumors

ROLL: Radioguided Occult Lesion Localization

RSL: Radioactive Seed Localization

SA: South Africa

SD: Standard Deviation

TNBC: Triple Negative Breast Cancer

WGL: Wire Guided Localization

LIST OF FIGURES

LIST OF TABLES

TITLE PAGE

HOOKWIRE GUIDED BREAST CONSERVING SURGERY AT CMJAH BREAST UNIT

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DISCLAIMERS

The authors declare no conflict of interest. No funding source to be declared.

ETHICS DECLARATION

Ethical approval was obtained from the Human Research Ethics Committee of the University of Witwatersrand (Ethics No. M230757 MED23-05-008) as well as the Chief Executive Officer of Charlotte Maxeke Johannesburg Academic Hospital. Due to the retrospective nature of this study, no patient informed consent was obtained.

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ABSTRACT

Background: Breast cancer is the most common cancer among South African (SA) women and a leading cause of cancer-related deaths. Historically, SA patients present with more advanced disease, but improved screening and radiological technology are increasing the detection of impalpable cancers. The gold standard for treating impalpable cancers is breast-conserving surgery (BCS), which requires pre-operative localization. At our institution, hookwire-guided localization, a method of wire guided localization (WGL), is the only method available. This study aims to assess if our practice of WGL aligns with international standards and to identify factors influencing recurrence.

Methods: We retrospectively reviewed records of patients who underwent hookwire guided BCS of breast carcinoma from 1 January 2016 to 31 May 2024 using the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) database.

Results: A total of 119 patients were eligible, with 55 having had malignancies excised via hookwire guidance. 76.7% presented with a self-palpated mass, and 14.5% were detected via screening. Most patients (50.9%) received neoadjuvant chemotherapy (NAC) to shrink the tumour. The median size of masses was 19mm. Of those undergoing hookwire guided BCS, 58.18% received radiation, with a median of 216 days from surgery to radiation (IQR 175 – 357). Margin positivity and re-excision rates were 10.9% and 12.7%, respectively. The recurrence rate was 25.5%, higher than international standards. TNBC (triple negative breast cancer) and NAC significantly increased the likelihood of recurrence.

Conclusion: Hookwire guided BCS at CMJAH has acceptable margin adequacy and re-excision rates compared to international standards. The higher recurrence rate likely results from delayed adjuvant radiation access. TNBC molecular subtype was a significant tumour-specific risk factor increasing recurrence risk.

1. INTRODUCTION

Breast cancer is the most common cancer globally and a leading cause of cancer-related deaths in women, accounting for 25% of all cancers worldwide[1]. In SA, breast cancer is the most frequently diagnosed cancer in women, comprising 24.1% of all cancer diagnoses[2]. The country is burdened with more advanced stages of the disease at presentation, with over 60% of patients presenting with stage 3 or 4 cancers. A local study has shown that only 8-10% of patients present with stage 1 disease[3]. The introduction of the Breast Cancer Control Policy in 2017, focusing on educational and screening programs, aims to improve early detection and reduce the late-stage presentation of breast cancer[4].

As imaging technology has improved, early detection of non-palpable breast cancers has increased. A case series in Soweto showed a reduction in stage 3 and 4 cancers from 66% to 46% over six years[5]. BCS involves a wide local excision (lumpectomy) followed by adjuvant radiation to eradicate any residual microscopic disease, is the preferred treatment for early-stage breast cancer. BCS offers survival rates superior to mastectomy when combined with adjuvant treatments[6-11]. The goal of BCS is to excise the entire mass while preserving cosmetic appearance and minimizing recurrence. Non-palpable cancers require pre-operative localization to ensure complete excision, with methods like wire guided localization (WGL), which is the standard at our institution.

While newer localization methods like radioactive iodine seed localization (RSL), radio-guided occult lesion localization (ROLL), and Magseed show potential, WGL remains the gold standard due to its effectiveness and cost efficiency. A 2015 Cochrane review affirmed that while newer methods may improve patient comfort and workflow, WGL still excels in localization, with no statistically significant differences in outcomes compared to RSL and ROLL[12,13].

More recently, the MELODY trial also recognized widespread use of WGL due to its favourable cost effectiveness and efficacy while also acknowledging its weaknesses including logistical difficulties, patient discomfort and the potential for dislodgement[14]. The comparison of different techniques differs from the Cochrane review as it shows although WGL, RSL and ROLL have similar excision success rates, WGL has both a higher rate of re-excision and positive margin rate compared to the newer methods[14]. This study aims to compare the safety, efficacy and outcomes of both WGL and the newer techniques in order to identify the most

effective and patient friendly methods of localization in order to assist with standardizing practices of preoperative localization.

Due to the high incidence of malignancies in non-palpable lesions, accurate diagnosis and excision of these lesions is therefore crucial [15 - 19]. Radiological features, such as microcalcifications and masses, can help predict malignancy in non-palpable lesions[17 - 19]. In impalpable malignancies the most common appearance for a malignancy on mammogram was calcifications (47%) followed by mass (41%), mass with calcifications (8%) and architectural distortions (4%)[20].

Recurrence is defined as breast cancer returning after a period of remission post treatment where no evidence of cancer was detected. Local recurrence refers to recurrence in the same breast or scar tissue of the same breast. Regional recurrence refers to recurrence in nearby lymph nodes. Distant recurrence refers to metastatic disease in distant anatomical sites. Multiple studies have focused on the factors that increase the risk of local recurrence and these include patient age, tumour size, tumour grade and multifocality[21]. These are factors inherent to the mass that are non-modifiable. The strongest predictor in local recurrence across all studies was the presence of a positive margin post excision[21, 22]. A large meta-analysis of 26 162 patients showed that a positive margin (defined as tumour present on the inked margin in this study) carried with it a two-fold increased risk of ipsilateral breast recurrence[22] and positive margins are an independent predictor of poor disease specific survival[21].

Positive margins are an important factor in BCS as it is a risk factor determined by the surgery itself and is therefore modifiable. The published rates of positive margins are 4 – 31%[23] with an average of 23%[13]. Tumour specific factors associated with positive margins include lobular histology, large tumour size, increased tumour grade, multifocality, extensive in situ component and lymphovascular invasion[23 - 25]. These factors are inherent to the tumour being excised and cannot be altered, however, a surgeon operating on a tumour with any of these known characteristics should keep that in mind when planning the surgery and amount of tissue to be excised.

Having a pre-operative diagnosis of carcinoma was a factor that was persistently and strongly associated with negative margins, most likely due to increased intent taken by the surgeon when operating on a confirmed cancer[23, 26]. Other surgical factors associated with negative margins include extra cavity dissection, correct specimen orientation and larger volumes excised[23].

These factors are important to be cognisant of as the surgeon as they can be altered intra-operatively to positive affect the margin status. The above factors are relevant

Due to the strong association of margin positivity on local recurrence and by association disease specific survival, it is normal practice to re-operate to achieve negative margins. Re-excision in itself is not harmless as it is associated with increased risk of morbidities associated with a second anaesthetic and reoperation as well as poorer cosmesis. A need for re-operation also delays the time to receiving adjuvant therapy, a factor that also negatively impacts the course of the disease. The number of re-excisions needed to achieve negative margins is also directly linked to an increased risk of local recurrence[27].

Patients at our institution are offered pre-operative systemic therapy if their tumour is >5cm, they are node positive or have a chemo sensitive tumour (TNBC and HER2+). Other indications include downstaging a tumour to facilitate BCS should the patient desire it. These decisions are all made with the input of a multidisciplinary team. Patients are chosen for WGL excision at our institution for tumours that are non-palpable clinically and require pre-operative localization to locate the tumour intra operatively. They may be impalpable due to being screen detected and are not clinically palpable or may fall under the cohort of patients that respond well to NAC to the point that the tumour is no longer palpable. WGL is done by placing a wire into the lesion under image guidance, done by the radiology department on the day of the surgery. At this centre, WGL is still used due to both its cost effectiveness and efficacy. WGL was recently compared to newer techniques, the results of which showed that WGL had comparable successful excision rates compared to newer techniques but with marginally higher positive margins and re-operation rates[14] After WGL and excision, all patients should then undergo post operative radiation as it is an absolute indication.

In this specific patient cohort, With the above in mind this study aimed to assess the practice of WGL and tumour excision at CMJAH. There were no published papers in SA regarding this and very little research from Africa. The study period was unfortunately affected by both the COVID pandemic as well as the CMJAH fire on 16 April 2021, both which significantly disrupted service delivery to the study population and stretched an already burdened radiation oncology service in the aftermath of both events[28]. This study will aim to assess whether our practice of wire guided localization in a South African context is in keeping with the current international standards of WGL.

2. STUDY OBJECTIVES

AIM: To describe the outcome of hook-wire guided BCS at CMJAH Surgical breast unit.

Primary Objectives

- To determine the re-excision rate following hookwire-guided breast conserving surgery
- To determine the local recurrence rate following a hookwire-guided breast conserving surgery

Secondary Objectives:

- To describe the clinical, radiological and pathological characteristics of patients undergoing hook-wire guided breast conserving surgery.
- To describe the clinico-pathological characteristics of patients with local recurrence following a hookwire-guided breast conserving surgery

3. METHODS AND SAMPLING

3.1 Study Design and Setting

This was a retrospective, descriptive study of patients using the Charlotte Maxeke Johannesburg Academic Hospital breast database (CMJAH), National Health Laboratory Services (NHLS) records and radiology database of patients undergoing hookwire guided excision of a breast carcinoma. After obtaining ethical approval from the University of the Witwatersrand's Human Research Ethics Committee (HREC), CMJAH Radiology Head of department (HOD), CMJAH management, NHLS database gatekeeper, Breast Unit electronic database gatekeeper and the Department of General Surgery HOD, all patients who met eligibility criteria were included in the study.

3.2 Study Population and Data Collection

Inclusion criteria: All women undergoing hookwire guided BCS of a breast carcinoma from the period of 1 January 2016 to 31 May 2024.

Exclusion criteria: Initial operation done at another centre, incomplete records, benign final histology.

A combination of records from the radiology department of incidences of hookwire insertions as well as theatre records were used to identify eligible women during this time period. Their details were then entered onto the CMJAH breast database, radiology record database and NHLS database to retrieve all the outstanding data needed for each participant. This data was then entered into data collection sheets.

This study was conducted at CMJAH, a quaternary hospital in the Johannesburg Metropole that serves a population of more than 5 million people and receives patients from 14 hospitals within its referral chain[28]. CMJAH has a high burden of breast cancer patients as a recent study showed that 1019 new cancer diagnoses occurred over a study period of 2 years and 4 months across CMJAH and CHBAH, with 849 of those cases coming from CMJAH[29]. Another important feature of this healthcare institute is that it is the only hospital to provide radiation oncology services in the Johannesburg Metropole public sector.

3.3 Measuring Tool and Data Collection

Information from included participants was captured on to Microsoft Excel for further analysis. Variables captured included: Age, reason for presentation, clinical stage, initial lymph node (LN) involvement, BIRADS (breast imaging and reporting data system) score, predominant imaging features, largest diameter of mass on imaging, estrogen receptor (ER) status, molecular subtype, neoadjuvant chemotherapy (NAC) reception, clinical RECIST (response evaluation criteria in solid tumours) response to NAC, excision histology size and type, closest margin on excision, margin adequacy, re-operation need and type, radiation received and days from surgery to radiation, disease recurrence and site. Adequate margins for invasive carcinoma was defined as no ink on tumour and for DCIS (ductal carcinoma in situ) the minimal acceptable margin is ≥2mm. Inadequate margins were any margins with positive ink or DCIS within 2mm of the excision margin.

3.4 Statistical Analysis

Data analysis was performed using STATA software version 16 and the assistance of the Wits Surgical Statistics Hub which is run under the auspices of the NIHR Global Surgery Unit. The distribution of numerical data variables was determined by the Shapiro-Wilks test and means with standard deviations (SDs) or medians with interquartile ranges (IQRs) reported as appropriate. Frequencies and percentages are reported for categorical data variables.

Mann-Whitney U and Kruskal-Wallis tests were used to determine associations between continuous data and outcome variables. The Pearson Chi-square or Fisher's exact tests were used, as appropriate, for categorical variables. A p-value of <0.05 was considered statistically significant.

4. RESULTS

A total of 119 patients were identified during the defined study period who underwent a hookwire guided excision for a breast mass using a combination of radiology departmental records and theatre registers. Of these, 55 patients met the inclusion criterion of undergoing a hookwire guided BCS of a malignant tumour. 15 cases were excluded due to missing records (histology reports not found, and/or no radiological reports). A further 49 cases were excluded due to final benign pathology results.

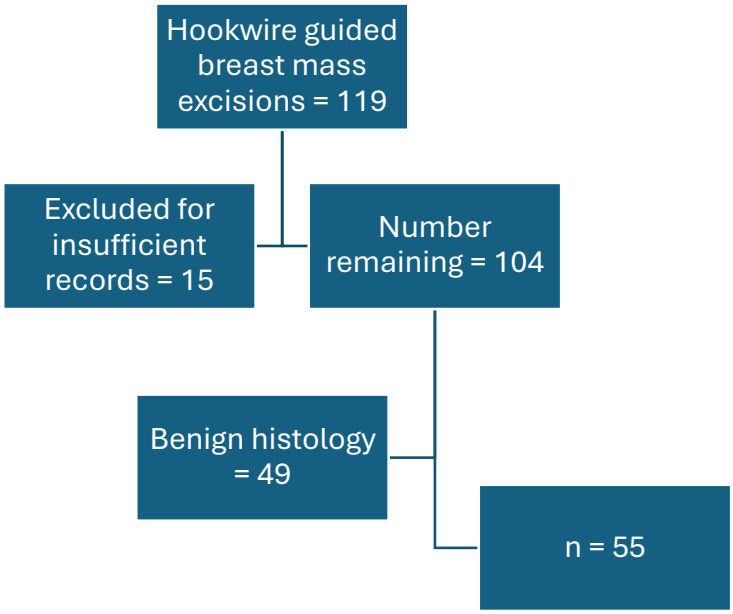

Figure 1: Flow diagram of study participants.

Table 1. Demographics, radiological, clinical and histopathological characteristics of patients undergoing Hookwire guided BCS

Parameter	All patients (n=55)
Age in years, median (IQR)	55 (47 – 62)
Presenting complaint, n (%)	
Palpable mass	42 (76.4)
Pain	4 (7.3)
Screening	8 (14.6)
Unknown	1 (1.8)

Predominant imaging features, n (%)	
Lesion	47 (85.4)
Asymmetry	3 (5.5)
Microcalcifications	3 (5.5)
Unknown	2 (3.6)
Size on imaging in mm, median (IQR)	19.0 (12.0 – 28.0)
Initial BIRADS score on imaging, n (%)	
3	1 (1.8)
4	9 (16.4)
5	41 (74.5)
6	4 (7.3)
Molecular subtype on biopsy, n (%)	
Luminal A	19 (34.5)
TNBC	16 (29.1)
Luminal B	9 (16.4)
HER2 enriched	5 (9.1)
Luminal B HER2 +	5 (9.1)
DCIS	1 (1.8)
ER positivity, n (%)	
Positive	33 (60.0)
Negative	22 (40.0)
Initial clinical stage, n (%)	
0	7 (12.9)
1a	19 (35.2)
2a	21 (38.9)
2b	6 (11.1)
3a	1 (1.9)
Lymph node involvement, n (%)	
Yes	23 (41.8)
No	32 (58.2)

Abbreviations: BIRADS: Breast Imaging Reporting and Data System; DCIS: Ductal Carcinoma in Situ; ER: Estrogen Receptor; HER2: human epidermal growth factor receptor 2; IQR: interquartile range; TNBC: Triple Negative Breast Cancer;

Table 1 shows that 42/55 (76.4%) of patients presented with a self-palpated mass, with only 14.5% of patients being picked up at screening mammograms. The majority of patients in this study 28/55 (50.9%) had primary systemic therapy in the form of NAC in order to downsize the lesion.

When looking at imaging features, 54/55 (98.2%) of patients would fall into the category of being suspicious, highly suggestive or known malignant (BIRADS 4-6 categories) and the median size of masses seen at imaging was 19mm (IQR 12 – 28).

Of note – 23/55 (41.8%) of patients had clinically detectable LN involvement at presentation.

Table 2: Clinical response to NAC according to RECIST criteria[30] in patients undergoing hookwire guided BCS.

Parameter	All patients (n=28)
Response to NAC (RECIST criteria) n (%)	
Complete response	6 (21.4)
Partial response	9 (32.1)
Stable disease	5 (17.9)
Progressive disease	7 (25.00)
Unknown	1 (3.6)

Abbreviations: NAC: neoadjuvant chemotherapy; RECIST: Response Evaluation Criteria in Solid Tumours

Of the patients in this study, 28 (50.9%) underwent NAC. Their response to NAC is outlined as per clinical RECIST criteria in Table 2 above.

Table 3: Post operative outcomes of patients undergoing hookwire guided BCS.

Parameter	All patients (n=55)
Excision margin adequacy n (%)	
Adequate	49 (89.1)
Inadequate	5 (9.1)
Positive	1 (1.8)
Radiation Received n (%)	
Yes	32 (58.2)
No	14 (25.4)

Awaiting	9 (16.4)
Time from surgery to radiation in days (median and IQR)	216 (175 – 357)
Re operation required n (%)	
Yes	7 (12.7)
No	48 (87.3)
Recurrence n (%)	
Yes	14 (25.5)
No	41 (74.5)
Site of recurrence n (%)	
Locoregional	9 (64.3)
Distant	5 (35.7)
Time interval to recurrence (mean and standard deviation)	836.5 (607)

Abbreviations: IQR: interquartile range

Of concern, Table 3 shows only 58.18% of all patients undergoing WGL BCS had received radiation at the time of final data collection. Of these, the median (IQR) number of days from surgery to the commencement of radiation was 216 (175 – 357) days with the total data set ranging from 92 to 1066 days. Our recurrence rate was 25.5% with 64.3% of recurrences being locoregional and 35.7% distant. The mean interval to confirmed recurrence was 836.5 days with a standard deviation of 607 days.

Table 4 Factors influencing recurrence in patients undergoing hookwire guided BCS.

Parameter	**No recurrence (n= 41)**	**Recurrent disease (n = 14)**	**p-value**
Clinical/radiological stage (%)			
Early (0 – IIa)	36 (87.8)	12 (85.7)	0.839
Locally advanced (IIb – IIIa)	5 (12.2)	2 (14.3)	
Molecular subtype (%)			

DCIS	1 (2.4)	0 (0)	
HER2 enriched	4 (9.8)	1 (7.1)	
Luminal B HER2 +	4 (9.8)	1 (7.1)	
Luminal A	18 (43.8)	1 (7.1)	0.055
Luminal B	5 (12.2)	4 (28.6)	
TNBC	9 (22.0)	7 (50.1)	
TNBC vs all others (%)			
All other subtypes	32 (78.1)	7 (50.0)	
TNBC	9 (21.9)	7 (50.0)	**0.046**
ER positivity (%)			
Positive	26 (65.0)	7 (42.9)	0.147
Negative	14 (35.0)	8 (57.1)	
Margin adequacy (%)			
Adequate	38 (92.7)	11 (78.6)	
Inadequate	3 (7.3)	2 (14.3)	0.225
Positive	0 (0)	1 (7.1)	
Initial LN positive (%)			
No	24 (58.5)	8 (57.1)	0.927
Yes	17 (41.5)	6 (42.9)	
NAC received (%)			
No	25 (60.9)	2 (14.3)	**0.004**
Yes	16 (39.1)	12 (85.7	
Radiation received (%)			
Awaiting	8 (22.2)	1 (7.1)	
No	8 (22.2)	4 (28.6)	
Yes	22 (55.6)	9 (64.3)	0.455
Days from surgery to radiation (median and IQR)	238 (172 – 450)	180 (180 – 221)	0.160

Abbreviations: DCIS: Ductal Carcinoma in Situ; ER: Estrogen Receptor; HER2: human epidermal growth factor receptor 2; IQR: interquartile range ; LN: Lymph Node; NAC: Neoadjuvant Chemotherapy; TNBC: Triple Negative Breast Cancer

Table 4 shows factors influencing tumour recurrence following WGL BCS, clinical stage at presentation was not found to be a significant factor (p = 0.839), and molecular subtypes of tumours showed borderline significant differences (p = 0.055). However, when separating TNBC and comparing their recurrence to all other molecular subtypes, 43.8% of TNBC patients had recurrence which was significantly higher than 17.9% recurrence in non-TNBC molecular subtypes (p = 0.046) As shown in Table 4.

ER status (p = 0.147) as well as initial LN involvement (p = 0.927) did not significantly influence recurrence. Margin adequacy also did not show to be a significant factor determining recurrence (p = 0.225), however, the single patient in this data set with positive margins at initial excision did go on to develop recurrence.

Receiving NAC affected recurrence significantly. In the 28 patients who received NAC, 42.9% developed recurrence compared to only 7.4% in those who did not receive NAC (P=0.004). When looking at the subset of patients who presented with a palpable mass, 70.2% of those patients went on to receive NAC.

Radiation time from surgery did not show a significant association with recurrence. In fact, median (IQR) radiation time from surgery was 180 (180-221) days in the recurrence group vs 238 (172 – 450) days in the non-recurrence group (p = 0.160).

5. DISCUSSION

When analysing the predominant imaging features compared to international data which shows microcalcifications as the most predominant imaging feature, we interestingly report a vastly different radiological appearance of lesions. 88.8% of our study patients exhibit a lesion, compared to international data showing microcalcifications being the most common; at 47% with masses only being shown in 41% of imaging appearances[20]. An explanation for this could be that the overwhelming reason for presentation in this study was a self-reported lump (76.4%) whereas only 14.5% of masses were detected during a screening mammogram. Importantly, the above may be influenced by the fact that SA does not have a formal breast cancer screening programme, with only opportunistic screening being done. This may explain the low rate of screening detected masses and higher incidence of self-reported masses as we rely mainly on self-detection followed by health care seeking. The reason why so many patients presenting with a palpable mass went on to require WGL may be explained by the fact that the majority of those patients (70.2%) received NAC which would explain the downsizing of the tumour to

being impalpable. Unfortunately, due to inadequate documentation, the reason for the remaining patients requiring WGL is unclear.

From the literature review and global consensus, a positive margin is the factor most strongly associated with recurrence in BCS and acceptable rates range between 4 – 31% with an average of 23%[13, 21 - 23]. In our study the rate of positive and inadequate margins was 10.9% which is well within internationally acceptable rates.

The overall re-excision rate in our study was 12.7%, which also falls below the reported acceptable re excision rate following WGL BCS of 14 – 19% [14]. However, in our data set 5 patients underwent mastectomy as re-excisions, 2 for inadequate margins, 2 for recurrent disease and 1 patient for which no indication could be identified. Mastectomies were performed as opposed to re-excision of margins upon patient request and preference.

The recurrence rate in our study is where we stray far from globally acceptable standards. The recurrence rate in this study was 25.5% which is far above the currently acceptable rate of recurrence following BCS of 5.7 – 12.0%[31, 32]. Of the incidences of recurrence in this study, 64.3% were locoregional and 35.7% were distant recurrences.

When looking at the factors potentially influencing recurrence, the presence of a TNBC significantly increased recurrence risk compared to all other molecular subtypes ($p = 0.046$). Patients who received NAC also had a significantly increased risk of recurrence ($p = 0.004$). The explanation for this likely relates to the indication for NAC, those patients requiring NAC would have intrinsic tumour factors (aggressive subtype, more advanced stage) making them more aggressive and therefore necessitating NAC. Other factors reported in the literature for recurrence, such as margin adequacy, ER status and LN involvement and whether or not radiation was received, were not significantly associated with recurrence in this study.

One explanation for our higher rates of recurrence could be due to the inadequate post-operative radiation received. BCS is defined as surgery, either a WLE or lumpectomy, followed by adjuvant radiation to eradicate residual microscopic disease[10]. However, only 58.2% of our patients had received radiation during the study period. There is also a subset of patients recorded as not having received radiation as opposed to awaiting – these patients fall under this category due to a loss to follow up and no record of radiation being received. This may certainly have been heavily influenced by the break in service delivery caused by both the COVID pandemic and the CMJAH fire. When considering those that received radiation, the median (IQR) number of days from surgery to the commencement of radiation was 216 (175 – 357)

days. Of note, even the patient who received radiation the soonest following surgery, received it only at 92 days.

The optimal timing of postoperative radiation following BCS does not have an international consensus, however the latest time suggested across all of the guidelines is less than 12 weeks (84 days)[33]. This means that not a single patient during our study period received radiation within the internationally accepted period of time that would constitute safe BCS. This could explain our higher recurrence rate when compared to international literature. The issue of access to radiation oncology services and the backlog is one that has been recognized at both the hospital, departmental and government health sector level. The addition of extra funding allocated at the 2023 budget speech as well as the plan to outsource services to the private sector should hopefully contribute to addressing the backlog and improving access to radiation oncology services thereby improving outcomes for patients such as those included in this study.

Limitations

The main limitation of this study was the low volume of patients. Even though data was collected over a long period of time, the total eligible number for was only 55 patients. This made it difficult to determine true statistical differences from the data. The period of study also fell within the COVID pandemic, during which elective surgeries were significantly delayed. The period of study also included the CMJAH fire, during which period of time no services were offered at the hospital at all.

Lessons Learnt and Future Research

This study highlights the effect that a lack of formal screening programme has on the clinical and imaging features of patients that undergo BCS compared to international data. The proper implementation of a screening programme could help to address this disparity and improve the detection of malignancies before they become palpable.

The most important factor to consider in this study is the delay to radiation and the possible repercussions that this has not only for breast cancer patient outcomes but all cancer patients in our catchment area. It is a severely limited resource that was negatively affected by the covid pandemic as well as the CMJAH fire which caused massive backlogs, restricting access to this treatment. It represents a crisis within the province with tangible negative outcomes being experienced by all patients reliant on radiation for treatment.

TNBC has also proved to be a factor that should be treated with extreme caution. Although the study comprised a small number of patients which limits the statistical power; even in this small sample size, there was a tendency for TNBC to be associated with recurrence. However, due to the small sample size, no multivariate analysis could be performed to determine whether TNBC is an independent predictor of recurrence when adjusted for confounders. For this reason, no treatment recommendation can be made.

6. CONCLUSION

Patients undergoing hookwire guided BCS at CMJAH have acceptable rates of margin adequacy and re-excision when compared to international rates. These reflect acceptable and good surgical practices by the breast unit at CMJAH and confirm that hookwire guided BCS is still an acceptable option for our unit. The glaring difference is our extremely high rates of recurrence when compared to international data, which is likely related to our inadequate access to timeous radiation following BCS. In this study TNBC has shown to be an entity that should be treated with caution when considering BCS as it was significantly associated with recurrence even in this small patient cohort.

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APPENDIX 1: Research Protocol

Research Protocol

Title: Hookwire-guided breast conserving surgery at Charlotte Maxeke Johannesburg Academic Hospital

Investigator: Dr Danielle Ferrar

MBChB (UCT)

Supervisors: Dr BP Phakati

Dr NH Mabe

Index

List of abbreviations

BCCP	Breast Cancer Control Policy
BCS	Breast Conserving Surgery
BCT	Breast Conserving Therapy
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
DCIS	Ductal Carcinoma in Situ
LVI	Lymphovascular Invasion
RFID	Radio Frequency Identification
ROLL	Radioguided Occult Lesion Localization
RSL	Radioactive Seed Localization
SANCR	South African National Cancer Registry
WHO	World Health Organization

Introduction and Literature Review

The WHO has recognized that breast cancer is the most common cancer worldwide and is also the highest cause of cancer related deaths amongst women, accounting for 25% of all cancers diagnosed worldwide [1]. The South African National Cancer Registry also shows that breast cancer is the most commonly diagnosed cancer in South African women with 21.78% of all diagnosed cancers being breast cancer, and was the cause of 0.9% of all deaths in 2015 [2].

Compared to higher income countries, South Africa is known to be burdened with more advanced breast disease at presentation. This is due to a variety of complex socio-economic factors, with the outcome being that 54% of patients present with late stage 3 and 4 disease, as shown in a 2014 study at CHBAH [3].

However, with the national Department of Health implementing the Breast Cancer Control Policy in 2017, this trend of late stage presentation will hopefully be improved. With a heavy focus on improved implementation of educational and screening programmes, it aims to ensure the earlier detection and treatment of breast cancer [4].

As the quality of radiological imaging has improved as well as these increased efforts to obtain community awareness and more widespread screening for breast disease, the number of cancers diagnosed early and before they are palpable can be expected to have increased. This is supported by a case series of 1218 patients in Soweto that showed the incidence of stage 3 and 4 tumours decreased from 66% to 46% over the 6-year study period [5].

The first-choice treatment for early breast cancer is breast conserving therapy. Due to the progress made with adjuvant treatments, breast conserving therapy in combination with adjuvant treatments has a survival that is comparable to mastectomy [6][7][8][9]. Breast conserving therapy (BCT) is defined as surgery (wide local excision/lumpectomy) followed by adjuvant radiation to eradicate any residual microscopic disease [10]. The goals of BCT are to provide a cosmetically acceptable result, low recurrence in the ipsilateral breast and to provide the same survival rate and outcome as a mastectomy [10].

An essential requirement for BCT to be successful in achieving its goals is that the entirety of the mass is excised. This may sound obvious, however with non-palpable masses, pre-operative localization of the mass is required to assist the surgeon in excising the entire mass. The principles of pre-operative localization are that a device is placed into the mass under image guidance pre-operatively, followed by intra-operative localization which serves as confirmation that the mass has been excised [11]. The outcomes for non-palpable breast cancers that are treated with excision have a disease free 5-year survival of up to 98% [12]. Therefore, early detection and correct treatment of these cancers will lead to better outcomes and increased quality of life with improved cosmesis in these patients.

Hookwire guided excision remains the mainstay of both diagnosis and treatment in nonpalpable breast masses at our centre. Hookwire guided excision uses a wire inserted under radiological guidance immediately pre-operatively which leads the surgeon to the mass. Imaging of the specimen is then taken intra-operatively to ensure that the entire mass has been excised before the surgery is continued. It is an older and more traditional method of localization. In recent years there have been advances and new methods of localisation and excision of these masses. These

include radioactive iodine seeded location (RSL) and non-radioactive methods of localization such as radioguided occult lesion location (ROLL), RFID tag, Magseed and SAVI SCOUT RADAR guided excision. All these methods require more advanced equipment not currently available in the public sector. The advantages that these methods have in common is that they all uncouple the radiology and surgical services which improves workflow as well as improving patient comfort [13].

Although this sounds attractive, a 2015 Cochrane review showed that the outcome of these different methods are comparable and that wire guided localization was still superior to the RSL method in localizing non-palpable lesions successfully [14]. This review also showed that although studies have reported improvements in localization, less positive margins and lower re-excision rates with RSL and ROLL when compared to wire guided excisions, none of this data reached statistical significance [14]. For this reason, our current practice of hookwire guided excision for non-palpable breast masses is still in line with the current gold standard of treatment.

Non-palpable breast lesions have the possibility of being either malignant or benign. Studies done in other countries show that the rate of malignancy in non-palpable lesions ranges from 20.3% - 56.6% of all non-palpable lesions biopsied [15][16][17][18][19]. This shows a very wide range of data and no data from Africa or any other developing countries exists. This high incidence of malignancy in all non-palpable tumours highlights the importance of correctly assessing, diagnosing and excising these masses. It also justifies the use of hookwire guided excisions and outweighs the negatives associated with excision of a benign mass.

The radiological features of non-palpable abnormalities identified on mammogram have been shown to predict the likelihood of a malignancy, to a degree. In previous

studies, the most commonly identified abnormalities on mammogram are microcalcifications, masses, architectural distortions and combinations of the above [17]. These could be used to group the mammogram appearance into a suspicious group (poorly defined masses, clustered microcalcifications) and a minimally suspicious group (well defined masses, dispersed microcalcifications). When grouped in this way, suspicious mammograms had an overall carcinoma incidence of 37.1% - 67% whereas minimally suspicious mammograms carried a carcinoma incidence of 4.5 – 11% [17][18][19].

There have also been further studies into the appearance of non-palpable malignancies alone. The results showed that the most common appearance for a malignancy on mammogram was calcifications (47%) followed by mass (41%), mass with calcifications (8%) and architectural distortions (4%) [20]. This study was interesting as it also showed that masses with calcifications were more often associated with lymphovascular invasion, an important predictor of recurrence that will be elaborated on later.

Local recurrence is one of the pervasive concerns for patients undergoing breast conserving surgery, due to the fact that not all breast tissue is removed on the first surgery. Studies showed that for every four local recurrences that occur after breast conserving surgery, 1 patient would die as a result of the recurrent disease [21]. In treating these patients, one should therefore be cognisant of both inherent risk factors as well as technical factors that may increase the risk of local recurrence in order to mitigate them when making decisions on the treatment of these tumours.

Multiple studies have focused on the factors that increase the risk of local recurrence and these include patient age, tumour size, tumour grade and multifocality [22].

These factors are factors inherent to the mass that are non-modifiable. The strongest predictor in local recurrence across all studies was the presence of a positive margin post excision [22][23]. A large meta-analysis of 26,162 patients showed that a positive margin (defined as tumour present on the inked margin in this study) carried with it a two-fold increased risk of ipsilateral breast recurrence [23] and positive margins are an independent predictor of poor disease specific survival [22].

The issue of positive margin is an important factor in treating this patient as it is a risk that is determined by the surgery itself and is therefore modifiable. The published rates of positive margins are 4 – 31% [24] with an average of 23% [14]. Tumour specific factors associated with positive margins include lobular histology, large tumour size, increased tumour grade, multifocality, extensive in situ component and lymphovascular invasion [24][25][26]. These factors are inherent to the tumour being excised and cannot be altered, however, a surgeon operating on a tumour with any of these known characteristics should keep that in mind when planning the surgery and amount of tissue to be excised.

Having a pre-operative diagnosis of carcinoma was a factor that was persistently and strongly associated with negative margins [24][27]. Other surgical factors associated with negative margins include extra cavity dissection, correct specimen orientation and larger volumes excised [24]. These factors are important to keep in mind as they can be altered intra-operatively to have a positive outcome on margin status.

Due to the strong association of margin positivity on local recurrence and by association disease specific survival, it is normal practice to re-operate to achieve negative margins. Re-excision in itself is not harmless as it is associated with increased risk of morbidities associated with a second anaesthetic and reoperation

as well as poorer cosmesis. A need for re-operation also delays the time to receiving adjuvant therapy, a factor that also negatively impacts the course of the disease. The number of re-excisions needed to achieve negative margins is also directly linked to an increased risk of local recurrence [28].

Justification for Study

Wire guided localization remains the method of pre-operative localization and excision in non-palpable breast cancers at CMJAH. This study will aim to assess whether our practice of wire guided localization is in keeping with the current international standards of wire guided localization. We will also be able to determine whether our practice is comparable to the more novel methods of localization that are currently available internationally.

Aim

AIM: To describe the outcome of hook-wire guided breast conserving surgery at CMJAH Surgical breast unit.

Primary Objectives

- To determine the re-excision rate following hookwire-guided breast conserving surgery
- To determine the local recurrence rate following a hookwire-guided breast conserving surgery

Secondary Objective:

- To describe the clinical, radiological and pathological characteristics of patients undergoing hook-wire guided breast conserving surgery
- To describe the clinico-pathological characteristics of patients with local recurrence following a hookwire-guided breast conserving surgery

Methods

Study design

Retrospective, descriptive study of patients on the Charlotte Maxeke Johannesburg Academic Hospital breast database undergoing hookwire guided excision of a breast carcinoma.

Site of study

Charlotte Maxeke Johannesburg Academic Hospital.

Study Population

All women diagnosed with breast cancer who had a hookwire-guided breast conserving surgery at CMJAH Surgical Breast Unit during the period 1 January 2016 - 31 December 2019.

Sampling

The Department of Radiology keeps a record of all patients undergoing hookwire insertion at CMJAH. This record will be used to obtain the details of all the patients that qualify for this study. Further data will be obtained from the CMJAH breast oncology database. This will be supplemented with radiology reports from the PACS system and histology results from the NHLS Traklab database.

Inclusion criteria

All women undergoing hookwire guided excision of a breast carcinoma

Exclusion criteria

Initial operation done at another centre

Incomplete records

Data Capturing

See Appendix 1 for data capturing form.

Data Analysis

Numerical data will be analysed by calculating values to indicate the central tendency such as the mean, median and mode. The variability of the data will be analysed by using the range and standard deviation. Percentages, proportions, rates and rations will also be calculated from the numerical data.

Inferential statistics may also be calculated to better understand any correlation or association between the data. This would include using the chi squared test as well as regression analysis.

Ethics

The proposal for this study will be submitted to the Protocol Review Committee and Human Research Ethics Committee (HREC) of the University of the Witwatersrand for approval. The patient details will be stored on a separate database, purely for keeping track of records. Only the investigator and supervisors will have access to

this information. The study and data capturing will not begin until ethics approval has been granted.

Timing

	Aug 2020	Sept 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021	Feb 2021	March 2021	April 2021
Literature review									
Preparing protocol									
Protocol assessment									
Protocol corrections									
Ethics application									
Collecting data									
Data Analysis									
Writing up report									
Writing up paper									

Cost

No major costs are expected.

Study Limitations

The study period may not be long enough to pick up all recurrences which may lead to a falsely lower rate of recurrences being reported.

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28. Menes TS, Tatter PI, Bleiweiss R et al. The consequences of multiple re-excisions to obtain clear lumpectomy margins in breast cancer patients. Breast Disease: Quarterly 2006;17(3):3-21

APPENDIX 2: Protocol Assessors Meeting and Faculty Approval Letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PROTOCOL ASSESSORS MEETING

Candidate Full Name: **Danielle Ferrar** Supervisors: **Phakathi/Mabe**

Student Number: **2202867** Date: **18th November 2020**

School / Department / Division: **Department of Surgery, Division of General Surgery**

Degree: **MMED**

Title: **The Outcome of Hookwire Guided Breast Conserving Surgery at CMJAH Breast Unit**

1. **Type of study** *(tick all that apply)*:

- Quantitative
- Qualitative
- Mixed Methods
- Laboratory
- Clinical ✓
- Other, please specify.....

2. **Is title of the study appropriate** (*preferably fewer than 20 words*)? Yes | No✓

Comments:
- CMJAH should be written in full
- Remove "outcomes" from the title

3. **Are the study objectives clear and linked to the research aim and title?** Yes✓ | No

Comments: Objectives are clear and appropriate

4. **Is the design of the study appropriate to meet the study objectives?** Yes✓ | No

Comments: Study design is appropriate

5. **Are the proposed methods and tools appropriate to meet the research objectives?** Yes✓ | No

Comments: Methods are appropriate

6. **Is the study feasible within the resources of:**

a) The applicant?	Yes✓	No
b) The department?	Yes✓	No
c) The time frame?	Yes✓	No

7. **If this is a PhD protocol assessment:**

a) Is the content original?	Yes	No
b) Does the content show the scope and depth of a PhD?	Yes	No

Comments: _____

_____

_____

_____

Do you recommend:

i. Additional revision/amendment of the protocol? Please be specific on the recommendations being made:

- Index- page is blank
- Coversheet should be typed
- Dr Phakhati is proposed to supervise 100%- this should be edited
- Define your abbreviations especially on first use
- Some missing words in synopsis e.g. last line of introduction …shown to have… and still on synopsis, under justification of study rather write study aims to establish whether, not see whether
- Add a section for limitations and include some of the limitations your supervisor recommended and any other
- Page 6- You mentioned "further studies" but reported just one
- Page 8, first line- change positive to negative
- You mentioned consenting patients however this is a retrospective study, clarify
- Clarify why mastectomy is not preferred or recommended over BCT, if you have not already done so.

ii. The appointment of the proposed Supervisor? Yes✓ No

Nominee/s: The assessors approve of the recommended supervisors

iii. The appointment of the proposed Co-Supervisor/s and/or additional co-supervisors? Yes No✓

Nominee/s: No additional co-supervisors recommended

iv. Has the Chair of the Assessor Group signed the RECOMMENDATION FOR APPOINTMENT Yes No✓

11 March 2019/MP

OF SUPERVISOR(S) OF RESEARCH REPORT, DISSERTATION OR THESIS form? Please attach.

v. Has the Chair informed the student and supervisor about the Wits ethics requirements, and that if required, they must have either a Wits Human Research Ethics clearance certificate
or a Wits Animal Research Ethics clearance certificate?

Yes✓	No

vi. Based on the protocol provided (including any proposed changes by the protocol assessor group),
does the student require:

1. Human Research Ethics clearance certificate	Yes✓ / No
2. Animal Research Ethics clearance certificate	Yes / No
3. No human or animal ethics certificate is required	Yes / No
4. Unclear, will seek appropriate guidance from the HREC/AREC committees	Yes / No

vii. Has the Postgraduate student and supervisor/s signed the ethics declaration form

Yes	No✓

Overall recommendation regarding the protocol:

i. Revision of the protocol to the satisfaction of the Supervisor (**NB: if HoD approval is also required, please specify**):
*(**Candidate**: one copy, list of corrections with page numbers and Supervisor approval letter – submit to PG Office).*

Yes✓	No

ii. Revision of the protocol to the satisfaction of the Assessor Group/Chair:
*(**Candidate**: one copy, list of corrections with page numbers, Supervisor approval letter – submit to PG Office and PG Office to forward to the Assessor Group Chair).*

Yes	No

iii. Revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting:
*(**Candidate**: six copies, list of corrections with page numbers, Supervisor approval letter – submit one copy to PG Office / 5 to school assessor group administrator / for PhD, all six copies to be submitted to the PG Office).*

Yes	No

iv. Candidate goes ahead (*no revision required*):

Yes	No

Details of Assessors:

Name:	Email:	Sign:
Prof Thifhelimbilu Luvhengo	thifhelimbilu.luvhengo@wits.ac.za	
Dr Marietha Nel	marietha.nel@wits.ac.za	

11 March 2019/MP

Dr Susan Williams	susan.williams@wits.ac.za	
Dr Pascaline Fru	Pascaline.fru@wits.ac.za	

Details of Assessor Group Chair:

Name:	Email:	Sign:
Dr Ekene Nweke	Ekene.nweke@wits.ac.za	

Date: **18th November 2020**

APPENDIX 3: Data Collection Sheet

1. Demographics

Age: _____

Race: _____

2. Clinical Stage

T:_____ N:_____ M:_____

Final stage:_____

3. Breast Imaging

Modalities done:

Mammogram:_____ Ultrasound:_____ MRI:_____

Contrast mammogram:_____

Description of lesion found: _____

_____

_____

_____

Size: _____

Quadrant: _____

4. Histopathology

Histological type: _____

Grade: _____

Receptor Status: ER_ PR____ HER2_____

Ki67: _____

Intrinsic subtype: _____

5. Surgery

Date: _____

Imaging modality used for hookwire placement: _____

_____

Specimen X-ray obtained: _____

Feedback from radiologist: _____

6. Final Pathology Results

Diagnosis: _____

Size: _____

Component of DCIS: _____

Margins: Superior:____ Lateral:_____ Medial:_____
Inferior:_____ Deep:_____

Lymphovascular invasion: _____

Final staging: _____

7. Re-excision

Yes/No: _____

If yes, margin re-excision/Mastectomy: _____

8. Radiation Therapy:

Starting date: _____

Duration: _____

Dose: _____

9. Adjuvant Therapy:

_____

10. Local Recurrence:

Yes/No:_____

If yes, clinical or histological: _____

Date of diagnosis: _____

Distant metastases: _____

APPENDIX 4: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Dr DS Ferrar
School of Clinical Medicine
Department of Surgery
Medical School
University

E-mail: dsferrar91@gmail.com

CC: Supervisor: Drs BP Phakathi and NH Mabe
Boitumelo.Phakathi@gmail.com
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 20 November 2023

REF: R14/49

PROTOCOL NO: **M230757** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Hookwire-guided breast conserving surgery at Charlotte Maxeke Johannesburg Academic Hospital*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE
WITWATERSRAND
JOHANNESBURG

R49 Dr DS Ferrar

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M230757

NAME: Dr DS Ferrar **DEGREE:** MMed
(Principal and Co-Investigators)

DEPARTMENT: School of Clinical Medicine
Department of Surgery
Medical School
University

PROJECT TITLE: *Hookwire-guided breast conserving surgery at Charlotte Maxeke Johannesburg Academic Hospital*

DATE CONSIDERED: 11 August 2023

DECISION: Approved unconditionally

CONDITIONS:

NOTE: If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR: Drs BP Phakathi and NH Mabe

APPROVED BY:

Professor P Ruff, Chairperson, HREC (Medical)

DATE OF APPROVAL: 20 November 2023 **EXPIRY DATE:** 19 November 2028

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

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

I/we fully understand the conditions under which I am/we are authorized 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 submit details to the Committee. **I agree to submit a yearly progress report** in the format available at https://wits.ac.za/research/researcher-support/research-ethics/ethics-committees/. This report is due annually, for the duration of the Clearance Certificate, beginning on the first anniversary of Date of Approval above. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator Date

APPENDIX 5: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

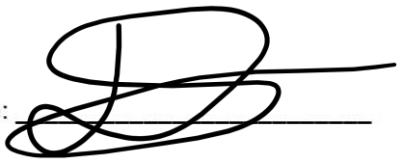
PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Danielle Simone Ferrar (Student number: 2202867) am a student registered for the degree of Master of Medicine in the academic year 6.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: 

Date: 28/3/2025

APPENDIX 6: Turnitin Report

Ferrar_Final Write up Draft 7_for turnitin.docx

ORIGINALITY REPORT

9%	6%	7%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	&NA;, . "15th Biennial Meeting of the International Gynecologic Cancer Society :", International Journal of Gynecological Cancer, 2014. Publication	1%
2	wiredspace.wits.ac.za Internet Source	1%
3	sislietfaltip.org Internet Source	1%
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9	www.researchsquare.com Internet Source	<1%
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11	Carla S. Fisher, Fatema Al Mushawah, Amy E. Cyr, Feng Gao, Julie A. Margenthaler.	<1%

	"Ultrasound-Guided Lumpectomy for Palpable Breast Cancers", Annals of Surgical Oncology, 2011 Publication	
12	H L Gururaj, Francesco Flammini, V Ravi Kumar, N S Prema. "Recent Trends in Healthcare Innovation", CRC Press, 2025 Publication	<1 %
13	Groot, . "Predicting local recurrence following breast conserving therapy for early stage breast cancer: The significance of a narrow (less than or equal to 2mm) surgical resection margin", Proquest, 2014. Publication	<1 %
14	"WORLD TRANSPLANT CONGRESS 2006 POSTER ABSTRACTS", American Journal of Transplantation, 8/2006 Publication	<1 %
15	bmcgastroenterol.biomedcentral.com Internet Source	<1 %
16	Naoto T. Ueno, Rie K. Tahara, Takeo Fujii, James M. Reuben et al. "Phase II study of Radium-223 dichloride combined with hormonal therapy for hormone receptor-positive, bone-dominant metastatic breast cancer", Cancer Medicine, 2019 Publication	<1 %
17	www.acumenresearchandconsulting.com Internet Source	<1 %
18	Lovrics, P.J.. "The relationship between surgical factors and margin status after breast-conservation surgery for early stage	<1 %

breast cancer", The American Journal of Surgery, 200906
Publication

19	link.springer.com Internet Source	<1%
20	www.sajch.org.za Internet Source	<1%

Exclude quotes	On	Exclude matches	< 8 words
Exclude bibliography	On		

APPENDIX 7: Letter of Approval to Conduct Research by Hospital Medical Advisory Committee

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: *Ms N. Mzila*
Email: Nolwazi.Mzila@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 10 September 2022

GP_202203_071

Dear Dr Danielle Ferrar

RE: PROVISIONAL APPROVAL OF STUDY

TITLE: HOOKWIRE-GUIDED BREAST CONSERVING SURGERY AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Permission to conduct the above-mentioned study is provisionally granted subject to:

1. Submitting an Ethics Clearance Certificate from the University of Witwatersrand Human Research and Ethics Committee (HREC).

Please submit the above documents at your earliest convenient within 3 months from the date of this letter. This will prompt the Chief Executive Officer (CEO) of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) to grant you a final approval. It is important to note that your research can only commence once a final approval is granted. Failure to comply with the above-stated requirements may result in the withdrawal of your application.

Supported / ~~Not Supported~~
Signed by:Jayshina Punwasi
Signed at:2022-09-13 15:21:58 +02:00
Reason:Witnessing Jayshina Punwasi

Dr J. Punwasi
Senior Clinical Manager

Approved / ~~Not Approved~~
Signed by:Gladys Magugudi Bogoshi
Signed at:2022-09-13 15:53:06 +02:00
Reason:Witnessing Gladys Magugudi Bo

Ms. G Bogoshi
Chief Executive Officer: CMJAH

APPENDIX 8: Letter of Approval Breast Unit Database

WITS HEALTH CONSORTIUM

Wits Health Consortium (Pty) Ltd
Reg No.: 97/15443/07

Tel: +27 11 274 9200

8 Blackwood Avenue, Parktown,
2193, South Africa

Postnet Suite 189, Private Bag
X2600, Houghton, 2041

7th March, 2023

RE: PERMISSION TO ACCESS BREAST CANCER DATABASES AND PATIENT CLINICAL RECORDS

To whom it may concern,

This document serves to grant access to the breast oncology databases involved in this retrospective research project with the title: "**Hookwire Guided Breast Conserving Surgery at Charlotte Maxeke Johannesburg Academic Hospital Breast Unit**".

Ethics reference: M211192 MED21-08-142
MMed student: Dr Danielle Ferrar: student number 2202867

This document also serves to grant access to patient clinical records stored in the Medical Oncology outpatient clinic in area 495 of the Charlotte Maxeke Johannesburg Academic Hospital

The study sites involved in this research is Charlotte Maxeke Johannesburg Academic Hospital.

Access is granted to the data from the period 1 January 2016 - 31 December 2020.

This access shall begin from date of Wits Human Research Ethics Committee (Medical) approval until completion of data collection. No data collection shall be undertaken before ethical approval for the study named above

Sincerely,

Dr Maureen Joffe
Director Strengthening Oncology Services Research Unit
Principal Investigator South African Breast Cancer and HIV Outcomes Study

APPENDIX 9: Consent for Access to NHLS Database

NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

SCHOOL OF PATHOLOGY
Division of Anatomical Pathology

NATIONAL HEALTH LABORATORY SERVICE

P.O. Box 1038, Johannesburg 2000
Tel : +27-11-489-8477
+27-11- 489-8479
Fax::+27-11-489-8512

Division of Anatomical Pathology
Faculty of Health Sciences
York Road
Parktown e-mail : Yvonne.perner@nhls.ac.za

Dr Y Perner MBBCh (Witwatersrand) FCPath (SA); MMed (Witwatersrand)

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
20000

April 5, 2022

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to grant Dr Danielle Ferrar access to the histology reports for the study entitled "The outcome of hookwire-guided breast conserving surgery at and Charlotte Maxeke Johannesburg Academic Hospital".

Publication of such work is encouraged and in the event that the information used comprises the diagnosis only then joint authorship from a member of staff in the Department of Anatomical Pathology would not be expected. However, should additional information be extracted from the report for purposes of further interpretation such as morphological details and immunohistochemical profiles, it would be expected that this would be done in conjunction with a member of staff in the Department of Anatomical Pathology and that joint authorship would follow in resulting publications. Dr Ferrar will be in contact with the Department of Anatomical Pathology in respect of this. Dr Ferrar will ensure that she registers on the NHLS AARMS system. Dr Carolina Nel from the Department of Anatomical Pathology will collaborate on this study.

Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Dr Yvonne Perner
Head: Department of Anatomical Pathology

APPENDIX 10: Letter of Approval Radiology Department

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL
DIRECTORATE: ALLIED SERVICES AND RADIATION SCIENCES
Office of the Clinical Head Diagnostic Radiology
Enquiries: Ms. Reneilwe Motjelele Tel: 011 488 3368 **Email:** Reneilwe.Motjelele@wits.ac.za

27 September 2021

Dear Dr Danielle Ferrar

Re: Request to conduct a study all women who underwent Hookwire guided breast mass excision.

Dr Ferrar is a Registrar in the Department of Surgery. Dr Ferrar would like to access the following records from the PACS/XIRIS system: images of all women who underwent Hookwire guided breast mass excision from the period 1/1/2016 -31/12/2019. Age group will be women above 18.

Provisional permission to conduct the above study is granted to Dr Ferrar provided that the ethics clearance certificate is obtained.

Kindly note that Diagnostic Radiology department should be properly acknowledged in any publications and Journals. In addition we require six monthly reports on the progress of the project.

Please liaise with the relevant Consultant and Radiography department manager in charge with regards to the logistics and practical aspects of conducting the study.

Yours faithfully,

Prof. D.P. Ramaema
Clinical Head of Department
Department of Diagnostic Radiology
Charlotte Maxeke Johannesburg Academic Hospital