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RADIOGUIDED OCCULT LESION LOCALISATION (ROLL) AS A DIAGNOSTIC AND THERAPEUTIC PROCEDURE: CLINICAL REVIEW AT A SINGLE TERTIARY HOSPITAL IN SOUTH AFRICA

by

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DECLARATION

I, Sumaya Ismail, declare that the contents of this dissertation/thesis represent my own unaided work, and that the dissertation/thesis has not previously been submitted for academic examination towards any qualification. Furthermore, it represents my own opinions and not necessarily those of the Cape Peninsula University of Technology.

02 December 2021

Signed **Date**

ABSTRACT

Introduction: Due to the increase in screening programmes and the advancement of technology and high resolution imaging, the detection frequency of impalpable occult breast lesions worldwide has increased. Occult breast lesions account for 25 - 35% of breast cancer. The early detection and management of early stage breast cancer lesions has a significant effect on the treatment outcomes for the patient. It is thus important that these lesions are accurately identified and localised to enable a successful histologic diagnosis. This has led to the use and modification of various localisation methods to overcome the challenge of diagnosing and managing these non-palpable lesions. Where a fine needle aspiration biopsy (FNAB) or large core needle biopsy (LCNB) fails to provide a definitive diagnosis, a surgical excision may be necessary. Accurate pre-operative localisation facilitates complete excision with minimal tissue damage. Various pre-operative localisation methods have been used to assist the surgeon to obtain an adequate resection. The wire-guided localisation (WGL) technique is the most widely used and is still the preferred method for preoperative localization of impalpable breast lesions. Despite its widespread use, WGL does have many reported drawbacks such as patient discomfort, technical difficulty, and risk of complications.

The radioguided occult lesion localisation (ROLL) is an alternative technique using a radioactive tracer injected into or close to the lesion under radiographic guidance. The surgical removal of the lesion is then aided by a hand-held gamma probe. The ROLL procedure has been shown to provide a simple, accurate and effective method of occult lesion localisation. The ROLL method has been reported to be technically easier, quicker and more accurate when compared to the WGL. An added advantage is it that in the case of histologically proven impalpable breast cancers, a sentinel lymph node biopsy can be done simultaneously (sentinel node with occult lesion localisation or SNOLL) to detect axillary metastases. In 2003 the ROLL procedure was implemented at this institution. The aim of this study was to evaluate the ROLL procedure, assess the accuracy and efficacy of the ROLL technique for diagnostic and therapeutic excisions at our institution.

Materials and methods: A retrospective analysis was done using data on 190 patients who underwent a ROLL procedure for diagnostic or therapeutic excision of occult breast lesions at Groote Schuur Hospital, Cape Town during the period January 2003 to December 2016. All data was collected from patient files, nuclear medicine reports, radiological reports, surgical notes and histology reports. Data was collected on patient and tumour characteristics, localisation procedures, surgical and diagnostic outcomes. Primary outcomes measured were successful localisation rates, volume of tissue removed, complete tumour resection rates (i.e. negative margins), number of re-operations performed and the proportion of SLN detection.

The Pearson's Chi Squared test was used to test for significance between variables. The level of significance was set at α = 0.05. The ROLL procedure was done after radiographic and percutaneous histology results. Depending on results, the procedure was done either as diagnostic or therapeutic intent (SNOLL) for highly suspicious lesions. ^{99m}Tc tin colloid or ^{99m}Tc hepatate (5-22 MBq) was injected intratumourally for the ROLL procedures whereas a single intratumoural injection of ^{99m}Tc nanocolloid (71-113MBq) was injected for the SNOLL procedures. Both same day and day before injection methods were used.

Results: Correct radiopharmaceutical placement was achieved in 177/190 (93.2%) lesions. In 9 (4.7%) cases, the excised lesion was not representative of the pathology, with 6 of them being repeated. Of those repeated, 3 were found to be malignant and the other 3 were benign. Where the intent of surgery was therapeutic, 37/37 (100%) of lesions were correctly excised on the first attempt. Histology examination of the excised specimens found 115/190 (61%) to be malignant. Of these, 37/115 (32.2%) had involved margins. Complete excision margins was achieved in 50/70 (71.4%) cases of invasive cancer based on tumour free margins and in 11/45 (24.4%) of DCIS lesions based on excision margins >2mm. Where lymphoscintigraphy was performed, the Sentinel node (SN) was successfully identified in 30/37 (81.1%) of cases.

Conclusions: ROLL is an effective tool in pre-operative localisation of occult lesions for surgical biopsy, especially in cases where percutaneous needle biopsy results are found to be indeterminate or inconclusive. The single intra-tumoural injection with ^{99m}Tc nanocolloid combined with lymphoscintigraphy is a reliable method of localising the SN. The procedure was able to obtain tumour free margins in 78/115 (68%) of malignant lesions, however special consideration should be given when suspected DCIS is involved as tumour margins are more likely to be involved due to the nature of the pathology.

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  It is my sincere wish that this research may be beneficial and contribute to the knowledge of the treatment and management of breast cancer.

DEDICATION

For my grandmother who bravely fought her battle against breast cancer and all others whose lives have been touched by this disease.

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GLOSSARY

Terms/Acronyms/Abbreviations	Definition/Explanation
LMIC	Low to middle-income country
BCS	Breast Conserving Surgery
ROLL	Radioguided Occult Lesion Localisation
SNOLL	Radioguided Occult Lesion Localisation with Sentinel Lymph Node Biopsy
WGL	Wire Guide Localisation
FNAB	Fine needle aspiration biopsy
LCNB	Large core needle biopsy
RSL	Radioactive Seed Localisation
ALND	Axillary Lymph Node Dissection
SN	Sentinel Node
SLNB	Sentinel Lymph Node Biopsy
BI-RADS	Breast Imaging Reporting and Data System
DCIS	Ductal carcinoma in situ
GSH	Groote Schuur Hospital
MBq	Megabecquerel – SI unit of radioactivity measurement where 1 becquerel equals 1 event of radiation emission or disintergration per second
WBRT	Whole Breast Radiotherapy
Nm	Nanometres
Cnts	Counts
MRI	Magnetic resonance imaging
^{99m}Tc	Technetium-99m (pertecnetate)
^{125}I	Iodine-125

CHAPTER ONE
INTRODUCTION

1.1 Background

Breast cancer has the highest incidence of cancer in females with a global number of new cases of 2 261 419 in 2020. This figure represents 24.5% of all cancers in females (Sung et al., 2021:209-249). The incidence of breast cancer is higher in high-income countries than in low-income and middle-income countries (Jedy-Agba et al., 2016:923-935). In sub-Saharan Africa, breast cancer is the most common cancer in females with the third highest mortality rate at 8.2% (Joko-Fru et al., 2020:2131-2141).

Due to the increase in screening programmes and the advancement of technology and high resolution imaging, the detection of impalpable occult breast lesions worldwide has increased (Green & Vidya, 2018:281-283). Occult breast lesions account for 25 - 35% of breast cancers (Lovrics et al., 2011:388-397). The early detection and management of these small early stage breast cancer lesions has a significant effect on the treatment outcomes for the patient (Aydogan et al., 2010:226-230). It is thus important that these lesions are accurately identified and localised to enable a successful histologic diagnosis (Besic et al., 2002:2684-2689). This has led to the use and modification of various localisation methods to overcome the challenge of diagnosing and managing these non-palpable lesions (Norman et al., 2021:141-148).

South Africa does not have a population-based mammographic screening programme. Instead, a risk based assessment is employed for symptomatic patients presenting with breast complaints as well as high-risk women (Moodley et al., 2016; Mutebi et al., 2017:4-9). Although a low to middle-income country (LMIC) there have been significant changes in service delivery in certain sectors of the health service in South Africa (Lince-Deroche et al., 2017:181-188). One of these has been the establishment of specialist breast cancer centres within larger tertiary centres. These centres comprise of multi-disciplinary teams where the global gold standard of triple assessment (clinical examination, imaging and biopsy) methods are employed (Lince-Deroche et al., 2017:181-188). Although these centres are often concentrated in urban areas, they receive patients referred from primary health care facilities and district hospitals (Moodley et al., 2016:181-188; Lince-Deroche et al., 2017).

Groote Schuur Hospital (GSH) is a tertiary public academic hospital, and its Breast Unit functions under the auspices of the Surgical Endocrine and Oncology Unit of the Division of General Surgery of the University of Cape Town. The hospital serves the Western Metro of Cape Town as well as the surrounding rural area with a population of 2, 5 million people. An open access “walk in breast diagnostic clinic is run every Friday. During a 3-month period

(January to March) in 2019 the clinic saw 1271 new patients, performed 401 mammograms, and diagnosed 190 new breast cancers (Cairncross et al., 2019:105-113).

A suspicious impalpable lesion detected on mammogram or ultrasound, needs to be further investigated. Percutaneous fine needle biopsy and core needle biopsy are performed on these lesions with the aid of ultrasound or mammography guidance to obtain a histological tissue result (Dua et al., 2011:246-253). However, surgical excision is indicated if the needle biopsies proved non-diagnostic or highly suspicious (Dua et al., 2011:246-253).

In order to accurately localise these lesions several techniques have been documented each with its own advantages and drawbacks (Dua et al., 2011:246-253; Green & Vidya, 2018:281-283; Obeng-Gyasi et al., 2018:377-385).The wire-guided localisation (WGL) technique is the most widely used and is still the preferred method for preoperative localization of impalpable breast lesions (Garzotto et al., 2021:93-105; Norman et al., 2021:141-148) Despite its widespread use, WGL does have many reported drawbacks such as patient discomfort, technical difficulty, and risk of complications (Dua et al., 2011:246-253; Sajid et al., 2012:852-858).

The radioguided occult lesion localisation (ROLL) is an alternative technique using a radioactive tracer injected into or close to the lesion under radiographic guidance prior to surgery where the localisation and removal of the lesion is aided by a hand-held gamma probe (Dua et al., 2011:246-253). The ROLL method has been reported to be technically easier, quicker and more accurate when compared to the WGL (Landman et al., 2015:6-14). An added advantage is it that in the case of histologically proven impalpable breast cancers, a sentinel lymph node biopsy can be done simultaneously (sentinel node with occult lesion localisation or SNOLL) to detect axillary metastases (Ahmed & Douek, 2013b:1034-1040).

During the period 2003 to 2016, the ROLL procedure was used to assist in the preoperative localisation of impalpable lesions at Groote Schuur Hospital, Cape Town, Western Cape, South Africa.

1.2 Research Rationale

While the efficacy of the ROLL technique with or without sentinel node biopsy has been well documented internationally, to the best of our knowledge there had been no local data published on the use of this technique.

1.3 Research Aims

This study evaluated the ROLL procedure as it was performed at a breast unit at a large tertiary hospital in Cape Town. This was achieved by performing a retrospective analysis of patient records from 2003 to 2016 to assess the accuracy and efficacy of the ROLL technique for diagnostic and therapeutic excisions.

1.4 Research Objectives

1.4.1 Research objective one:

This objective described the ROLL technique as an accurate and effective localisation technique with reference to its:

I. Successful localisation rates.
II. Localisation failures.
III. Cosmetic outcome in terms of volume excised.

1.4.2 Research objective two:

This objective described the therapeutic effectiveness of the combination of ROLL with Sentinel lymph node biopsy (SLNB) as an effective therapeutic tool in patients diagnosed with breast carcinoma, as determined by:

I. Complete tumour excision.
II. Re-excision rates.
III. Sentinel lymph node detection.

1.4.3 Secondary outcomes

I. Technical difficulties encountered or experienced.
II. Time and ease of the procedure.
III. Radiation Safety.

1.5 Thesis structure

Below is an outline and overview of the structure of the thesis.

CHAPTER 2: Literature Review

In this chapter a summary of the related literature and previously published studies is reviewed and discussed. This includes a brief introduction to the detection and management of occult breast lesions as well as a brief contextual background to breast anatomy and neoplasms. The chapter further proceeds to discuss in depth theoretical and methodology aspects as related to ROLL and SNOLL in the pre-operative localisation of non-palpable breast lesions.

CHAPTER 3: Research Methodology

This chapter will describe the localisation procedure used at the study site when removing non palpable lesions for diagnostic purposes (ROLL) as well as the ROLL procedure performed with simultaneous SNB for therapeutic purposes (SNOLL). It will also describe the methodology; data collection and technique; ethics approval and permission; statistical analysis as well as limitations of the study.

CHAPTER 4: Results

In this chapter all the relevant findings contributing towards the outcomes of the study objectives is presented. Results on successful lesion localisation rates, tumour characteristics, pre- and post-operative findings as well as successful SN detection rates are recorded. Any further additional findings are also presented.

CHAPTER 5: Discussion and recommendations.

In this chapter main results and findings of the study are discussed and compared to previous studies. The strengths of the study as well as limitations and recommendations are noted and conclusions drawn.

CHAPTER TWO
LITERATURE REVIEW

2.1 Introduction

Occult impalpable breast lesions are detected either by mammographic screening programmes or via opportunistic imaging investigations done for symptomatic breast disease. Globally, as a result of increased access to breast imaging a large number of lesions with subtle changes are being detected necessitating the need for further histological diagnosis (Sajid et al., 2012:852). It is reported that 15 - 25% of occult lesions are malignant (De Cicco et al., 2002:145).The early detection and management of small, early stage malignant lesions have shown to significantly improve the long term survival outcomes for these patients (Aydogan et al., 2010:226). When an occult breast lesion is detected on mammogram or ultrasound, further histological evaluation is necessary to confirm the diagnosis, this is often performed by percutaneous fine needle aspiration or core biopsy (Thind et al., 2005:684-685). In instances where the needle biopsies proved non-diagnostic, a surgical excision is indicated as a diagnostic intervention to obtain a diagnosis or as a therapeutic intervention to highly suspicious or confirmed breast cancers (Dua et al., 2011:246). It is therefore important that precise localisation and accurate surgical removal of the lesion is achieved to minimise disfigurement of healthy breast tissue when done with diagnostic intent (Nadeem et al., 2005:287). Likewise small malignant lesions are amenable to breast conservative surgery (BCS) where the aim is to remove the tumour with as little normal tissue as possible (Thind et al., 2011:833).

The management of occult breast lesions is therefore dependant on clinical, radiological and histological outcomes (Obeng-Gyasi et al., 2018:377-385).

The next section will discuss a brief overview of breast anatomy, malignancies of breast tissue and histology, as well as the management of impalpable breast lesions.

2.2 Anatomy of breast tissue

The following types of tissue occur in the breast namely:

- Glandular tissue – This comprises of lobules or glands responsible for producing milk and the ducts which carry the milk to the nipple.
- Stromal or supporting tissue – These include the fatty tissue that makes up breast size and fibrous tissue which holds all breast tissue in place.
- Lymph vessels – Transport lymph fluid and connects to lymph nodes in the axilla or chest area.

  (Sharma et al., 2010:112-113)

2.3 Histology of breast malignancy

The types of breast neoplasms are classified according to the type of tissue it originates from and also whether it has breached the basement membrane (Sharma et al., 2010:109-126).

2.3.1 Non-invasive cancer

The neoplasm occurs in the milk ducts and has not breached the basement membrane and therefore does not invade the surrounding tissue. The most common type is ductal carcinoma in situ (DCIS) (Sharma et al., 2010:109-126). Presenting as microcalcifications, DCIS is mainly detected by mammography (Kuerer et al., 2017:2653-2662). Breast conservative surgery (BCS) is the treatment of choice as the cancer has not spread beyond the ducts (Kuerer et al., 2017:2653-2662).

2.3.2 Invasive Cancer

In invasive breast cancer, tumour cells extend beyond the basement membrane and into the surrounding tissue (Sharma et al., 2010:109-126). The most common type of invasive cancer is infiltrating ductal carcinoma (IDC). It starts in the milk ducts extending into the surrounding stroma of the breast and from there it can invade lymphovascular spaces which can lead to distal spread elsewhere in the body. Other less frequent types include infiltrating lobular cancer, tubular carcinoma and mucinous carcinoma (Sharma et al., 2010:109-126).

2.4 Breast imaging methods

There are currently 3 breast imaging modalities used to image and diagnose breast lesions. These are mammography, ultrasound and magnetic resonance imaging (MRI) (Iranmaki et al., 2020:51-57).

2.4.1. Mammography

The current screening method for breast lesions is mammography with a sensitivity rate of 75% although in dense breasts sensitivity is decreased to 50% (Iranmakani et al., 2020:51). Low energy x-rays of 20-32 kVp are passed through breast tissue to identify masses, microcalcifications and breast tissue abnormalities (Iranmakani et al., 2020:51-57). Advances in mammographic technology includes digital breast tomosynthesis and contrast enhanced mammography (Iranmakani et al., 2020:51-57). Digital breast tomosynthesis allows for 3D imaging of the breast thereby increasing the sensitivity of lesion detection (Iranmakani et al., 2020:51-57). Contrast enhanced digital mammography is performed by administering iodine based contrast media allowing visualisation of the vasculature of breast lesions (Iranmakani et al., 2020:51-57). Despite the advantages and widespread use of mammography it must be kept in mind the high radiation risk it poses to the patient (Iranmakani et al., 2020:51-57).

2.4.2 Breast Ultrasound

Ultrasonography uses high frequency sound waves passed through tissue and forms an image based on the intensity of the waves as it is reflected and detected by a transducer (Iranmaki et al., 2020:51-57). Ultrasound is more sensitive in dense breasts than mammography and combined with mammography it allows for a 97.3% sensitivity rate (Iranmakani et al., 2020:51-57). Doppler ultrasound allows for the visualisation of blood flow to the lesion (Iranmakani et al., 2020:51-57).

2.4.3 MRI

MRI technology uses a magnetic field and the magnetic properties of hydrogen atoms in tissues to produce an image (Iranmakani et al., 2020:51-57). Due to its high cost it is not used for screening, however due to its high specificity it is useful in surveillance of high risk patients (Yilmaz et al., 2012:395) .

2.4.4 The Breast Imaging Reporting and Data System (BIRADS system)

The Breast Imaging Reporting and Data System (BIRADS system) is a classification system developed by the American College of Radiology allowing for a standardised method of reporting on mammograms (Liberman et al., 1998:35-40). It allows for the findings on imaging to be classified according to several well-defined categories. By using this standardised system, it allows for communication between radiologists and referring physicians (Liberman et al., 1998:35-40). It also reduces the variability in reporting by different radiologists allowing for better follow up. These classifications are based on the finding of masses (its shape, margins and mass), calcifications, distortion of the normal appearance of the breast, location of the lesion and other associated findings such as nipple retraction, skin retraction etc. (Liberman et al., 1998:35-40).

This system of classification is universally used in breast screening programmes. Although originally only used for mammography the system was updated to include ultrasonography (Liberman et al., 1998:35-40). The BIRADS categories are described below in Table 2.1.

Table 2.1: BIRADS categories and classification

0	Incomplete, need for an additional imaging evaluation
1	Normal. Normal interval follow-up
2	Typically benign. Normal interval follow-up
3	Probably benign. A short interval follow-up is recommended (4 months follow-up for masses and 6 months follow-up for microcalcifications)
4	Suspicious abnormality: a biopsy should be considered

4a	Lesions with a low probability of malignancy. If the biopsy is benign a follow up at 6 months is recommended.
4b	Lesions with an intermediate probability of malignancy. Fine needle biopsy (FNAB) or core needle biopsy is recommended.
4c	Findings with a moderate concern of malignancy.
5	Highly suggestive of malignancy. Biopsy or surgery should be performed.
6	Histologically proven malignancy. Imaging is performed for cancer staging or evaluation after chemotherapy
Categories according to breast tissue	
Type 1	Fatty breast (less than 10% of dense tissue)
Type 2	Fibroglandular (10–49% of dense tissue)
Type 3	Heterogeneously dense (49–90% of dense tissue)
Type 4	Dense and homogeneous (>90% of dense tissue).

(Balleyguier et al., 2007:193-194)

Biopsies are therefore considered for BIRADS classification 4-5 (Balleyguier et al., 2007:194).

2.5 Biopsy methods

2.5.1 Percutaneous needle biopsy

Also referred to as minimally invasive breast biopsies, this method is the preferred initial method of obtaining a tissue diagnosis for breast abnormalities seen on imaging or detected during physical examination (Obeng-Gyasi et al., 2018:377-385). Percutaneous needle biopsies are less traumatic, carries less risk and are more cost effective than surgical methods (Pijnappel et al., 2004:595-600; Bhayroo et al., 2016:1-6). The biopsy can be aided by imaging guidance such as ultrasound and mammographic stereotaxis (Davis et al., 2021:542-555). Percutaneous biopsy can be performed either by fine-needle aspiration biopsy (FNAB) or large core needle biopsy (LCNB) (Pijnappel et al., 2004:595-600).

2.5.1.1 Fine needle aspiration biopsy (FNAB)

FNAB is a simple method requiring only local anaesthesia. It can be done in a doctor's office (Obeng-Gyasi et al., 2018:377-385). A 10-20ml syringe with a 22G needle attached is inserted into the area and cells are aspirated or suctioned into the syringe. These cells are submitted for cytology (Obeng-Gyasi et al., 2018:377-385). False-negative results with FNAB are common and therefore the absence of malignant cells in lesions that are suspicious on imaging should be further investigated (Bhayroo et al., 2016:1-6; Obeng-Gyasi et al., 2018:377-385). FNAB has been reported to have a high rate of inconclusive diagnosis especially in lesions detected as microcalcifications. It can also result in an overestimation of DCIS and cannot

differentiate between in situ and invasive carcinomas. This is especially important since treatment differs between the two types of breast cancer especially with regards to treatment of the axilla (Pijnappel et al., 2004:595-600).

2.5.1.2 Large core needle biopsy (LCNB)

LCNB is performed under local anaesthesia which is followed by small incision made into the skin after which a large bore needle is used to collect a tissue sample. Imaging guidance can be used with ultrasound or stereotaxis (Bhayroo et al., 2016:1-6). Different size needles can be used ranging from 14-18 gauge (Pijnappel et al., 2004:595-600). A vacuum assisted device with a spring loaded needle can be used enabling multiple tissue samples to be taken in succession (Bhayroo et al., 2016:1-6). Vacuum-assisted breast biopsy (VABB) has the advantage of obtaining larger tissue samples. Stereotactic breast biopsy is also very useful in obtaining a tissue biopsy of microcalcifications only seen on mammography although the radiation exposure with this procedure is high and also requires specialised equipment which is a key factor especially in developing countries (Bhayroo et al., 2016:1-6). In the case of microcalcifications, a larger volume of tissue for biopsy increases the reliability of the histology result. Therefore for these lesions a core biopsy using a 14 gauge needle with at least five to six passes will increase the sensitivity as opposed to using an 18 or 16 gauge needle (Pijnappel et al., 2004:595-600).

2.6 Pre-operative localisation techniques

In the absence of a diagnosis after percutaneous needle biopsy, surgical removal of these lesions may be necessary (Postma et al., 2012:469-478). In order to guide surgical excision, accurate pre-operative localisation is essential for successful excision with limited breast mutilation, and, when indicated, for complete tumour removal (Sajid et al., 2012:852; Garzotto et al., 2021:93-105).

There are various localisation techniques which have been used to localise impalpable breast lesions for surgical excision (Dua et al., 2011:246-253; Green & Vidya, 2018:281-283).

These techniques include:

- Wire-guided localisation (WGL)
- Radioguided occult lesion localisation (ROLL)
- Sentinel lymph node biopsy with radio occult lesion localisation (SNOLL)
- Radioactive seed localisation (RSL)
- Carbon marking
- Magnetic tracers and Magnetic sentinel node and occult lesion localisation (MagSNOLL)

- Magnetic seed localisation

A description of each of these techniques and their advantages and disadvantages will be discussed below.

2.6.1 Wire-guided localisation (WGL)

The wire-guided localisation technique has been the gold standard technique and is still widely practised (Garzotto et al., 2021:93-105; Norman et al., 2021:141-148). The technique is performed under local anaesthesia using a hooked wire which is placed in the centre of the lesion by ultrasound or mammographic guidance. Placement of the wire is confirmed by performing a check mammogram. The procedure is done on the same day as theatre and the wire stays in place while the surgeon assesses where the tip of the needle lies before making the incision to remove the wire and the lesion (Dua et al., 2011:247).

Despite its wide use, wire guided localisation has several reported disadvantages. These include:

- Reports of incidences where wires have dislodged, frayed, or migrated from its original placement before surgery (Homer, 1983:929; Davis et al., 1988:777-778).
- Poor cosmetic outcomes as the skin incision to remove the lesion may be far from the lesion and thereby increasing damage to surrounding normal tissue (Thind et al., 2005:685).
- High rates of repeat surgery due to incomplete tumour resection, up to 40-50% in some studies (Dua et al., 2011:247).
- The wire must remain in place until surgery which can be uncomfortable for the patient (Nadeem et al., 2005:284).
- The technical difficulty of placement in dense breast tissue (Dua et al., 2011:247).
- Diathermy burns to the skin can occur close to the localisation wire (Dua et al., 2011:247).
- Increased anxiety levels for the patient due to an additional procedure on the day of theatre (Thind et al., 2005:685; Dua et al., 2011:247).
- There is a risk of needle stick injury to both the surgeon and the pathologist from the sharp wire tip (Dua et al., 2011:247).
- Reports of pneumothoraces and pericardial injuries following needle insertion (Dua et al., 2011:247).
- Patients have reported the procedure to be uncomfortable and painful (Rampaul et al., 2004:1576).

2.6.2 Radioguided occult lesion localisation (ROLL)

The ROLL procedure was first published by Luine et al. (2002:522-525) from the European Institute of Oncology in Milan. This technique has since gained popularity and several studies have been done comparing favourable results to the hook wire technique (Rampaul et al., 2004; Nadeem et al., 2005; Thind et al., 2005; Lovrics et al., 2011; Sajid et al., 2012).

The technique involves an intralesional injection of a radio-labelled tracer. As with the hook wire, the injection is performed under stereotactic or ultrasound guidance. A check mammogram can be done to assess the placement of the needle before injection. Contrast media can also be injected with the radioactive tracer allowing confirmation of radiotracer placement by mammographic imaging (Rampaul et al., 2004:1576). Scintigraphic images performed after administration helps to assess the localisation of the radiotracer (Luini et al., 2002:522-525). A skin marking corresponding to the location of the area of tracer activity seen on imaging is done which aids the surgeon in placing the initial incision (Gennari et al., 2000:693). The procedure can be performed up to 24 hours prior to surgery or on the same day. On the day of surgery, a handheld gamma probe is used by the surgeon to localise the area of maximum activity and thus guide the removal of the lesion (Dua et al., 2011:248). The excised lesion is radiographed, orientated, and sent for histological testing (Gennari et al., 2000:693).

The ROLL technique has many advantages such as:

- Technical ease, quick to perform and fewer complications, resulting in improved surgical and cosmetic outcomes (Landman et al., 2015:6).
- An important and useful advantage of the ROLL technique is that the radiopharmaceutical follows the route of lymphatic drainage and accumulates in the sentinel lymph node (SLN) which allows for the simultaneous localisation of the breast lesion as well as the draining axillary nodes (Ahmed & Douek, 2013b:1034).

Despite its advantages, ROLL has also been found to have disadvantages and therefore it has been suggested that ROLL cannot entirely replace WGL especially in large breast lesions (Sajid et al., 2012:857). According to Sajid et al. (2012:857), some disadvantages of the ROLL technique include:

- Errors of depth due to the compression of breast tissue during stereotactic guidance
- The limited half-life of the radiopharmaceutical in terms of scheduling surgery. However, several studies have been performed successfully from 4 up to 24 hours prior to surgery.
- Non visibility of the radionuclide on mammography making localisation with stereotactic guidance difficult.

- The extent of microcalcifications can be delineated with the placement of several wires and this is not possible with the ROLL technique.

2.6.3 Radioguided occult lesion localisation with Sentinel lymph node biopsy (SNOLL)

Feggi et al. described the addition of sentinel lymph node biopsy (SLNB) to the ROLL procedure by using a single intra-tumoural injection of a Technetium-99m (^{99m}Tc) labelled radiocolloid to both localise the occult lesion and to identify the sentinel node (Feggi et al., 2001:1589-1596). In 2007 this technique was publicised by the European Institute of Oncology and referred to as the Sentinel node with occult lesion localisation (SNOLL) procedure (Monti et al., 2007: 2929). The concept of lymphatic mapping and sentinel node biopsy was introduced by Morton in 1992 for patients with melanoma. Since then the procedure has been applied to other tumours (Morton et al., 1992:392-399). The theory behind the sentinel node is that the first node in the lymphatic drainage pathway of the tumour would be the first node to be affected by metastases. More than one lymphatic channel may be draining the area and therefore it is possible to have more than one sentinel node. SLNB has become one of the most important developments in the treatment of early stage breast cancer (Keshtgar & Ell, 1999:57-67). Systematic studies have shown that cancer spreads from the sentinel node to other nodes and that SLNB is a reliable method to investigate the sentinel node (Veronesi et al., 1999:371). For patients with early-stage breast cancer if the sentinel node can be identified and found to be negative for metastatic involvement then it can be safely assumed that any other lymph nodes in the chain would be negative as well. The patient can thus be spared an axillary lymph node clearance dissection (ALND) which carries an associated risk of lymphedema and high morbidity rate thereby improving the patient quality of life (Lyman et al., 2005:7703).

The SLNB has now become the preferred method of staging the axilla in patients with clinically and radiologically node–negative breast cancer, thereby sparing an ALND. Studies have shown that SLNB has been accurate in predicting the status of axillary nodes in more than 95% of cases (van Rijk et al., 2007:627-632; Giacalone et al., 2012:222-229; Ahmed & Douek, 2013b:1034-1040). An ANLD is only performed in patients with confirmed nodal metastases and locally advanced breast cancers (De Cicco et al., 1998:2080-2084). The SNOLL technique has been found to be a cost-effective method that is reliable, easy to use and patient friendly (Thind et al., 2011: 839).

2.6.4 Radioactive seed localisation (RSL)

Another radioguided technique which has been used is radioactive seed localisation. This technique was originally employed in brachytherapy for prostate cancer patients (Ahmed & Douek, 2013a:383). A titanium seed measuring about 4x8mm is labelled with Iodine-125 (^{125}I) and is placed percutaneously into the lesion under stereotactic or ultrasound guidance (Frost

et al.,2021:124-125). Placement of the seed into the lesion can be verified using mammography imaging (Ahmed & Douek, 2013a:383). Iodine-125 emits gamma rays of 27 keV and therefore combined sentinel node mapping can be performed by changing the sensitivity on the gamma probe to the 140 keV emissions of ^{99m}Tc (Dua et al., 2011:250). In this way the emissions from the lesion will not affect the detection of the sentinel node as different energy windows can be set on the probe (Dua et al., 2011:250). After excision and pathology analysis the radioactive seed is removed and stored in a lead container to allow for decay (Dua et al., 2011:250).

Advantages:

- Due to the long 60-day half-life of ^{125}I, placement of the seed can take place up to several days prior to the surgery (Gray et al., 2004:379).

Disadvantages:

- Radioactive seeds requires specific radiation safety regulation and knowledge with regards to receiving, handling, use and proper disposal of the radioactive seed (Frost et al., 2021:124-133; Goudreau et al., 2015:1321).

2.6.5 Carbon marking

This technique involved the administration of carbon particles in a suspension under radiographic imaging guidance. A tattoo is formed with a discoloured pathway that leads to the lesion (Rose et al., 2003:264-269).

Advantage:

- The technique is relatively inexpensive and discolouration can last for a few weeks (Green & Vidya, 2018:281-283; Rose et al., 2003:264)

Disadvantage:

- It is not widely used due to the associated risk of reaction to a foreign body (Rose et al., 2003:264; Green & Vidya, 2018:281).

2.6.6 Magnetic tracers

This technique involves injecting iron oxide particles into the lesions under stereotactic or ultrasound guidance. A magnetometer is used during surgery to detect the magnetic signal and localise the tumour. Since the tracer is filtered by the lymphatic drainage a simultaneous SNB can be performed (MagSNOLL) (Green & Vidya, 2018:281-283; Davis et al., 2021:542-555).

Advantage:

- The iron oxide particles can be placed up to 7 days before surgery allowing for scheduling flexibility (Davis et al., 2021:542-555; Garzotto et al., 2021:93-105).

Disadvantages:

- The procedure is still relatively new and requires the acquisition of a magnetic probe, with added expense (Davis et al., 2021:542-555).
- There is the risk of possible interference from ferromagnetic instruments during theatre (Green & Vidya, 2018:281-283).

2.6.7 Magnetic seed localisation

For this technique, a magnetic seed marker (Magseed) is placed during imaging guidance intralesionally. During surgery the lesion is localised using a magnetic probe (Sentimag) (Davis et al., 2021:524-555).

Advantage:

- Seed placement is easy and can be placed for up to 30 days before theatre (Green & Vidya, 2018:281-283; Davis et al., 2021:542-555).
- No radioactivity is used (Green & Vidya, 2018:281-283) .

Disadvantages:

- The probe has a detection limitation depth of 30 mm and therefore may not be useful in deep lesions (Green & Vidya, 2018:281-283)
- The probe may also be affected by ferromagnetic instruments and also requires the acquisition of the probe (Green & Vidya, 2018:281-283; Davis et al., 2021:542-555).

The implementation and choice of a localisation procedure at an institution is based upon physician experience and preference, published literature, ease of use, workflow efficiency and most importantly cost effectiveness and resource availability (Davis et al., 2021:542-555). Since 2003 the ROLL procedure replaced the WGL technique at the study site.

2.7 Requirements of a good localisation method

There are several factors which determine the accuracy and effectiveness of localisation procedures for non-palpable breast lesions (Dua et al., 2011: 246–253). The localisation procedure should be able to precisely localise the lesion; allow for easy and accurate surgical removal; enable better lesion centricity facilitating adequate clear surgical margins; reduced re-operation or re-excision rates; and smaller excision volumes (Dua et al., 2011:246-253; Lovrics et al., 2011:388-397)(Lovrics et al., 2011; Dua et al., 2011). Other outcomes include

minimal excessive damage of healthy tissue, shorter procedure times and better patient tolerance (van der Ploeg et al., 2008:1-5; Duarte et al., 2016:1140-1145). In highly suspicious or malignant lesions where BCS is employed it is imperative that the procedure allows the removal of the lesion with adequate free tumour margins as well as facilitate simultaneous SN identification (Ahmed & Douek, 2013:1034-1040).

In this section we will discuss these aspects in detail and look at how ROLL compares to WGL in those respects.

2.7.1 Accurate lesion localisation

The correct localisation of non-palpable lesions is essential both for diagnostic purposes as well as for therapeutic purposes. An accurate localisation method allows for better centring of the lesion within the excised specimen and therefore aids in achieving a free margin (De Cicco et al., 1998:2080-2084; Nadeem et al., 2005:283-289). The properties of the localisation marker should be that it remains at the site of the lesion after placement until commencement of surgery and that it is easily identifiable by the surgeon (Dua et al., 2011:246-253).

The radiopharmaceutical used in the ROLL procedure fulfils most of the criteria to perform accurate lesion localisation. Once injected into the lesion it is retained in the lesion and does not migrate (Luini et al., 2002:522-525). Confirmation of the needle placement within the lesion can be done with ultrasound imaging or mammography (Thind et al., 2005:681-686). Contrast medium can also be injected at the site and verified with mammography (Gennari et al., 2000:692-698). The technique of using a gamma probe when performing the ROLL procedure, to detect the lesion location allows the surgeon to constantly verify the location as well as the extent of the lesion (Gennari et al., 2000:692-698). After lesion resection a survey with the gamma probe to detect any residual activity verifies that the lesion has been completely resected. The resected specimen is x-rayed to verify the presence of the lesion within the specimen (Gennari et al., 2000:692-698).

Accurate placement of the radiotracer and subsequent successful localisation of the lesion with the ROLL procedure has been reported to be between 95-99.5% (Gennari et al., 2000:692-698; De Cicco et al., 2004:349-354; Rampaul et al., 2004:1575-1577). In a study of 647 patients Gennari et al. reported successful lesion localisation in 99.5% of patients with the ROLL technique. There were no reported recurrences at follow up (Gennari et al., 2000:692-698). Thind et al. reported 100 % lesion localisation in their study of 70 ROLLS (Thind et al., 2005:681-686). In another study by Giacalone et al. (2012:222-229) ROLL was reported to have a lower rate of re-excisions (13.9%) when compared to WGL (31.3%). The rate of clear tissue margins was also significantly greater in the ROLL group ($p = 0.03$) than in the WGL

group (Giacalone et al., 2012:222-229). The accurate and successful removal of the lesion spares the patient from having a second operation or re-excision and allows for less tissue damage during the surgical exploration (Dua et al., 2011:246-253).

2.7.2 Resection volume and margin status

Complete removal of the lesion with acceptable clear margins allows for radical resection in the event of a suspicious lesion being confirmed as malignant upon histology (Luini et al., 2002:522-525). The aim is to achieve an adequate surgical margin whilst still removing as little healthy tissue as possible. The presence of involved surgical margins has been shown to be a prognostic factor for local recurrence of disease (Atkins et al., 2012:109-115).

According to Singletary margins are described and classified as:

- Negative margin is defined as the absence of tumour cells from the edge of the specimen at the specified distance for free margin.
- Positive margins are when tumour cells are found at the edge of the cut or at the inked margin.
- A close margin is defined by the presence of tumour cells between the defined boundary of the tumour and the cut edge of less than 1mm.
  (Singletary, 2002:383-393).

Although consensus exists that a negative margin reduces the rate of residual disease it does not exclude the possibility of a local recurrence (Singletary, 2002:383-393). Therefore it is still advised to follow up with adjuvant therapy (Houssami et al., 2010:3219-3232). The absence of a negative margin can lead to a decision to perform a re-excision (Landheer et al., 2004:824-828). There is no defined negative margin width. Margin widths differ according to different authors as well as the type of cancer. For invasive cancer the margin status has been described as >1-2mm while even the absence of tumour cells at inked edge regardless of the margin width is accepted and >5mm for DCIS (Nadeem et al., 2005; Bernardi et al., 2014; Marinovich et al., 2016; Kuerer et al., 2017). Whereas in a study by Sarlos et al. (2008:403-408) a margin of >1mm for invasive cancer and >10mm for DCIS was considered clear. The decision to re-excise is often based on a positive or close margin (Kuerer et al., 2017:2653-2662). However, many of these re-excised specimens have been found to be free of residual tumour on histology (Kuerer et al., 2017:2653-2662). In addition to margin status, factors such as multifocality, positive nodal status and patients age, are risk factors for residual disease (Landheer et al., 2004:824-828). All these factors should be considered before the decision is made to perform a re-excision. Therefore, in most instances even with a close margin re-operations can be avoided (Kuerer et al., 2017:2653-2662).

There is no evidence that proves that a larger margin width reduces the risk of local recurrence (Singletary, 2002:383). In a study done on 1192 patients with histologically confirmed invasive breast cancer, Bernardi et al. reported no significance to the distance of the tumour from the margin with respect to recurrence and survival rates. The most important factors were the biological aggressiveness of the tumour. The following conclusions were drawn; the absence of tumour cells at the inked margin of the resected lesion is sufficient as a negative margin; increasing the margin width would lead to an increase in the rate of re-operations and psychological trauma to the patient and reduced cosmetic effects. Furthermore, the amount of tissue resected will depend on the size of the lesion and the determined margin required (Bernardi et al., 2014: 2279-2287).

The ROLL procedure has been reported to have a better tumour free margin compared to WGL. Thind et al. reported that 84% of patients in their study had a tumour free margin versus 60% of patients who had WGL (Thind et al., 2005:683). Nadeem et al. (2005:286) demonstrated clear margins in 83% of ROLL patients compared to 57% WGL technique.

2.7.3 Cosmetic outcome

The aim of breast conserving surgery (BCS) is to successfully locate and excise the lesion and if the procedure is done for therapeutic purposes, to completely remove the tumour with an adequate free margin to ensure that no tumour cells are left at the excision site (Thind et al., 2011:833-834). To ensure a good cosmetic outcome this should be achieved with as little tissue damage as possible (Dua et al., 2011:246).

The ROLL procedure allows for accurate localisation of the lesion as the gamma probe can be used on the surface of the skin to detect the maximum count which would represent the injection site. This allows the surgeon to make the incision in the appropriate area (De Cicco et al., 2004:148). At the point where the detected number of counts drops sharply this would indicate the margin of the lesion. This allows for better centring of the lesion within the excised tissue resulting in less unnecessary removal of healthy tissue while still maintaining a tumour free margin (Giacalone et al., 2012: 223). The exact location of the lesion can be checked constantly throughout the procedure using the gamma probe (Giacalone et al., 2012:223).

When using the WGL technique the placement of the initial incision depends on the placement of the wire. The length of the wire needs to be followed until the tip of the wire is found, representing the location of the lesion (Dua et al., 2011:247). As the surgeon cannot see the tip of the wire, he must estimate the extent of the resection margins. This can lead to unnecessary tissue damage and bigger specimen excision volumes (Sarlos et al., 2009:243).

The specimen volume for ROLL has been reported to be significantly smaller than that of WGL (Besic et al., 2002:2684-2689). Although Postma et al. observed a larger tissue volume of 71cm^3 with ROLL and 64cm^3 with WGL, there was however, no significant difference in the cosmetic outcome (Postma et al., 2012:469).

Patients rated their cosmetic outcome post-surgery more favourably in the ROLL groups than those in the WGL groups based on subjective ratings of patients after the procedure (Nadeem et al., 2005:283-289; Thind et al., 2005:681-686; Medina-Franco et al., 2008:108-111). Thind et al. reported a 73% excellent outcome and 27% good outcome for the ROLL procedure against a 54% excellent outcome and 46% good outcome for the WGL technique (Thind et al., 2005:683). Nadeem et al. reported similar with a 74% excellent outcome and 26% good outcome for the ROLL procedure against a 55% excellent outcome and 45% good outcome for the WGL technique (Nadeem et al., 2005:286). In the study done by Medina-Franco et al. 76% of patients who had the ROLL technique rated their outcome as excellent versus 52% in the WGL group (Medina-Franco et al., 2008:109).

2.7.4 Rate of re-excisions

A positive margin has been reported to be one of the prognostic factors for disease recurrence (Singletary, 2002: 383). Failure to obtain adequate disease-free margins on excision can lead to the decision to perform a re-excision (Houssami et al., 2010:3320). WGL has been reported to have high rates of positive margins (Nadeem et al., 2005:283-289; Dua et al., 2011:246-253). Re-operation rates with WGL due to incomplete tumour clearance has been reported as high as 40-50% (Dua et al., 2011:247). Nadeem (2005: 286) reported clear margins in 83% of patients with ROLL and 57% for patients using the WGL technique. Giacalone et al (2012: 226) reported re-excision rates of 13.9% (n=6) for the ROLL and 31.3% (n=27) for the WGL technique.

2.7.5 Time and ease of the procedure

The time taken to perform the procedure has a financial impact. The shorter the duration of the procedure will allow for more available theatre time to perform more procedures (Dua et al., 2011:251). A randomised control study Moreno et al (2008:29) reported a significantly shorter procedure time for ROLL versus WGL (26min and 37min respectively). Nadeem et al (2005: 286) reported procedure times for ROLL as 6-12min and WGL as 15-20min. Thind et al (2005: 683) also reported shorter times for ROLL as 5-7min versus 20-25min for WGL.

The relative technical ease of performing the procedure does not require highly skilled operators (Rampaul et al., 2004:1577). Rampaul et al (2004:1575-1577) conducted a randomised control study comparing ROLL with WGL in terms of the difficulty of the procedure

as reported by the performing physician. The conclusion was that radiologists and surgeons found the ROLL procedure easier to perform.

2.7.6 Patient safety and tolerance

Undergoing a surgical procedure for diagnosis or therapy of suspicious lesions is no doubt psychologically and emotionally traumatic for the patient. It is important that the procedure be safe, risk free and effective (Dua et al., 2011: 246). WGL involves the placement of a guide wire into the lesion usually a day before surgery. For the patient this is an added procedure during an already anxious period. The discomfort to the patient is high as the wire needs to stay in place until surgery. In some instances, displacement of the wire may occur. Associated risks have been reported as risk of a pneumothorax and diathermy burns to the skin (Dua et al., 2011: 247). In the study performed by Rampaul et al. patients reported the ROLL to be less painful than the WGL (p=0.012) (Rampaul et al., 2004:1575-1577). Moreno et al. reported a significantly longer hospital stay in the WGL when compared to the ROLL group (19 hours versus 2 hours). The patients pain scores for the two procedures were also significantly different being with it being higher for WGL than for ROLL (Moreno et al., 2008:29) .

Even though ROLL requires the administration of a radioactive dose, data has shown that the radiation dose to the patient and staff is very low due to very low radioactive doses that are administered (Rampaul et al., 2003:150-152). Once injected the radiopharmaceutical localises in the lesion which is subsequently excised. An administered dose of 74 mega Becquerel (MBq) is only 20% of 925 MBq which is the administered dose for a bone scan of which no isolation or special radiation protection is necessary (Aydogan et al., 2010:226-230). The total effective dose based on an injected dose of 15 MBq is well below the accepted annual limits of 1 millisievert (mSv) and thus no additional radiation protection measures are necessary for the patient or medical personnel (Waddington et al., 2000:382; Rampaul et al., 2003:150). Milner et al (1999:80) demonstrated that one would need to perform 5000 SLN biopsies before reaching the effective skin dose limit of 50 rem per year. It would also be unlikely that a surgeon would perform even 500 procedures in a year which would achieve an exposure sufficient enough to require the need for wearing a radiation monitoring badge. Stratmann et al (1999:454-457) quantified it in time determining that a surgeon would need to perform 2190 hours of surgery per year before exceeding the annual dose limit for the hands of 75 000 rem per year.

2.8 Technical Aspects in performing the SNOLL procedure

Several methods for performing the SNOLL procedure have been described with these methods differing in:

- the type of radiopharmaceutical/s used

- the administered dose and volume
- site of injection
- single or dual radiotracer technique
- the administration of contrast media
- acquisition of scintigrams
- time of injection prior to theatre and
- the use of blue dye during theatre.

2.8.1 Radiopharmaceuticals used

The ideal radiopharmaceutical for lymphoscintigraphy should be able to migrate to the lymphatic node following the lymphatic pathway from the site of injection. Uptake in the lymph node is by phagocytosis. Based on this principle radio-labelled colloids are used for lymphoscintigraphy and SLN localisation because of its ability to migrate from the injected site to the lymphatic system and be retained in the SLN (Núñez et al., 2009:742). While there is no standard colloid of choice, particle size has been reported to have an influence on the rate of drainage of the injected particles from the injected site to the lymph nodes as well as phagocytosis by the lymph nodes since drainage of colloids into the lymphatic system is inversely proportional to its particle size (Núñez et al., 2009:742). Smaller particles have been shown to be taken up better by lymphatic channels and have better accumulation in SLNs. This allows for a smaller dose to be administered which results in less radioactivity at the injection site eliminating the problem of shine through effect which can make localisation of the SLN difficult (Jinno et al., 2002:215). Smaller particle sizes have also been shown to increase the number of nodes visualised. Although this poses a surgical problem because there is an increased risk of removing too many nodes as some might be second or echelon nodes, an increase in the number of SNs detected has been reported to reduce false-negative rates (Jinno et al., 2002:215; Yararbas et al., 2010:805). Smaller particles move from the injection site through exchange by blood capillaries. Medium sized particles usually with a diameter of tens of nanometres travel across lymphatic capillaries after which they are trapped in the SN. Particles with a diameter of more than a hundred nanometres (nm) are trapped in the interstitial space where they can remain for a long time before draining. The choice of radiopharmaceutical and its size will therefore have an influence on the timing of surgery after injection (Yararbas et al., 2010:808-809).

Radiopharmaceutical kits should be prepared using standardised procedures to ensure a consistent particle size range (Jimenez et al., 2008:166). General agreement exists that the best radiopharmaceutical is one with a particle size of between 100-200nm (Buscombe et al., 2007:2155).

Different radiotracers have been employed these include:

- ^{99m}Tc antimony trisulphide (Ahmed & Douek, 2013b: 1037)
- ^{99m}Tc albumin-based colloid radiopharmaceuticals (Buscombe et al., 2007: 2155)
- ^{99m}Tc sulphur colloid (Buscombe et al., 2007: 2155
- ^{99m}Tc Tin colloid (Klienjan et al., 2013:433)

2.8.1.1 ^{99m}Tc antimony trisulphide Colloid

This radiopharmaceutical was the first ^{99m}Tc agent to be used for lymphoscintigraphy. Its particle size ranges from 3 to 30 nm (Eshima et al., 2000: 26). It is generally used in Canada and Australia (Buscombe et al., 2007: 2155).

2.8.1.2 ^{99m}Tc albumin-based colloid radiopharmaceuticals

These include:

- Nanocolloid,
- Microaggregated albumin
- Macroaggregated albumin (MAA)

(Eshima et al., 2000:25-32)

^{99m}Tc nanocolloid

This radiopharmaceutical has varying particle size ranges with 95% of the particles smaller than 80nm, 4% between 80-100nm and 1% of the particles being larger than 100nm (Eshima et al., 2000: 26). Nanocolloid is registered as an intravenous agent for bone marrow scintigraphy and inflammation scintigraphy in areas other than the abdomen. It can also be injected percutaneously to demonstrate the integrity of the lymphatic system and differentiation of lymphatic veins or lymphatic obstruction. When injected subcutaneously 30-40% of ^{99m}Tc albumin colloid particles is filtered into the lymphatic capillaries and then trapped by functioning lymph nodes. When used in breast imaging there is 1-1.5% uptake in regional lymph nodes (Gommans et al., 2009:1550).

^{99m}Tc microaggregated albumin

This radiopharmaceutical has particle size distribution range of 200 to 2,000 nm in size with 90% of particles less than 1,000 nm. Due to its big particle size migration form the injected site is slow (Eshima et al., 2000:26).

^{99m}Tc macroaggregated albumin (^{99m}TcMAA)

Macroaggregates are larger particle sizes in the range of 10,000 to 90,000 nm. As with microaggregated albumin this radiopharmaceutical is not very useful in lymphoscintigraphy due to slow migration from the injection site (Eshima et al., 2000:26).

2.8.1.3 ^{99m}Tc sulphur colloid

When using a reduced heating protocol these radiopharmaceutical yields particles smaller than 300 nm (Eshima et al., 2000: 27). It is the most used radiopharmaceutical for SLN detection in the United States (Buscombe et al., 2007: 2155).

2.8.1.4 ^{99m}Tc tin colloid

The radiopharmaceutical has a standard particle size of 400-1000nm, but kits with smaller sized particles are also available with particle sizes of 200-400nm (Jinno et al., 2002:214). The smaller sized particles were shown to provide a higher SLN identification rate than the larger sized particles (Jinno et al., 2002:213-216). Hepatate™ II is a commercially produced tin colloid kit manufactured by GE Healthcare with 95% of particles of sizes between 190-255nm (GE Healthcare LTD, 2005). Other commercial kits available include locally manufactured NTP tin colloid kit with particles sizes ranging 100-600nm (NTP Radioisotopes (Pty) Ltd, 1997).

2.8.2 Administered dose and volume

Adequate radioactive doses should be used allowing for decay of the radiopharmaceutical. If injections are performed the day before surgery, then doses more than 10 MBq should be administered depending on when surgery will be performed (Buscombe et al., 2007:2156). The required dose should be delivered in a small volume (0.2-0.5ml) as larger volumes can disrupt local lymphatics. A similar amount of air should be in the syringe to clear any dead space in the syringe and the needle (Buscombe et al., 2007: 2155).

2.8.3 Site of injection

The injection is given under stereotactic or ultrasound guidance. The different injection sites employed are:

- Intralesional
- Perilesional
- Subdermally in the skin overlying the tumour or
- Periareolar region

(Lyman et al., 2005:7709; Thind et al., 2011:681).

There is no agreement on the injection site which should be used (De Cicco et al., 2004:350). Perilesional injections may lead to significantly higher incidence of non-visualisation of SN versus injecting in the skin or periareolar region (Lyman, 2005:7709). Feggi et al (2001:1589-1596) performed the SNOLL procedure on 73 patients using a single tracer technique. ^{99m}Tc nanocolloid with a particle size of <80nm was injected half intratumourally and the other half subdermally close to the lesion. Failure to identify the SLN occurred in only 2 cases. Tanis et al (2002:436-438) also demonstrated success using the single tracer technique.

Lavoué et al (2008:2556-2561) also used a single nanocolloid tracer injecting the tracer in two perilesional sites. They justified this technique by the fact that most of the radiotracer remained at the injected site and that only 0.1-1% of the dose migrated to the axilla. They also demonstrated 100% lesion localisation.

2.8.4 Single or dual radiotracer technique

A single or dual radiotracer technique can be used. With the single radiotracer technique, a single dose of ^{99m}Tc nanocolloid is injected intratumourally which is used to localise both the tumour and the SN. The radiopharmaceutical is retained in the lesion while still following the lymphatic pathway, thus identifying the sentinel node (Ahmed & Douek, 2013b: 1036).

With the dual method technique ^{99m}Tc MAA is injected intratumourally where the radiotracer will remain in the lesion. The second injection namely the nanocolloid is given subdermal or periareolar in the region close to the lesion. The nanocolloid will follow the lymphatic drainage and pathway and accumulate in the sentinel node. During surgery both the lesion and sentinel node is located with the handheld gamma probe and excised. If histopathological results for the sentinel node are negative for metastases, then ANLD is deemed not necessary (Ahmed & Douek, 2013b: 1037).

De Cicco et al. (2004: 349) investigated the effect of different types of injection sites and radiopharmaceuticals on the outcome of the SNOLL procedure. The study evaluated 3 groups of patients.

- Group 1 had a dual radiotracer technique using ^{99m}Tc MAA injected intralesionally and a second radiotracer ^{99m}Tc nanocolloid injected peritumourally.
- Group 2 had ^{99m}Tc MAA injected intralesionally and ^{99m}Tc nanocolloid was injected subdermally.
- Group 3 had a single dose of nanocolloid injected intralesionally which was used to evaluate both the lesion and the SLN.

No statistical significance was reported in the rate of successful lesion localisation between the three groups. There was however a statistical significance with regards to the percentage rate of failure with regards to SLNB. In Group 1 failure to identify SLNs were found in 12 of 62 patients and 9 of 79 patients in Group 3, while in Group 2 in only 1 out of 86 patients failed to identify a SLN. In their study they therefore concluded that the dual tracer technique using ^{99m}Tc MAA injected intralesionally and nanocolloid injected subdermally was the method of choice for localising non palpable lesions and SLN. However, in a systematic review of the literature, Ahmed et al. (2013b: 1038) found no evidence to support the added benefit of using the dual tracer technique.

2.8.5 Use of contrast media

The radiotracer can be mixed with contrast media to confirm the accurate placement of the radiotracer into the lesion. This was reported by Patel et al. (2004: 918-923) who mixed 0.2mls of Iohexal with a dose of ^{99m}Tc nanocolloid. After injection mammographic images were performed to confirm the correct placement of the radiotracer.

2.8.6 Simultaneous use of dyes as a dual technique in SNOLL

In some techniques a subdermal or periareolar injection of patent blue or methylene blue dye is injected in theatre before starting operating procedure. Its use is to optimise the visualisation of the lymph node during surgery (Adamczyk et al., 2011: 218). This technique is widely used and has been shown to decrease false-negative rates (Noguchi, 2002: 22).

2.8.7 Acquisition of scintigrams

After injection, usually about 15min after, scintigrams of the area are done on a gamma camera. The patient lies supine on the bed and anterior, 45^{o} anterior oblique images are obtained with the arm on the affected side extended laterally to 90^{o} in the same position it would be during surgery. If necessary, imaging can also be done 2-3 hours or later to ensure visualization of the SN (Buscombe et al., 2007: 2157). The advantage of performing imaging allows for the determination of whether the radiopharmaceutical has drained to the axilla or other sites such as the internal mammary, intramammary, and contralateral or supraclavicular nodes. Also, the position of the SN can be marked on the skin at the time of imaging and checked using the gamma probe. Scintigraphy is therefore an adjunctive to the gamma probe localization (Lyman, 2005: 7714).

2.8.8 Time of surgery after radiopharmaceutical injection

The SN can generally be seen at 2 hours post injection (Buscombe et al., 2007: 2157). Commencing imaging too soon after injection can result in lower detection of positive lymph nodes. Surgery should preferably commence at least 6-18 hours after injection (Lyman, 2005: 7715). When performing delayed surgery, colloid particle sizes of 200-1000nm is recommended as these particles can be retained in SNs for longer (Buscombe et al., 2007: 2155).

The next chapter will discuss the research methodology used to achieve the research aims and objectives.

CHAPTER THREE
RESEARCH METHODOLOGY

3.1 Introduction

It is important before surgical removal of non-palpable lesions that accurate lesion localisation is done pre-operatively to aid and guide the surgeon in terms of incision placement to be able to successfully excise the lesion while achieving adequate tumour free margins and minimal tissue damage (Dua et al., 2011:246-253).

Since 2003 the ROLL procedure was used to localise non-palpable breast lesions at Groote Schuur hospital. This technique has been well documented globally as an effective and accurate localisation method with high successful localisation rates, lower re-excision rates and smaller surgical excision volumes when compared to the more frequently used WGL technique (Lovrics et al., 2011:388-397).

3.2 Research objectives

The objectives of this study were to evaluate efficacy and accuracy of the ROLL and SNOLL procedure performed at Groote Schuur Hospital.

3.2.1 Research objective one:

This objective described the ROLL technique as an accurate and effective localisation technique with reference to its:

I. Successful localisation rates.
II. Localisation failures
III. Cosmetic outcome in terms of volume excised

3.2.2 Research objective two:

This objective described the therapeutic effectiveness of the combination of ROLL with Sentinel lymph node biopsy (SLNB) as an effective therapeutic tool in patients diagnosed with breast carcinoma, as determined by:

I. Complete tumour excision
II. Re-excision rates
III. Sentinel lymph node detection

3.2.3 Secondary outcomes

I. Technical difficulties encountered or experienced
II. Time and ease of the procedure
III. Radiation Safety

This chapter will describe the localisation procedure used at the study site when removing non palpable lesions for diagnostic purposes (ROLL) as well as the ROLL procedure performed with simultaneous SNB for therapeutic purposes (SNOLL). It will also describe the methodology; data collection and technique; ethics approval and permission; statistical analysis as well as the limitations of the study.

3.3 Patients and Methods

3.3.1 Study Sample

A retrospective review and analysis was done at a larger tertiary institute in the Western Cape for the period of 2003 to 2016 on all patients who were investigated for BIRADS 3, 4 and 5 non-palpable breast lesions as identified on radiographic imaging and had undergone the ROLL procedure for localisation and surgical excision of suspected or confirmed malignant non palpable lesions. Patients were grouped into two categories i.e. those who had ROLL only and those who had ROLL plus SLNB (will be referred to as SNOLL studies). Patients were identified from the surgical and nuclear medicine databases.

3.3.2 Inclusion Criteria

All records of patients older than 18 years investigated for non-palpable breast lesions who had undergone a previous percutaneous biopsy in which the results were inconclusive or highly suspicious for malignancy and had undergone a subsequent ROLL or SNOLL procedure for impalpable lesion localization within the period January 2003 to December 2016 were included.

3.3.3 Exclusion Criteria

All records of patients that had palpable lymph nodes were excluded who had incomplete or missing data (such as reports on pathologic margin status and final histopathological outcome) were also excluded.

3.4 The procedure/protocol followed at the research site

At the research site, the criteria for the procedure was:

1. Diagnostic intent (ROLL) where the core needle guided biopsy failed to provide a diagnosis or there was discordance between radiological appearance and histology diagnosis.
2. Therapeutic intent (SNOLL) where the core needle guided biopsy provided a diagnosis of breast cancer that warranted surgical removal of the lesion as well as a SLNB.

3.4.1 ROLL technique as performed at the institution

Tracer

The ROLL injection was administered on the day before or on the same day as scheduled theatre. ^{99m}Tc tin colloid or ^{99m}Tc hepatate (particle size 100-600nm) was used. The radiopharmaceutical kit was prepared in a volume of 3mls with a total activity of 300MBq of Technetium-99m Pertechnetate (^{99m}Tc) added to the kit. A period of 20 minutes was allowed for incubation before dispensing. Doses ranging from 5 – 22 MBq made up to a volume of 0.1mls were dispensed.

Lesion Localisation

Injection of the radiopharmaceutical was done in the diagnostic department by a radiologist. Image guidance was performed by either mammography, ultrasonography or stereotaxis depending on the modality the lesion was initially seen on. In cases where lesion was seen on both, then ultrasound was preferred. During mammographic localisation a lateral image was done to calculate the location and depth of the lesion using x, y and z co-ordinates. The radiologist positioned the tip of a 22G needle intra-lesionally under local anaesthetic. When done using ultrasound localisation the placement of needle was constantly checked during scanning. In cases of microcalcifications the placement of the needle was in the bulk of the microcalcifications determined by the radiologist under mammographic stereotaxis. After needle placement, its position was verified again with a control mammogram or ultrasound (Figure 3.1). The syringe with the dose was then attached to the spinal needle and the radiopharmaceutical was injected followed by 0.2mls of air (Figure 3.2 and Figure 3.3). After administration the needle was removed taking care not to cause any possible skin contamination.

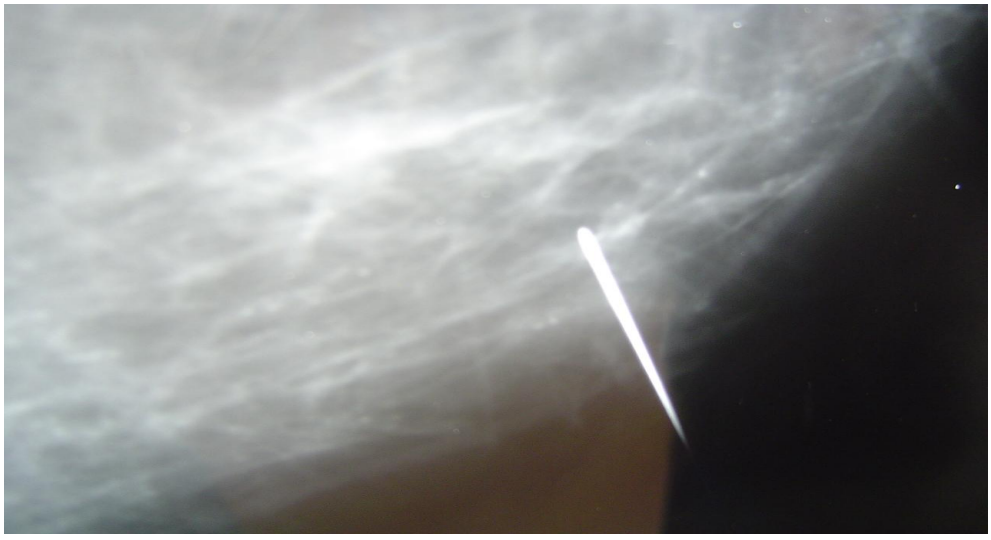

Figure 3.1: Mammogram image of needle in position for radiocolloid injection
(Image from the PACS at the research site)

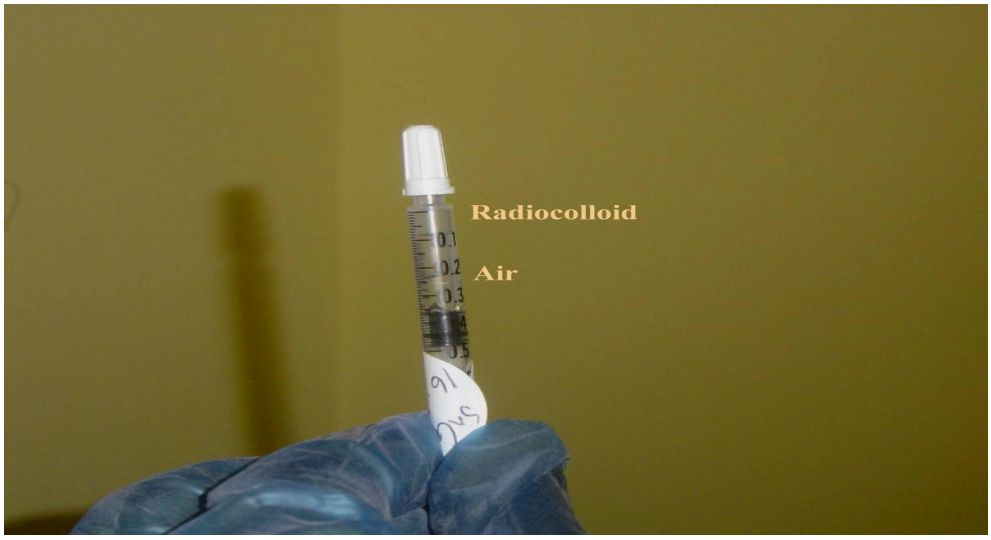

Figure 3.2: Syringe with dose demonstrating volume of air behind it (Image taken at research site)

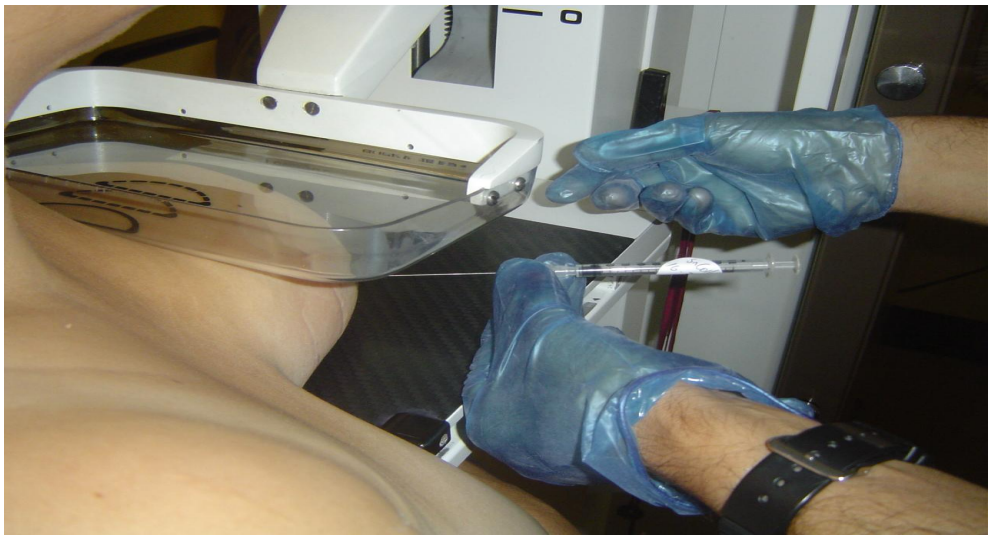

Figure 3.3: Administration of the radiocolloid through the localisation needle (image taken at research site)

Scintigraphy

The patient was then brought to the Nuclear Medicine department where localised anterior and lateral static images were done at about 30 minutes after injection or even later to localise the site of the injection and to make sure that the radiopharmaceutical was localised and there was no migration from the injection site (Figure 3.4). All images were acquired on a dual headed camera (Siemens gamma camera). A rectangular cobalt source was used to outline the body contour allowing correlation of the injection site. Images were acquired using a 256x256 matrix for 1000 counts (cnts) or 5 minutes using either a low-energy high resolution parallel hole collimator or a medium energy parallel hole collimator.

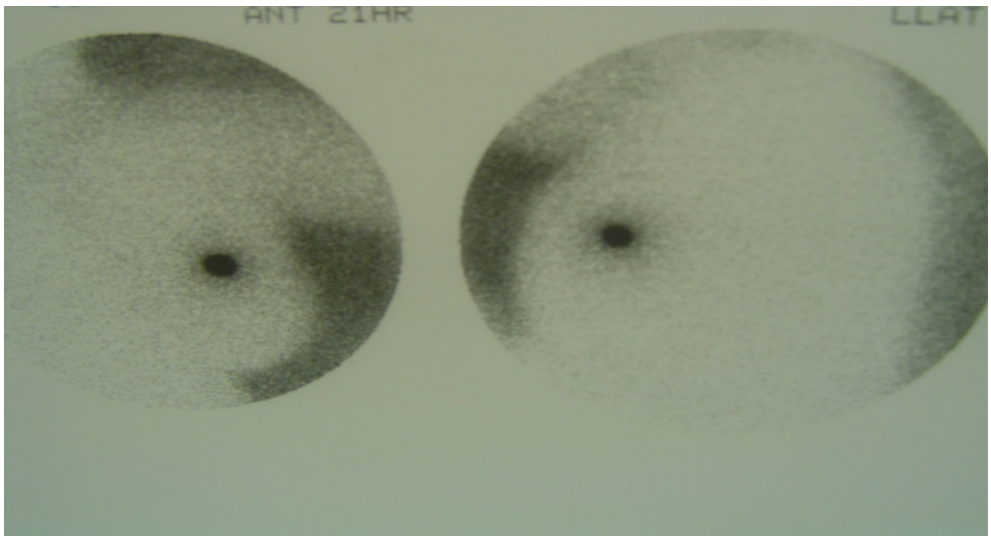

Figure 3.4: Scintigraphic images showing localisation of the radiopharmaceutical at the injection site with no migration from injection site (Images from the PACS system at reasearch site)

Surgery

Surgery was performed under general anaesthesia. A C-Track gamma probe with a remote display was used at the research site (Figure 3.5). The location of the lesion was assessed percutaneously with the gamma probe using the skin marking as a reference point. The incision was made at the point of highest level of radiation detection. An excision biopsy was performed using the gamma probe to constantly check the area of maximum activity and to define the margins of the lesion corresponding to where levels of detected radioactivity sharply decreased within the surgical field (Figure 3.6). Once excision of the lesion was complete (see Figure 3.7), the area was surveyed to ensure that there was no residual radioactivity in the resected area. Upon removal the excised lesion was placed on a surface away from the surgical field and a 10 second radioactive count was performed with the gamma probe. The lesion was then sent to be x-rayed to ensure excision of the lesion within the specimen or the presence of microcalcifications as seen on the pre-operative mammogram (Figure 3.8 and Figure 3.9). If necessary, more tissue would be removed. A histological evaluation on the resected tissue was performed by a pathologist.

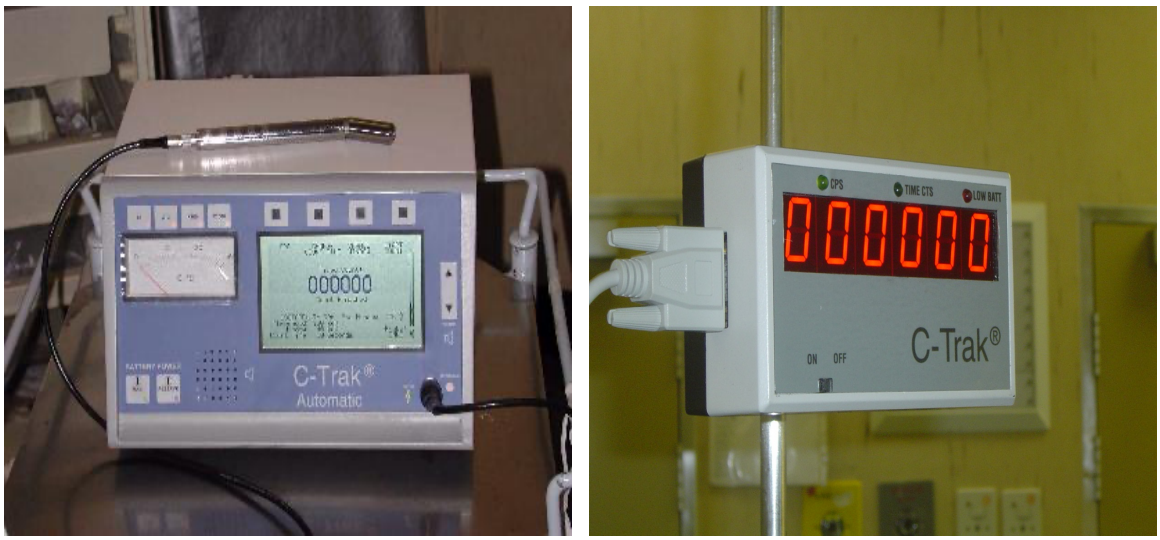

Figure 3.5: C- Trak gamma probe with remote display used at the research site

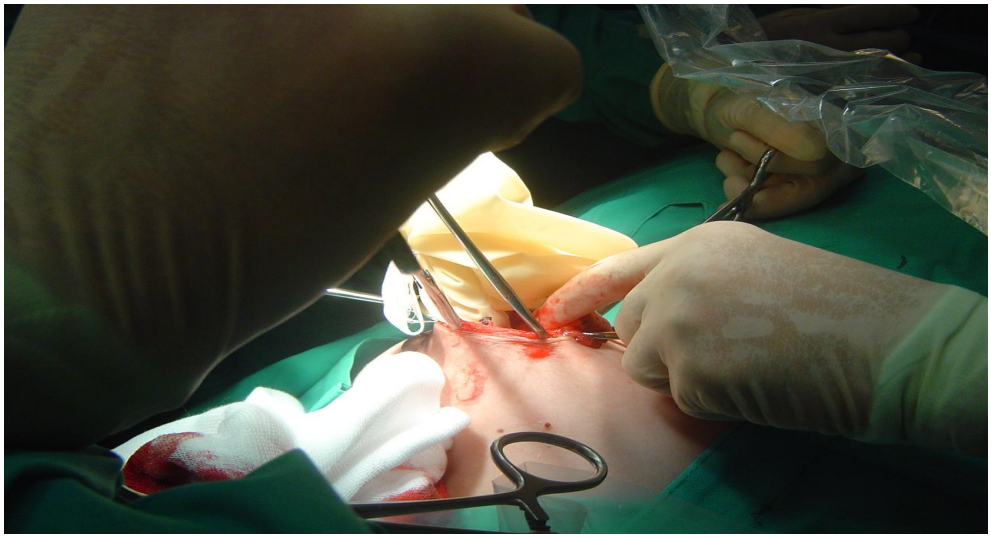

Figure 3.6: Probe used in incision to define margins of the lesion (image taken at the research site)

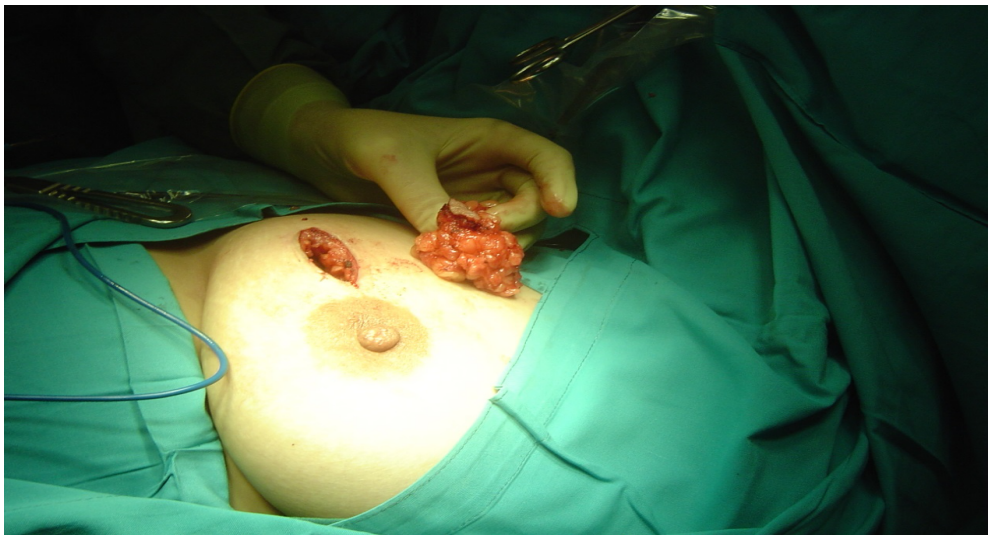

Figure 3.7: The excised lesion (image taken at research site)

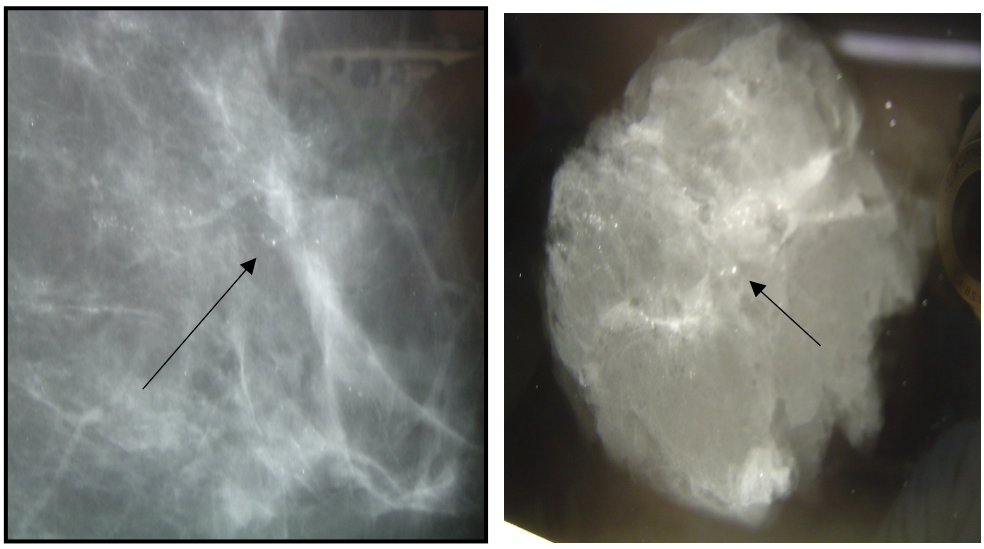

Figure 3.8: Mammogram of excised tissue demonstrating microcalcifications (images from the PACS at research site).

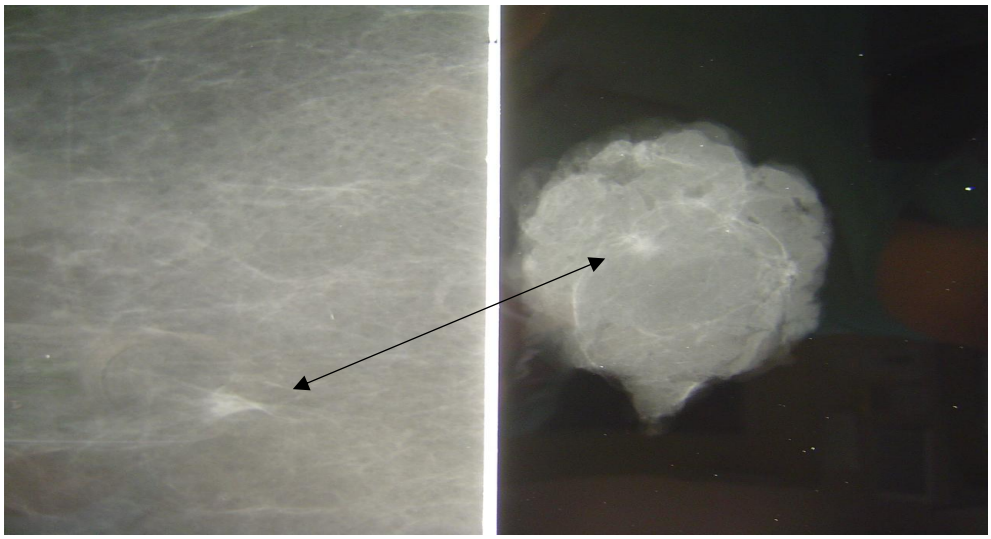

Figure 3.9: Mammogram demonstrating opacity/mass within excised specimen (images from the PACS at research site)

3.4.2 SNOLL technique as performed at the institution

Tracer

The SNOLL technique was usually performed the day before surgery. A single radioactive tracer was used namely ^{99m}Tc nanocolloid. Ninety five percent of the particle size has a diameter of ≤ 80nm. A dose in the range of 70 – 113 MBq of activity contained in 0.2ml was injected intra-tumourally followed with 0.2 ml of air.

Lesion Localisation

Localisation was done the same as for the ROLL procedure.

Scintigraphy

Scintigraphic imaging was performed at least 30 minutes after injection and static images were done in the anterior, lateral (90^0) and oblique (45^0) positions. The patient was supine on the bed with the affected side arm extended at 90 to the body as it would be in theatre. A rectangular cobalt-57 flood source was used to outline the body contour and to help delineate any SN in relation to the injection site. Images were repeated at 2 hours and continued later if no SN were visualised at the time. When the SN was visualised skin markings were made in relation to the position on the images. Thereafter the gamma probe was used to locate the maximum reading, to account for distortion of the position caused by imaging, and a final marking was made as a guide for optimal surgical incision of the SN. Markings were made in both the anterior and lateral positions on the patient's skin using a non-washable ink marker. The maximum skin readings were recorded with the gamma probe.

Surgery

As with the ROLL the procedure was performed under general anaesthesia. Injection of 0.5mls of methylene blue dye was administered subcutaneously periareolar in the quadrant of the lesion. The procedure followed the same as for the ROLL. Once the lesion was removed the SN was located using the skin markings and gamma probe readings as a guide. Once located intraoperatively the SN was assessed to see if it was stained blue. After excision of the SN the area was surveyed again using the gamma probe to check for any residual activity. A frozen section was done on the SN and on confirmation of histological results the decision was made to perform an ALND or not. The success of the SNOLL procedure was confirmed with histopathological results on complete resection of the lesion.

3.5 Data Collection and Techniques

A retrospective search was conducted on the nuclear medicine database for the period January 2003 to December 2016 for all patients that had undergone a ROLL or SNOLL procedure on the breast. This list was cross referenced against a list of patients identified on the surgical database of all patients that had undergone radioguided surgical excision of occult breast lesions. The compiled list of patients was used to retrieve demographic data; radiological and histological data; lesion localisation and pre- and post-surgical outcomes.

Data was retrieved from:

- Patient hospital notes
- Surgical notes
- Nuclear medicine records
- Histology reports
- Radiology reports

Data was collected on patient and tumour characteristics, localisation procedures and diagnostic outcomes.

Primary outcomes were:

- Localisation failures
- Specimen volume
- Margin status
- Re-operation rates
- SLN detection

Secondary outcomes were:

- Technical difficulties
- Duration of surgery
- Radiation dose administered

All data were collected and accessed through the hospitals electronic archiving systems as well as physical notes from hospital files. The pathology and histology reports were accessed via the National health laboratory system (NHLS) as well as the DISA system. Surgical notes were obtained via the Department of Surgery database. Data pertaining to radiopharmaceutical administration and scintigraphic imaging were obtained via the Nuclear Medicine Department data base.

3.5.1 Data collection tool

All necessary data was captured retrospectively on a data spreadsheet
(See Appendix A and B).
Data collected included:

- Patient demographics (age)
- Preoperative findings
    - Imaging used for detection i.e., Mammography, Ultrasound or both mammography and ultrasound.
    - Site (right or left breast)
    - Outcome of pre-operative histology results based on a needle biopsy classified as benign, malignant, inadequate, indeterminate or not recorded.
    - Radiological findings classified as Density/mass, Microcalcifications or Other.
    - Indication for performing procedure whether the intent was Diagnostic or Therapeutic outcome.
    - BIRADS classification score based on imaging as reported by the radiologist.

- Radiopharmaceutical administration
  - Date of radiopharmaceutical injection
  - Time of radiopharmaceutical injection
  - Dose administered
  - Type of radiopharmaceutical injected
  - Imaging guidance used for injection (Mammography or Ultrasound)
  - Injection site – Breast quadrant
  - Whether scintigraphic imaging was performed after injection
  - Same day or day before theatre injection

- The surgical procedure
  - Date and time surgery was performed
  - Time delay of theatre after injection
  - Time of excision- This was the recorded time at which the lesion was excised
  - Duration of surgery – interval from the beginning of the procedure until the lesion was excised
  - Skin surface counts (the highest reading detected with the gamma probe on the patients skin before incision is made)
  - Bench counts (gamma probe reading performed on the excised specimen after removal)
  - Background Counts (any residual counts detected by the gamma probe in the surgical field after excision)
  - Number of SLN identified
  - Site of SLN
  - In vivo counts (highest reading detected by gamma probe before excision of SLN)
  - Bench Counts (gamma probe reading performed on the excised SN after removal)
  - If the excised SN was stained blue
  - Results of the frozen section performed on SN whether it was positive for malignancy or not.

- Post-Operative Findings
  - Lesion within excised specimen (confirmed by check mammogram or histology report)
  - Margin status - these were recorded as reported on the histology report. These were later classified as clear, close or involved.
  - Volume of excised specimen

- Weight of excised specimen
- Size of tumour – calculated as a product of all three dimensions in cm^3
- Pathological diagnosis or tumour type (DCIS, Benign or IDC)
- Whether a re-operation was performed

3.5.2 Data validation process

The process of validity and inclusion of the data is shown in the flow chart below (Figure 3.1). All ROLL and SNOLL breast lesion localisation procedures identified from the nuclear medicine database was cross checked against a list of patients identified from the surgical database that had radioguided excision biopsy for non-palpable breast lesions. A list of 235 patients were identified. A spreadsheet was compiled with all necessary data captured. All data was anonymised. A second spreadsheet was compiled excluding all patients who had missing post op histology reports. This further excluded patients who had no surgical margin status recorded. A total sample number of 190 patients was included.

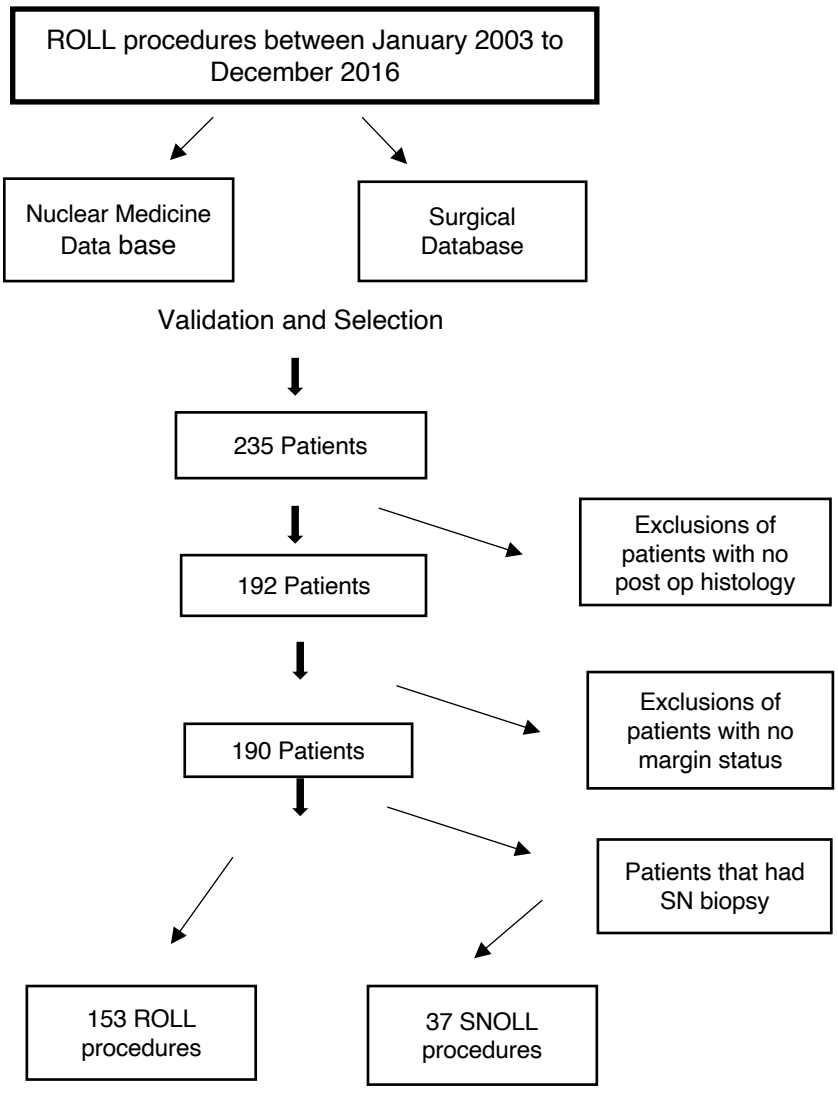

Figure 3.10: Data validation flow chart

3.6 Ethics and confidentiality

Ethics approval and permission for this study was sought and granted by:

- Research Ethics Committee (REC) of the Faculty of Health and Wellness Sciences, Cape Peninsula University of Technology, REC Approval Reference No: CPUT/HW-REC 2016/H27/Renewal (See Appendix C)
- Human Research and Ethics Committee (HREC), University of Cape Town, HREC Ref No:281/2017 (See Appendix D)
- The Western Cape Health Research Committee (See Appendix E)
- A letter of approval for the researcher to access departmental patient data for the purposes of the research study was received from the head of department (HOD) in the nuclear medicine department at the institution as well as the Clinical Director of the breast unit (See attached letters Appendix F and Appendix G).

All data was anonymised and patient's records were given study numbers to maintain confidentiality and privacy. All data was stored on a password protected laptop. Access to the data was limited to the principal researcher, supervisors and statistician.

3.7 Statistical analysis

Data was analysed using Microsoft Excel and statistical package NCSS, LLC, 2021, v21.0.2 (Utah, USA) software package. The level of significance was set at $\alpha = 0.05$. Categorical data are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation (SD) for normally distributed variables and median and 25^{th}-75^{th} percentiles for skewed variables. Normality testing was done on continuous data using the D'Agostino Skewness test (probability level <0.05 to reject normality). The Analysis of variance to look at the relation of variables were done using the ANOVA method. The level of significance was set at $\alpha = 0.05$. Comparisons on discreet data was done using the Pearson's Chi Squared test. Log transformations were done to correct for skewness.

3.8 Definition of outcome variables

3.8.1 Time taken to excision

The time recorded in minutes to excise the lesion from the time the initial surgical incision was made until the lesion was excised.

3.8.2 Margins

Margins status was recorded as Involved, Close or Clear. In this study the following classifications was used for each:

- Involved margin – any margin at which presence of tumour cells were reported at the inked edge of specimen
- Close margin – the presence of tumour cells within >2mm of the inked edge
- Clear margin - the absence of tumour cells < 2mm and more

3.8.3 Volume

Volume of the resected specimens were calculated as a product of all three dimensions in cm^3.

CHAPTER FOUR
RESULTS

In this chapter we report the findings of the research in order to assess the aims of the study which were to evaluate the ROLL procedure in terms of its efficacy and accuracy as a diagnostic tool when localising non palpable breast lesions for surgical excision as well as a therapeutic tool when used in conjunction with SLNB.

To achieve this the following objectives were defined:

- Successful localisation rates
- Failures
- Volume of tissue excised
- Margin status
- Number of patients requiring re-operation
- Proportion of SLNB

Secondary outcomes:

- Technical difficulties
- Duration of surgery
- Radiation dose administered

All the data collected was analysed and presented as the following findings in the study:

- Sample size and demographics
- Pre-operative lesion characteristics
- Localisation technique of the lesion for excision biopsy
- The excision biopsy
- Post-operative findings
- SLN biopsy
- Indications for repeat operation
- Sentinel Node biopsies

4.1 Sample size and demographics

There were 235 patient records identified from the data bases which met the inclusion criteria. Forty-five records had to be excluded due to missing data, resulting in 190 complete patient records being included in the retrospective analysis.

The records indicated that the majority of the procedures were ROLL procedures 153/190 (80.5%). A total of 37 lesions (19.5%) were done as therapeutic procedures with simultaneous SLNB (SNOLL).

The mean age of the patients was 56 years (range 28-85 years).

4.2 Pre-operative lesion characteristics

The clinical and radiological characteristics of the lesions pre-operatively are summarised in Table 4.1.

4.2.1 Location of the lesion

Lesions were classified according to the affected breast and their positions within the breast. Ninety-four (49.5%) lesions were found in the right breast and 96 lesions (50.5%) were found in the left breast. The difference between lesion location in the right and left breast was not statistically significant (p=0.47). Most lesions were found to be in the Upper Outer quadrant (45.8%). This was true whether in the right or left breast (p = 0.013).

4.2.2 Radiological appearance

On initial radiographic appearance, 119/190 (62.6%) lesions were classified as a density/mass and 67/190 (35.3%) were classified as microcalcifications.

4.2.3 Pre-operative histology

One patient did not have a needle biopsy done. Biopsy results could only be found for 173 of the lesions. Results of needle biopsy showed that 59/173 (34.1%) of lesions were reported as malignant. In 59/173 (34.1%) of lesions, the needle biopsy was unable to return a result due to indeterminate or inadequate tissue samples. A benign result was found in 55/173 (31.8%) lesions.

Table 4.1: Clinical and radiological characteristics of all lesions pre-operatively

Procedure	n	(%)	Mean age ±SD	Age Range
ROLL	153/190	(80.5%)	56.02 ±11.05	(28-85)
SNOLL	37/190	(19.5%)	56.70 ±9.07	(38-72)
Radiological Appearance	n	(%)		
Density/mass	119/190	(62.6%)		
Microcalcifications	67/190	(35.3%)		
Not recorded	4/190	(2.1%)		
Pre-operative histology				
Malignant	59/173	(34.1%)		
Benign	55/173	(31.8%)		
Inadequate/Indeterminate	59/173	(34.1%)		
Not recorded	(17)			
Location in Breast	Right Breast	Left breast	Combined	

Breast	94 (49.5%)	96(50.5%)	190	*p*= 0.47
Quadrant				*p*= 0.013
Upper Inner Quadrant	11 (5.8%)	12 (13.6%)	23 (12.1%)	
Upper Outer Quadrant	44 (23.2%)	43 (22.6%)	87 (45.8%)	
Retroareolar	4 (2.1%)	1 (0.5%)	5 (2.6%)	
Midline	5 (2.6%)	5 (2.6%)	10 (5.3%)	
Lower Inner Quadrant	7 (3.7%)	10 (5.3%)	17 (9%)	
Lower Outer Quadrant	7 (3.7%)	14 (7.4%)	21 (11.1%)	
Not recorded	16 (8.4%)	11 (5.8%)	27 (14.2%)	

Values presented as means ± standard deviations (SD), median and 25th-75th percentiles, or %

4.3 The localisation of the lesion for excision biopsy

4.3.1 Radiopharmaceutical administration and dose

^{99m}Tc hepatate was injected in 42/190 (22%) of lesions, ^{99m}Tc tin colloid in 104/190 (55%) and ^{99m}Tc nanocolloid was injected in 44/190 (23%) of lesions. Where the intent was therapeutic and a SLN biopsy was done, all lesions (37/190) were injected with ^{99m}Tc nanocolloid. Doses for diagnostic intent (ROLL), were in the range of 5 – 22MBq and for therapeutic procedures (SNOLL) they ranged from 71- 113 MBq (refer to table 4.2).

Table 4.2: Radiopharmaceutical and dose administered

Radiopharmaceutical used	n	%
^{99m}Tc hepatate	42	(22%)
^{99m}Tc tin colloid	104	(55%)
^{99m}Tc nanocolloid	44	(23%)
Mean dose Mbq	Mean dose (MBq)	Range
Diagnostic intent (ROLL)	12.46	(5-22MBq)
Therapeutic intent (SNOLL)	91.13	(71 – 113MBq)

4.3.2 Scintigraphy

Seven patients did not have any scintigraphy done after injection. Scintigraphy was performed in 183/190 (96.3%) of cases. Scintigraphic image reporting on ROLLS commented on focal localisation of radiopharmaceutical as well as whether there were any tracts visible. Reporting on SNOLLS included visualisation of the localised injection site and the presence and location of sentinel nodes seen.

4.4 Excision biopsy

One patient had a ROLL done with a simultaneous mastectomy performed on confirmation of the frozen section result. One patient had bilateral occult lesions, one of which was highly suspicious and had simultaneous ROLL and SNOLL done on opposite breasts. In this instance two injections were given, ^{99m}Tc tin colloid for the ROLL and ^{99m}Tc nanocolloid for the SNOLL. Four other patients had an occult lesion on the one breast and a confirmed malignancy on the other. Simultaneous ROLL for the occult lesion and SLNB with a mastectomy was performed on the other breast in these instances.

4.4.1 Time relation of the biopsy to the Radiopharmaceutical administration

In the whole group only 35 cases had same day surgery, the remainder had surgery performed the day after injection, with recorded times of up to 29 hours after radiopharmaceutical injection. The time to localisation of lesions following initial incision in theatre ranged from 5 – 45 minutes. Table 4.3 compares the same day and day after protocols in terms of time to localisation, volume excised and margin status. There was no statistically significant difference between the time to localisation between the same day and day after injection protocols (p=0.60). There was also no statistically significant difference between the volume of tissue excised (p = 0.60). Margin status was also found to be independent for same day or day after protocols (p = 0.70).

Table 4.3: Comparison of Same day and Day after Protocols

Parameter	Same Day Protocol	Day After Protocol	Not recorded	p-value
Number of cases	35/190 (18.4%)	137 /190 (72.1%)	18/190 (9.5%)	
Time to localisation (min)	Mean (range) 25 (5 - 45)	Mean (range) 21 (5 - 45)		p= 0.60
Volume excised cm^3	Mean (IQR) 140.4 (30;167)	Mean (IQR) 122 (37;143)		p= 0.60
Margin Status Clear Close Involved	n=25 10 (40%) 6 (24%) 9 (36%	n= 133 43 (49%) 20 (23%) 25 (28%)		p= 0.70

4.5 Post-operative findings

Table 4.4 shows the post-operative surgical characteristics of the lesions and margin statuses. Overall, 93.2% of lesions were correctly localised and removed on the first attempt. After removal the excised specimen was sent to radiology for a check mammogram to confirm the presence of the lesion within the excised specimen. Where the intent of the procedure was therapeutic, all 37 lesions were correctly identified on the first attempt. Of the lesions excised 115 (60.5%) was found to be malignant.

Table 4.4: Post-Operative lesion characteristics

Lesion in specimen		Number (%)	
Yes No Not Recorded		177 (93.2%) 9 (4.7%) 4 (2.1%)	
Post- operative histology			
Benign Malignant Invasive cancer DCIS		75 (39.5%) 115 (60.5%)	 70 (61%) 45 (39%)

4.5.1 Margin status

In lesions that were confirmed malignant (See Table 4.5), clear margins were achieved in 53/115 (46.1%) of excised specimens. Close margins were reported in 25/115 (21.7%), while involved margins were found in 37/115 (32.2%) of lesions. Table 4.6 shows the distribution of margins according to the type of tumour. There was a statistically significant difference in margin status and the type of tumour (p = 0.0004). A higher percentage of clear margins were found in infiltrating cancers 42/70 (60.0%) vs DCIS 11/45 (24.4%). For infiltrating cancer lesions a radical excision was considered when margins had no tumour cells present at the ink margin regardless of whether margins were close (<2mm), whereas in the case of DCIS only margins greater than 2mm were considered a radical excision. Therefore, with the combined close and clear margin status, radical or complete excision for infiltrating cancer was achieved in 50/70 (71.4%) of cases. There was also a statistically significant difference in the margin status and the radiologic appearance of lesions (p=0.0044). It was more likely to achieve clear margin status in lesions classified as density/mass on imaging than those that were microcalcifications. The position of the lesion in the breast did not influence the margin status (p = 0.33).

Table 4.5: Margin status of malignant lesions

Margin status of malignant lesions			
	Clear	**Close**	**Involved**
Total n=115	53 (46.1%)	25 (21.7%)	37 (32.2%)
Diagnostic n=83	34 (41%)	23 (27.7%)	26 (31.3%)
Therapeutic n=32	19 (59.4%)	2 (6.3%)	11 (34.4%)

Table 4.6: Margin Status and type of tumour

	Clear >2mm	**Close <2mm**	**Involved**	
	n (%)	n (%)	n (%)	***p-Value***
Type of Tumour				
Infiltrating cancer n=70	42 (60)	8 (11)	20 (29)	*0.0004*
DCIS n=45	11 (24)	17 (38)	17 (38)	
Total n=115	53 (46)	25 (22)	37 (32)	
Radiologic Appearance				0.0044
Density/Mass n=78	45 (58)	13 (17)	20 (26)	
Microcalcifications n=44	12 (21)	15 (34)	17 (39)	
Position of lesion in breast				0.33
Lower Inner Quad n= 11	4 (8)	3 (13)	4(12)	
Lower Outer Quad n=11	8 (15)	1 (4)	3 (9)	
Retroareolar n=2	2 (4)	0	0	
Midline n=7	5 (10)	0	2 (9)	
Upper Inner n=17	7 (14)	7 (29)	3 (9)	
Upper Outer n=59	26 (50)	13 (54)	20 (61)	

4.5.2 Volume of tissue excised

The mean excised volume regardless of surgical intent, was 114.02 cm^3 (refer to table 4.7) Where the intent was therapeutic, the mean excised volume was 148.17 cm^3 while for diagnostic purposes the mean lesion size was 105.61cm^3, this was not statistically significant (p=0.54). Table 4.8 represents the logarithmic calculation of the volume excised to see if there was a difference in the amount of tissue excised based on the preoperative histology as well as the radiologic appearance on imaging before surgery. On analysis there was no statistically significant difference in the amount of tissue resected for either variable (p=0.76 and 0.55 respectively).

Table 4.7: Mean excised volume

Volume excised cm^3		
Mean Diagnostic Therapeutic	114.02 105.61 148.17	p=0.54

Table 4.8: Volume of tissue excised based on preoperative histology result and radiologic appearance

	Mean size Tissue Excised (Ln)	p-value
Preoperative Histology Result Inadequate Indeterminate Benign Malignant	 4.155 4.420 4.041 4.079	0.76
Radiologic Appearance Microcalcification Density/Mass	 4.193 4.060	0.55

*(LN) – Logarithmic mean

4.6 Sentinel Node biopsies

Table 4.9 summarises the outcomes of the SNOLL procedure. Simultaneous SLNB and lesion excision was performed in 37 patients. A significant number of them were reported densities (92%) as opposed to microcalcifications on mammogram. Pre-operatively 46% were classified as malignant on percutaneous biopsy. On post-operative histology 75.7% were found to be infiltrating cancers. In 19/32 (59.4%) cases of SNOLL the procedure was able to achieve clear margins while in 2/32 (6.2%) the margins were close and in 11/32 (34.4%) the resected margins were involved. Most of the surgeries were performed the day after injection with times up to 28 hours after injection. There were 4 cases in which the SN was not identified, one of which was due to an increased BMI. In 30 cases the SN was successfully localised while 3 was unknown as these were not documented. Positive nodes were identified in 3 patients A

total of 55 sentinel nodes were examined. Six of them were found to be malignant. Most of the sentinel nodes were found in the axilla except for 1 which was intramammary.

Table 4.9: Summary of SROLL procedure

	Number (%)		
Radiological appearance			
Density/mass	34 (92)		
Microcalcifications	3 (8)		
Pre-operative histology			
Benign	3 (8)		
Inadequate	10 (27)		
Indeterminate	6 (16)		
Malignant	17 (46)		
Not done	1 (3)		
Post-operative histology			
Infiltrative Cancer	28/37 (75.7)		
DCIS	4/37 (10.8)		
Benign	5/37 (13.5)		
Margin status n=32 (malignancies)			
Clear	19 (59)		
Close	2 (6.3)		
Involved	11 (34.4)		
Margin status and tumour type			
	Clear	**Close**	**Involved**
Infiltrating Cancer n=28	18(64.3)	2(7.1)	8(28.6)
DCIS n=4	1(25)	0(0)	3(75)
	19(59.4)	2 (6.3)	11(34.4)
Lesion in Specimen			
Yes	37/37 (100)		
No			
Volume excised			
Mean	148.17		
Number of cases in which SN was identified			
Yes	30 (81.0)		
No	4 (10.8)		
Not documented	3 (8)		
Total number of Lymph Nodes examined	55		
Number of patients with positive nodes	3		

Position of sentinel node	
Axilla	32/33 (96.9)
Intramammary	1/33 (3)

4.7 Indications for repeat procedures

4.7.1 Technical difficulties

Two cases were repeated due to technical difficulties due to the injection. In one case there was no activity detected during theatre and the study was rescheduled. In the other case the patient did not go to theatre as there were significant number of lymphatic tracts seen on scintigraphy after the injection. Both these studies were repeated successfully.

4.7.2 Re-operations

In 9 cases (4.74%) lesions or microcalcifications were not found in the specimen or of being representative of the pathology (on confirmation of mammogram and/or histology). Six of these were repeated. In 3 of them the histology changed from benign to malignant on re-excision. The other 3 remained benign, however in 1 case an excision biopsy of the scar performed three years later, was found to be malignant.

CHAPTER FIVE
DISCUSSION

To facilitate management and treatment of non-palpable breast lesions detected on imaging, a definitive histological diagnosis is necessary and often this requires a surgical excision of these lesions especially where a FNAB or LCNB fails to provide a definitive diagnosis (Thind et al., 2005:685). Various localisation methods have been published and used to assist in the pre-operative localisation of the lesion to assist the surgeon in adequate surgical resection (Pijnappel et al., 2014:595-600; Davis et. al., 2021:542-555).

The ROLL procedure has been shown to provide a simple, accurate and effective method of occult lesion localisation. Several studies comparing it to WGL have shown it to be favourable in terms of better localisation rates, smaller excision volumes, shorter procedure times, better tumour free margin widths, improved cosmesis and less risk and better tolerance by patients (Rampaul et al., 2004; Thind et al., 2005; Lovrics et al., 2011; Sajid et al., 2012). An added advantage of the ROLL procedure is that it can facilitate the identification of the SN in patients with highly suspicious lesions using the same procedure (Ahmed & Douek, 2013:1034).

While the use of the ROLL procedure has been well published internationally, to the best of our knowledge this study was the first to document the effectiveness of ROLL in the South African context.

The primary objective of this study was to review the experience of the ROLL technique at a tertiary institute and to evaluate its accuracy and effectiveness for diagnostic and therapeutic excisions as performed at a single tertiary centre in the Western Cape during the period 2003 to 2016.

Secondary aims were to look at technical difficulties; duration of surgery and radiation dose administered.

5.1 Results of ROLL and SNOLL at the study site

5.1.1 Sample size and demographics

We were able to retrieve data on 190 patients. Thirty-seven of which had undergone therapeutic excision. This is a significant number of patients when compared to other reviewed published studies evaluating efficacy of the ROLL technique as a diagnostic and therapeutic tool, where numbers ranged between 48 -73 (see Table 5.1). Few others had a sample number over 100.

The mean age of patients in our sample was 56 years which was similar to those in other studies reviewed by Besic et al; (2002) (54) and Thind et al.; (2005) at 57.

The age range (28- 85 years) was comparable to the study group of Sarlos et al (2008:403-408). Typically, in South Africa, as in other developing countries, presentation of breast cancer is usually at later stages of disease. This is due to various socio-economic factors, lack of community awareness and lack of access to health care facilities (Moodley et al., 2016:1-5).

Table 5.1: Age range comparative

Author	No. of patients	Mean age	Age Range
De Cicco et al. (2004)	227	52	25-77
Feggi et al. (2001)	73	60	46-80
Thind et al. (2005)	70	57	36-77
Rampaul et al.(2004)	48	-	-
Sarlos et al. (2009)	100	62	27-85

5.1.2 Pre-operative lesion characteristics

5.1.2.1 Radiologic Appearance

In this study lesions we categorised by their appearance on imaging as density/mass and microcalcifications. Other studies such as Patel et al. (2004:918-923) and Thind et al. (2005:681-686), further subdivided this category into spiculated masses and lesions that have microcalcifications with density. On initial radiographic appearance 119/190 (62.6%) lesions were classified as a density/mass while a smaller proportion 67/190 (35.3%) were classified as microcalcifications. Microcalcifications are more likely to be associated with DCIS. This result would also be supported by the fact that final histology results of lesions that were malignant showed a smaller proportion of lesions 45/115 (39%) were DCIS as opposed to a bigger proportion of infiltrative cancer which appears as a density or mass on imaging. This was similar to the proportion in the large series published by De Cicco et al (2002:145-151) who reported 52.6% invasive breast cancers and 31.6% DCIS. This can also be explained by the fact that in South Africa there is no routine screening based programme as in other developed countries, leading to later stage of presentation (Kruger & Apffelstaedt, 2007:29-31; Mutebi et al., 2017:4-8).

5.1.2.2 Location of lesions in the breast

It has been shown that there is a higher incidence of breast lesions in the upper outer quadrant, with a possible reason being that this area has more breast tissue (Lee, 2005:151-152). This is comparable in this study as most lesions investigated were found to be in the upper outer

quadrant (45.8%). On analysis a statistical significance was found between quadrants (p = 0.013).

5.1.2.3 Pre-operative histology

Pre-operative histology was obtained by an image guided core biopsy using ultrasound or mammography. All the patients in our group except one had undergone a percutaneous needle biopsy. Unfortunately, due to the retrospective nature of the study, histology results of these biopsies in our group could only be found in 178 patients.

Needle biopsy reported 59/190 (31.1%) of lesions as malignant while 59/190 (31.1%) lesions were unable to return a result due to indeterminate or inadequate tissue samples. In a study by Pilkington et al. (2011:197-203) histological diagnosis by FNAB and LCNB was done on 40/105 lesions. Insufficient material was obtained in 24/40 (60%) of lesions. Of the lesions in this study reported as indeterminate or inadequate, 18/59 (30.5%) were microcalcifications. As mentioned by Pijnappel et al. (2004) microcalcifications can often be missed especially if an inadequate amount of tissue was obtained for histology (Pijnappel et al., 2004). Of the lesions in this study classified as benign on needle biopsy a total of 20/55 (11.6%) were found to be malignant on excision biopsy. In 11 lesions a malignant diagnosis on biopsy was found to be benign after excision. The total missed rate for needle biopsy was 31/172 (18.02%).

5.2 The localisation of the lesion for excision biopsy

5.2.1 Radiopharmaceuticals used, administration and dose

Two commercially available tin colloid kits (Amerscan™ Hepatate II™ agent, Nycomed Amersham Health Inc., London, U.K. and Tin Colloid, NTP Radioisotopes Pty Ltd, Pretoria) were used for ROLL localisation at the study site. Particle sizes of these radiopharmaceuticals were in the region of 100 – 600nm. Large colloid particle sizes >100 nm are preferred as they do not drain easily and stay at the injection site (Paganelli et al., 2015). In the reviewed studies an intratumoural injection of ^{99m}Tc MAA was used which has particle size >10 000nm (Rampaul et al., 2004; Thind et al., 2005; Moreno et al., 2008; Medina-Franco et al., 2008). All injections were performed intratumourally.

Volumes of nuclear traces used by others were similar to this study 0, 2-0.3 mls. Injected doses ranged from 1- 5.55 MBq but unlike this study all the surgeries were done on the same day (Thind et al., 2005; Medina-Franco et al., 2008; Moreno et al., 2008). In this study administered doses ranged from 5 – 22 MBq to allow for radioactive decay as most surgeries (72.1%) took place the following day.

Several studies administered contrast at the time of injection to assess the accurate placement of the injection with mammography (Feggi et al., 2001; Rampaul et al., 2004; Patel et al., 2004;

Moreno et al., 2008). However, this adds to the radiation burden. In this study we relied on ultrasound and stereotactic imaging alone to confirm accurate needle placement.

When the ROLL was done with concomitant SNB various methods were reported. De Cicco et al (2002) used 3 different methods in his study injecting one group with ^{99m}Tc MAA and ^{99m}Tc nanocolloid, another group 99mTc MAA intratumourally and the ^{99m}Tc nanocolloid subdermally and in the third group a single intratumoural injection of ^{99m}Tc nanocolloid. Feggi et al. (2001) used an injection of ^{99m}Tc nanocolloid but injected half of the dose superficially and the other half into the tumour. Postma et al. (2012), Patel et al. (2004) and Lavoué et al. (2008) all used a single intratumoural injection of ^{99m}Tc nanocolloid to perform SNB as in our group of SNOLL patients.

We administered doses in the range of 70 – 133 MBq for SNB. This was comparable to other studies where administered doses were 120 and 123 MBq (Patel et al., 2004; Lavoué et al., 2008; Postma et al., 2012).

5.2.2 Scintigraphy

Scintigraphic imaging was usually performed within 30 minutes or at later times to check for focal concentration of the radiopharmaceutical within the injection site and to check for any possible skin contamination sites. In one case possible skin contamination was noted and this was verified by washing the area with decontamination wash and repeating the scintigram.
Timing of the images were not crucial so they could thus be easily fitted in between the scheduled workload on the gamma cameras. Imaging was short and did not cause any delays with camera schedules. Scintigraphy was done for all patients except 7.

Even though Thind et al. (2004) questioned the use of scintigrams since needle placement is already verified by mammography or ultrasound, we report at least one case where no check scintigram was done and the study had to be repeated as no trace of radioactivity was found at the time of surgery. In this instance a scintigram done after the injection would have concluded if there was any radiopharmaceutical present, thus saving unnecessary theatre time and preparation. In another case theatre was postponed as initial scintigram showed diffuse activity beyond injection site. It was not clear whether this could be due to early lymphatic tract or quality control issues with the radiopharmaceutical. On repeat of the study a few days later, subsequent imaging showed the same pattern and it therefore could be concluded that this was due to lymphatic tracts. The preoperative image is therefore useful in checking the technical quality of the injection and determining any early migration or possible contamination at the injection site. A single well defined hot spot on the scintigram provides evidence of a successful injection.

Our observations on imaging were in concordance to that of De Cicco et al. (2002), once injected, the radiopharmaceutical did not diffuse into surrounding tissue except where it had been introduced into lymphatic vessels or ducts.

5.3 The excision biopsy

At this research site the ROLL procedure was performed to localise non palpable lesions identified on imaging with confirmed, indeterminate or inadequate core biopsy results. Many of the studies reviewed had performed the ROLL technique on patients with confirmed histology (De Cicco et al., 2002; Patel et al., 2004; Postma et al., 2012). Our sample, as that of other previous studies consisted of radiologic suspicious lesions with confirmed or indeterminate core needle biopsies and therefore the ROLL was done as a diagnostic as well as therapeutic procedure (Rampaul et al., 2004; Medina-Franco et al., 2008; Mariscal Martínez et al., 2009; Woll et al., 2011).

One patient had a ROLL done with a simultaneous mastectomy performed on confirmation of the frozen section result. One patient had bilateral occult lesions, one of which was highly suspicious and had simultaneous ROLL and SNOLL done on opposite breasts. In this instance two injections were given, tin colloid for the ROLL and nanocolloid for the SNOLL.
Four other patients had an occult lesion on the one breast and a confirmed malignancy on the other. Simultaneous ROLL for the occult lesion and SLNB with a mastectomy was performed on the other breast in these instances.

5.3.1 Time relation of the biopsy to the Radiopharmaceutical administration

The time of the operation after radiopharmaceutical injection ranged from between 1 hour up to 29 hours in this study. Ideal theatre time would be at least 2- 18 hours after injection (Buscombe et al., 2007:2158). Starting too early might not allow for sufficient uptake in the SN when performing SNB and waiting too long might allow for uptake in echelon nodes making the SN difficult to identify. Another concern would be the decay of the radioactivity affecting the detection of radioactivity with the probe. Imaging and marking of the SN on scintigraphy allowed the identification of the SN. Other studies have reported surgery times of up to 24 hours after injection (Giacalone et al., 2012) while in this study delayed theatre times of up to 29 hours was still achieved successfully. Even though the administered activity for ROLLS in this were in the range of 5- 22 MBq, we found that there was still sufficient activity present at the time of surgery even at delays of up to 29 hours.

5.3.2 Indications for repeat operation

A repeat surgery was defined as a re-operation done when the localisation procedure failed to accurately localise the lesion during surgery. Furthermore, if a malignant lesion is excised

without sufficient clear margins a re-operation would be necessary. Factors which can affect the complete resection of the tumour on the first attempt is the biological characteristics of the tumour. An example in the instance of DCIS is the extent of microcalcifications which can be difficult to determine, in large breasts it can be difficult to locate small deep tumours and the dependence on the centricity of the lesion within the resected specimen (Lovrics et al., 2011:388-397). In this study the rate of repeat excisions due to incomplete or involved margins could not be assessed as insufficient data was available. In the SNOLL group where the intention was therapeutic, 11 lesions had involved margins. Four records of re-excision were found. Two of these were for DCIS where re-excision came back positive for residual disease in only one. The other two for infiltrative cancer came back negative for residual disease.

Intra-operative localisation failed in 9 cases (4.7%) where lesions or microcalcifications were not found in the specimen or of being representative of the pathology (on confirmation of mammogram and/or histology). Six of these were repeated. In 3 of them the histology changed from benign to malignant on re-excision. The other 3 remained benign, however in 1 case an excision biopsy performed three years later in the scar came back as malignant. Similarly, Pilkington et al. (2011) also reported 5 /105 (4.8%) intra-operative failures.

5.4 The accuracy and efficacy of the ROLL technique for diagnostic and therapeutic excisions as performed at this institution

5.4.1 Successful localisation rates

FNAB and LCNB are preferred over surgical methods for determining histology in breast lesions due to the low risk, ease of procedure and its cost effectiveness. They also have high sensitivity rates in breast lesions. The sensitivity rate of LCNB in breast cancer is 97% (Verkooijen et al., 2000:1017-1021). However, the results of pre-operative core needle biopsies performed in this study were inconclusive in 46/172 lesions (26.74%). Of these lesions 18 were microcalcifications.

Accurate lesion localisation and successful histological diagnosis was achieved in 93.2% of the lesions in this study. Results of this was comparable to that of Pilkington et al. (2011:197-203) of 95.2%. Only in 9 patients (4.7%) in this study the histology was found to be non-representative of the pathology. A successful excision biopsy is therefore very useful especially where there is discordance or indeterminate histology.

As stated by Dua et al. (2011:246-253) the properties of the localisation marker should be that it remains at the site of the lesion after placement until commencement of surgery and should be easily identifiable by the surgeon. No migration of the radiopharmaceutical was noted and documented on scintigraphic reports except for one where lymphatic drainage was noted. The

radiopharmaceutical used thus showed the ability to localise and be fixed in the lesion until surgery. This finding confirms the results of a previous study done by Aydogan et al. (2011:241-245) who showed that there was no diffusion of macroaggregates from the injection site unless the radiopharmaceutical had been introduced into milk ducts or lymphatic vessels. This allows for accurate localisation of the lesion even after hours of delay between injection and surgery.

Skin markings made during scintigraphy and correlated with readings using the gamma probe also helped to guide the surgeon to make the incision accurately.

5.4.2 Rates of clear margin excisions

The ROLL technique has been shown to have better margin status when compared to the WGL (Nadeem et al., 2005:283-289; Thind et al., 2005:681-686). Even though the ROLL is a diagnostic procedure in order to determine the histology of a suspicious lesion, the removal of such a lesion with adequate margins will allow for a radical resection if histology comes back as malignant. This will therefore also negate the necessity for further re-excision allowing for a better cosmetic outcome (Landheer et al., 2004).

At the research site, margin status changed over time. Initially prior 2015 the accepted margin for Invasive cancer was >2mm which subsequently changed to any margin where there were no tumour cells at inked margin. For DCIS a clear margin was any margin >2mm.

There was a statistically significant difference between margins and the type of tumour ($p=0.0004$). Sixty percent of Invasive cancers had clear margin status while only 20.75 % of DCIS margins were found to be clear. This was in concurrence with Dillon et al. (2008) who found that DCIS was associated with higher incidence of involved margins in patients undergoing BCS. This could be due to the multifocal nature of DCIS and the presence of microcalcifications which could be difficult to localise in its entirety (Dillon et al., 2008:39-45; Atkins et al., 2012:109-115; Marinovich et al., 2016:3811-3821). Other factors that have been cited as influencing involved margin rates are an initial underestimation of the size of the lesion before surgery, inaccuracy of the localisation, too little tissue excised and the injection not placed central into the lesion (Garzatto et al., 2021:93-105)

In the SNOLL group, 4 re-excisions due to involved margins were identified and 3 of those was found to have no residual disease upon re-excision. This is in line with the findings of Landheer et al. (2004:824-828) who reported that often histology of these re-excised specimens are found to be negative.

5.4.3 Volume of excised tissue

In their systematic review Ahmed & Douek (2013) alluded to the fact that perhaps a bigger dose of radioisotope could result in a bigger excised volume due to radioisotope diffusion. They explained this by the fact that Postma et al. (2012) reported a statistical difference in volume size when comparing it to the WGL in their study, while Giacalone et al. (2012) using a smaller dose reported smaller volume sizes comparing it to WGL in theirs.

In this when comparing administered doses for ROLL and SNOLL group, where the dose is much higher in the SNOLL group (range of 71MBq – 113 MBq vs 5 – 22 MBq) the mean excise volume for SNOLL was 148.71 cm3 while ROLL was 105.61 cm3 which, although larger, was not statistically significant (p=0.54).

Mean excised volume was 114.02 cm^3 regardless of the surgical intent. For the SNOLL group to achieve better radical results a bigger volume was removed with a mean of 148.17cm^3. Excision volumes in this study are bigger in comparison to other studies, namely; Giacalone et al. (2012) 96.3 cm^3, Adamczyk et al. (2011) 81.6 cm^3 for ROLL and 79.55 cm^3 for SNOLL, and Postma et al. (2012) who reported an excised volume of 64cm^3. The larger excised volumes in this study could be due to surgical technique or due to us treating a group of patients with larger lesions due to the unscreened nature of our patients. The amount of tissue excised has a direct impact on the cosmesis of the procedure. The aim of BCS in early stage cancer is to remove as little healthy tissue as possible whilst still achieving the desired outcome. However due to the retrospective nature of this study complete records could not be found with regards to actual lesion size to compare whether the bigger excision volumes were due to the size of the lesion. Furthermore, at the research site additional shavings were done during theatre at the discretion of the surgeon.

5.5 Effectiveness of the SNOLL as a therapeutic tool

5.5.1 Excision margins

Clear excision margins in reviewed studies were reported to be between 86.5% to 94.8% (van Rijk et al., 2007; Mariscal Martínez et al., 2009; Thind et al., 2011; Giacalone et al., 2012; Postma et al., 2012). Thind et al. (2011) had the highest complete excision rate. They used the dual radiopharmaceutical technique with ^{99m}Tc MAA and ^{99m}Tc nanocolloid. Giacalone et al. (2012) used subdermal injection of colloid for SNB. In this study clear margins for invasive cancers were the absence of tumour cells at the inked margin. We achieved a clear margin rate for all invasive cancers of 71.4%. In the SNOLL group the margin was clear in 19/32 (59.3%) of cases. There were only 4 DCIS lesions in this group and 3 of them had involved margins. This result shows that extra caution should be exercised when removing DCIS lesions due to the higher probability of incomplete excision.

5.5.2 Re-excisions

All lesions were identified on the first attempt 37/37 (100%). Therefore, no re-excisions were done due to intra-operative lesion localisation failure.

5.5.3 SLN detection

In this study we used the single intratumoural injection of ^{99m}T nanocolloid to perform lesion localisation with simultaneous SNB. Other studies used the same method (Postma et al., 2012; van Rijk et al., 2007; Feggi et al., 2001). Giacalone et al. (2012) used the dual radiopharmaceutical technique with an intratumoural injection and a subdermal injection for SN detection. SN detection rate in this study was 30/37 (81%). In their study to evaluate different injection techniques for SN detection, De Cicco et al. (2004) showed a significant difference in SN detection rate amongst the different methods favouring subdermal injection method. However, in the large groups of van Rijk et al. (2007) and Postma et al. (2012) with study groups of 293 and 100 patients respectively, they were able to demonstrate 98% and 100% SN detection rate respectively while using the single intratumoural method. Factors which can influence the drainage from the breast include size of the breast, previous surgery to the axilla or breast and the location of the tumour within the breast (van Rijk et al., 2007:627-632). In one patient in this study where the SN was not located it was reported that the patient had an increased BMI. Some of the procedures were also performed on patients that had had previous surgery in the area.

The use of blue dye has been used to help identify and locate the SN during surgery. In their study van Rijk et al. (2007) used patent blue dye. In this study the surgeon injected methylene dye in theatre to help identify the SN. We were unable to find sufficient data to assess how many of the SNs removed were stained blue.

At the study site, only one study showed multiple linear areas of activity inferior and laterally to the injection site 20 minutes after injection. The study was repeated at a later stage and the same pattern was seen. These were therefore noted to most likely be prominent lymphatic tracts. On delayed 20 hour images these tracts were no longer visible. Although there were multiple foci of activity seen on the delayed images superiorly to the injection site, the focus of activity inferiorly to the injection site could be identified as the sentinel node since this was visible on the earlier images.

A total number of 55 SNs were identified and examined. Only 3 patients had positive SN. All SNs were in the axilla except for one which was found in the intramammary region. In one patient no SN was identified on scintigraphy or in theatre.

5.6 Technical difficulties encountered or experienced

There were only 2 cases rescheduled due to technical difficulties due to a failed injection and another because of suspicious initial uptake that needed to be verified on repeat. In this case on the repeat, the uptake looked the same and it could be concluded that it was due to prominent tracts and not the radiopharmaceutical quality control. The use of scintigraphy proved useful in this regard. Both these studies were repeated successfully. Similarly, De Cicco et al. (2002) also reported diffusion of the injection into large area of the breast in 20 cases in which the localisation had to be repeated with an alternate method. This was found in the central quadrant where the probability of injecting into a milk duct is high (De Cicco et al., 2002).

5.7 Time taken and ease of the procedure

The ease of procedure from the view of the surgeon was not assessed in this study. However, there was no additional training for the surgeons performing the ROLL and SNOLL procedure as they were already familiar with the SNB procedure performed for breast cancer patients at the site.

ROLL has been found to have shorter surgical times when compared to the WGL (Sajid et al., 2012; Postma et al., 2012). The mean duration of operation times reported in other studies ranged from 22min – 31 min (Rampaul et al., 2003; Moreno et al., 2008; Medina-Franco et al., 2008; Sarlos et al., 2009). In this study we recorded the time taken to excision rather than the time taken for the entire surgery. This time was calculated from the time initial incision was made until the lesion was excised. The mean time to excision in this study was 16.67 min with times ranging from 5 – 45 minutes. The use of the gamma probe to constantly guide the surgeon in terms of an audible alarm allowed for easier localisation.

Since the research site has an on-site nuclear medicine department, radiopharmaceutical injections could easily be scheduled and administered in collaboration with the radiology and nuclear medicine department. On confirmation of correct positioning and administration of the needle placement and injection, the patient could easily walk the short distance to the nuclear medicine department. Surgery times could therefore be based on available surgery slots with flexibility during unforeseen delays. Patients were usually admitted the day before their scheduled surgery except for some (20%) cases where surgery was performed on the same day. This allowed for other admission administration and baseline tests to be done in preparation for surgery. Scintigraphy was also flexible between patient and gamma camera availability.

5.8 Radiation dose

A dose in the range of 71- 113 MBq was administered to patients undergoing SNOLL procedure. The doses used in this study allowed for extra time delay after radiopharmaceutical administration to optimise time of accumulation in the SN. Several studies have reported using doses in the range of 74 MBq to 123 MBq (van Rijk et al., 2007; Giacalone et al., 2012; Postma et al., 2012; Ahmed & Douek, 2013b). An average dose of around 130 MBq will result in a dose of about 10 MBq at 17 hours (Feggi et al., 2001). These higher doses do not carry with it an added radiation exposure risk (Aydogan et al., 2010).

5.9 Limitations and strengths of the study

Due to the retrospective nature of this study, there was limitations encountered in terms of retrieving and finding all histology, radiology and nuclear medicine reports. These were in terms of analysing data due to missing data such as histology reports, doses administered, lesion location, time to excision, and reasons for re-excision. Furthermore, the format of histology reporting was not the same between different pathologists and while some reported on specimen weights or lesion dimensions others did not. The surgical reports indicating the identification of SLN and whether it was stained blue were limited and this made it impossible to comment on any benefits of using methylene blue dye. Additionally, during the period of this study, the pathology department had changed over to different electronic systems and not all reports on the old system could be retrieved. Records at the study site was only kept for a period of 6 years and therefore manual retrieval of data which were not found on databases was not always possible.

The strengths of the study are that this was the first study to investigate the efficacy of ROLL and SNOLL in a tertiary institute in the Western Cape, South Africa. Furthermore, the sample size in this study was bigger than most other reviewed studies included in this analysis with only two studies having bigger sample sizes viz., Monti et al. (2007) (n=959) and De Cicco et al. (2002) (n=812).

5.10 Recommendations

A further study could perhaps be done to investigate the rate of local recurrence after SNOLL as local recurrence rates was out of the scope of this study as this would require a longer follow up. The results of this study could be used to compare the ROLL technique with the magnetic tracer localisation method currently being used at the study site.

5.11 Conclusion

In conclusion our experience with the ROLL and SNOLL procedure confirms those of previous studies proposing it is practical and relatively easy to perform. Most lesions were successfully located, and the technique was especially useful in cases where needle biopsies were inconclusive. There was a high rate in involved margins where the procedure was done as a therapeutic outcome especially in patients with DCIS. Our observations on imaging confirmed the current literature. Once injected, the radiopharmaceutical did not diffuse into surrounding tissue except where it had been introduced into lymphatic vessels or ducts.

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APPENDICES

APPENDIX A: DATA COLLECTION EXCEL SPREAD SHEET ROLL

PATIENT DEMOGRAPHICS		PRE-OPERATIVE FINDINGS				RADIOPHARMACEUTICAL ADMINISTRATION					
PATIENT IDENTIFIER NR	AGE	IMAGING (MAMM0/US	SITE	DIAGNOSIS	BIRADS CLASSIFICATION	INJ DATE AND TIME	DOSE	RADIO-PHARMACEUTICAL	GUIDANCE	SCINTIGRAPHIC IMAGING (Y/N)	IMAGING SEQUENCE

SURGICAL PROCEDURE							POST OPERATIVE FINDINGS					
USE OF PROBE : DATE & TIME	TIME DIFFERENCE INJ-SURGERY (HRS)	TIME OF EXCISION	DURATION OF SURGERY	SKIN SURFACE (CPS)	BENCH/TISSUE (CPS)	BGD (CPS)	LESION IN SPECIMEN (Y/N)	SIZE OF EXCISED SPECIMEN	POST OPERATIVE HISTOLOGY	RE EXCISON PERFORMED (Y/N)	FOLLOW UP	LOCAL RECURRENCE (Y/N)

APPENDIX B: DATA COLLECTION EXCEL SPREAD SHEET SNOLL

PATIENT DEMOGRAPHICS		PRE-OPERATIVE FINDINGS				RADIOPHARMACEUTICAL ADMINISTRATION					
PATIENT IDENTIFIER NUMBER	AGE	IMAGING (MAMM0/US	SITE	DIAGNOSIS	BIRADS CLASSIFICATION	INJ DATE AND TIME	DOSE	RADIO-PHARMACEUTICAL	GUIDANCE	SCINTIGRAPHIC IMAGING (Y/N)	IMAGING SEQUENCE

SURGICAL PROCEDURE												POST OPERATIVE FINDINGS							
USE OF PROBE : DATE & TIME	TIME DIFFERENCE INJ-SURGERY (HRS)	TIME OF EXCISION	DURATION OF SURGERY	SKIN SURFACE (CPS)	BENCH/TISSUE (CPS)	BGD (CPS)	SLN IDENTIFIED (Y/N)	NO OF SLN	LOCATION OF SLN	BLUE STAIN	FROZEN SECTION ANALYSIS	LESION IN SPECIMEN (Y/N)	SIZE OF EXCISED SPECIMEN	SURGICAL MARGINS		POST OPERATIVE HISTOLOGY	RE EXCISON PERFORMED (Y/N)	FOLLOW UP	LOCAL RECURRENCE (Y/N)
														CLEAR/ INVOLVED	SIZE OF MARGIN				

APPENDIX C: ETHICS APPROVAL (CAPE PENINSULA UNIVERSITY OF TECHNOLOGY)

Cape Peninsula University of Technology

HEALTH AND WELLNESS SCIENCES RESEARCH ETHICS COMMITTEE (HWS-REC)
Registration Number NHREC: REC- 230408-014

P.O. Box 1906 • Bellville 7535 South Africa
Symphony Road Bellville 7535
Tel: +27 21 959 6917
Email: sethn@cput.ac.za

23 April 2021
REC Approval Reference No:
CPUT/HW-REC 2016/H27/renewal

Faculty of Health and Wellness Sciences – Medical Imaging & Therapeutic Science Department Dear

Ms Ismail

Re: APPLICATION TO THE HW-REC FOR ETHICS CLEARANCE

Approval was granted by the Health and Wellness Sciences-REC on 15 September 2016 to Ms Sumaya Ismail for ethical clearance. This approval is for research activities related to student research in the Department of Medical Imaging & Therapeutic at this Institution.

TITLE: Radioguided occult lesion localization (ROLL) as a diagnostic and therapeutic procedure: Clinical review at a single tertiary hospital in South Africa

Supervisor: Mrs Davidson Co-
Supervisor: Mrs Philotheou

Comment:

Data collection permission is required and has been obtained.

Approval will not extend beyond 24 April 2022. An extension should be applied for 6 weeks before this expiry date should data collection and use/analysis of data, information and/or samples for this study continue beyond this date.

The investigator(s) should understand the ethical conditions under which they are authorized to carry out this study and they should be compliant to these conditions. It is required that the investigator(s) complete an **annual progress report** that should be submitted to the HWS-REC in December of that particular year, for the HWS-REC to be kept informed of the progress and of any problems you may have encountered.

Kind Regards

Ms. Carolynn Lackay
Chairperson – Research Ethics Committee
Faculty of Health and Wellness Sciences

APPENDIX D: ETHICS APPROVAL (HUMAN RESEARCH ETHICS COMMITTEE UNIVERSITY OF CAPE TOWN)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.11.2022
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	16/11/2021

Comments to PI from the HREC	Thank you for your Study Deviation HREC Chair Signature Date: 16/11/2021

Principal Investigator to complete the following:

1. Protocol information

Date when submitting this form	29/10/2021		
HREC REF Number	281/2017	Current Ethics Approval was granted until	22/06/2021
Protocol title	Radioguided occult lesion localization (ROLL) as a diagnostic and therapeutic procedure: Clinical review at a single tertiary hospital in South Africa.		
Protocol number if applicable			
Are there any sub-studies linked to this study? If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study	☑ Yes ☐ No		
Principal Investigator	Dr Francois Malherbe		
Department / Office Internal Mail Address	Division of General Surgery J Floor OMB		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

APPENDIX E: ETHICS APPROVAL (RESEARCH COMMITTEE, GROOTE SCHUUR HOSPITAL

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
E-mail : *Bernadette.Eick@westerncape.gov.za*

Dr Lydia Cairncross
Division of General Surgery

E-mail: sumaya.ismail01@gmail.com / lydiacairn@gmail.com

Dear Dr Cairncross,

RESEARCH PROJECT EXTENSION: Radio Guided Occult lesion Localisation (ROLL) As A Diagnostic and Therapeutic Procedure: Clinical Review At A Single Tertiary Hospital in South Africa – Sub-Study linked to 672-2016

Your recent communication to the hospital refers.

The extension of your research is approved in accordance with UCT Ethics clearance, until 30 June 2019.

As previously mentioned:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No hospital consumables and stationary may be used.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Once the research is complete, please submit a copy of the publication or report.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 10 September 2018

C.C. Mr L. Naidoo
Dr B. Jacobs

G46 Management Suite, Old Main Building,
Observatory 7925

Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935

www.capegateway.go.v.za

APPENDIX F: Data collection permission approval (Nuclear Medicine Department, Groote Schuur Hospital)

Western Cape Government
Health

Topic: ROLL as a diagnostic and therapeutic procedure: Clinical review at a single tertiary hospital in South Africa.

For: Master in Science (MSc) Radiography degree at the Cape Peninsula University of Technology (CPUT).
Dear Mrs Ismail

PERMISSION TO CONDUCT RESEARCH

Thank you for submitting your research protocol.

You are hereby granted permission to proceed with your research. Please take not of the rules and regulations for conducting research.
On completion of research, please submit a copy of the publication and or report.

I would like to wish you every success with the project.
Yours sincerely

Dr Tessa Kotze

Specialist Nuclear Medicine Phycision HOD
Nuclear Medicine
Groote Schuur Hospital

Main Road, Observatory, 7925 Private Bag X4, Observatory, 7935
www.westerncape.gov.za

APPENDIX G: DATA COLLECTION PERMISSION APPROVAL (DEPARTMENT OF SURGERY, GROOTE SCHUUR HOSPITAL)

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Surgical Endocrine Oncology Unit
Ward F17
(Tel) 021 404 3543 or 021 404 3036

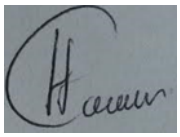
19/08/16

Dear Colleague

This letter serves to confirm that, as head of diagnostic and surgical breast services at Groote Schuur hospital, I have agreed to co supervise Sumaya Ismail's MSc project entitled: *ROLL as a diagnostic and therapeutic procedure: Clinical review at a single tertiary hospital in South Africa.*

The project involves a retrospective audit of patient records who have undergone this procedure. As a senior clinician within this area of work, I give permission for her to conduct this research with the proviso that ethical permission is granted by the UCT Human Research Ethics Committee and then subsequently by Groote Schuur Hospital management. I have undertaken to assist in the standard procedures required to obtain this permission.

Yours sincerely



Dr. L. Cairncross

Head: Surgical Endocrine Oncology Unit

Division of General Surgery

Department of Surgery

Groote Schuur Hospital

Email: lydia.cairncross@uct.ac.za

APPENDIX H: ORIGINALITY REPORT

24 November

ORIGINALITY REPORT

SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS
13%	10%	7%	3%

PRIMARY SOURCES

1	etd.cput.ac.za Internet Source	2%
2	hdl.handle.net Internet Source	1%
3	creativecommons.org Internet Source	1%
4	worldwidescience.org Internet Source	<1%
5	Submitted to Cape Peninsula University of Technology Student Paper	<1%
6	link.springer.com Internet Source	<1%