School of Public Health

Radiopharmaceuticals and the PET Probe in the Detection of Ductal Carcinoma in Situ of the Breast

Kerryn Butler-Henderson

This thesis is presented for the Degree of
Doctor of Philosophy
of
Curtin University

March 2014

Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Signature: .....

Date: 13 MARCH 2014

ACKNOWLEDGEMENTS

Without the goodwill of so many this research would not have been realised. This research was funded by a number of organisations. The Cancer Council of Western Australia contributed towards the purchase of the PET probe equipment. Cancer Australia and the National Breast Cancer Foundation Australia, provided funding to conduct the surgical research aspect of this thesis.

I would like to acknowledge the involvement of the following people and give my thanks to them.

I would like to thank my three supervisors for their support and encouragement. I would like to make particular reference to the support Professor Andy Lee dedicated during the last year of this PhD study, meeting with me frequently, quickly returning feedback and advice and responding to communications immediately. Dr Lee assisted me to expand my knowledge and skills in research design, biostatistics, and journal article production. Professor Roger Price for making the time to attend meetings, provide both academic and personal advice, allowing me to use the facilities at Medical Technology & Physics, Sir Charles Gairdner Hospital, and the wonderfully detailed and thought provoking feedback on chapters and articles that helped me grow as an academic. And Dr Nat Lenzo for giving up weekends to review images and results with me, providing clinical advice, organising PET scanner time and assisting with the recruitment of breast surgeons.

My thanks to my Thesis Committee Chairperson, Dr Kay Sauer, for provided governance, guidance and support, both academic and personal, and fighting in my corner when needed. You helped me to keep going and stay on track.

All the staff of the RAPID team at the Department of Medical Technology & Physics, in particular Christopher Jones and Charmaine Jeffery, and the Department of Nuclear Medicine, in particular Drs Peter Robins, Nelson Loh and Jan Boucek, at Sir Charles Gairdner Hospital, Perth Western Australia, for donating their laboratories, equipment, resources, expertise and time.

The staff at the Breast Assessment Centre at Royal Perth Hospital, Perth Western Australia, for assisting with patient recruitment. The Cancer Registry of Western Australia, in particular Dr Tim Threlfall, and the Data Integrity Directorate at the Department of Health, Western Australia, in particular Elisabeth Sallur and Mike Yun, for the provision of data.

Dr Geoff Bower and the staff at the Mount Nuclear Medicine, Perth Western Australia, for receiving the radiopharmaceutical doses, injecting the patients, organising the return couriers, providing iron aprons and offering advice. And the ward and theatre staff at the Mount Hospital, Perth Western Australia, for monitoring patients and assisting with the surgical research.

My thanks to the breast surgeons involved with this research: Dr Christobel Saunders at Royal Perth Hospital for the recruitment of patients in the PET imaging study; Drs Peter Willsher, Diana Hastrich and David Ingram at the Mount Hospital for the recruitment of patients, the use of the PET probe in surgery and giving of their personal time to review results.

To the Curtin Health Information Management research team who assisted me with various parts of this study: Kaylene Waring, Emma Amozig, Lunchana Kariyakarawana and Dinithi Siriwardhane. I am very grateful to you all. And to the academic staff in the Department of Health Information Management who picked up the load when I needed to focus on this research: Melanie Griffiths, Brian Stanley, Tim Nelson, Julie Newland, Sharon Campbell, Matthew Painter, Rajaswari Kandiah, Julie Bennett, Chantal Orgeas, Sonia Harwood and Raymond Neo. Thank you for being understanding and supportive.

To my employer for supporting this research. In particular Dr Sue Fyfe for her mentorship, support, encouragement and faith. I hope one day to be as achieved and competent as you and to inspire others.

To my Mum, Lesley, and Dad, Rick, for not complaining about me not being there to support them and not asking when I will be finished. Thank you for helping my family over the last year whilst I was absent. To Mum for being my role model. And Dad for keeping me sane. And my extended family, including my brother (Chad), in-laws and nephews, and my dear friends, in particular Terri, Berlinda, Natasha, Katherine and

Melanie, for forgiving me missing important events to go sit in a windowless room and helping me through “the Valley”.

I will be in debt to my family for a long time for their support and encouragement. My husband, David, who became a single father for the last year, cooking, cleaning, chauffeuring and keeping tabs on my own health and safety. He became an expert in breast cancer and PET technology and read the final thesis from start to end for me. Thank you so much Dave. To my eldest two daughters Asher and Kayla, for supporting Dave and me, and being so patient. You are now young adults who I am very proud of and have wonderful lives ahead. Ash – your fried rice sustained me on more than one late night. And little Ava, who has known nothing but this PhD, being born in the middle of it. I will now get to spend more time playing with bubbles with you on the lawn. Thank you my wonderful family.

Lastly, but most importantly, to all the women who agreed to be part of this research. I will be forever grateful for your participation. In particular to that one lady who joined me on the media trail – I still cry every time I hear your story – thank you!

This thesis is dedicated to

All the women diagnosed with breast cancer in Australia

You are beautiful, courageous and inspirational.

PREFACE

Due to the study design of this research, this Doctor of Philosophy was undertaken on a part-time basis.

Two articles have been accepted for publications:

1. Butler-Henderson, K., Lee, A.H., Price, R.I., & Waring, K. 2014. Intraoperative assessment of margins in breast conserving therapy: a systematic review. Breast. 27 January 2014 (Article in Press DOI: 10.1016/j.breast.2014.01.002).

2. Butler-Henderson, K., Lee, A.H., Lenzo, N.P., & Price, R.I. 2014. Epidemiology of ductal carcinoma in situ in Western Australia: implications for surgical margins and management. Breast Cancer. 29 April 2014. (Article in Press DOI 10.1007/s12282-014-0531-5)

The outcome of a number of other articles are pending.

ABSTRACT

Ductal carcinoma in situ (DCIS) is characterised as neoplastic cells confined to the mammary duct system of the breast. DCIS initially develops within and has the potential to extend along these ducts. When these neoplastic cells spread outside the ducts into the tissue, the lesion becomes invasive ductal carcinoma. Whilst the cause of DCIS has not been confirmed, there is a close association between DCIS and invasive ductal breast cancer, with approximately half of reported invasion found at or close to the original DCIS site. It is therefore important to ensure all the DCIS has been removed during the first operation. Yet the literature varies between 5 to 72% of cases require a second operation to obtain adequate margins. This additional surgery has implications for the patient's quality of life and an impact on the health service in terms of cost and management.

The hypothesis for this thesis was a preoperative radiopharmaceutical injection and the use of an intraoperative positron emission tomography (PET) probe would accurately (≥80%) determine the margin status during breast conserving therapy (BCT) for DCIS. The significance of this study was the ability to determine adequate margin clearance during surgery would reduce the need for a second operation (re-excision) and potentially reduce subsequent breast cancer events (defined as a recurrence or invasion).

This study recruited 39 patients at a private hospital in Perth, Western Australia, who were planned to undergo BCT for primary DCIS. The distance between the edge of the DCIS and the edge of the excised tumour is measured to determine the width of normal tissue. This distance is referred to as the clearance of the margin. The probe findings were compared against the pathology findings, with a 10mm clearance of the margin used as the gold standard and a 2mm clearance of the margin as a reference against other intraoperative assessment techniques. The probe was 89.7% accurate at assessing the surgical margin in the cavity at a 10mm clearance of margins and 92.5% at a 2mm clearance of margins. It was 94.5% accurate at assessing the surgical margin on the excised specimen at a 10mm clearance of margins and 96.5% at a 2mm clearance of margins. Compared to other intraoperative margin assessment methods the PET probe performed better in accuracy, sensitivity and specificity. The one exception was frozen section analysis that was more accurate but delayed the result (~20-30 minutes). Using simple and multiple linear regression modelling the study was able to confirm the

hypothesis that the PET probe could accurately determine the margin status intraoperatively during DCIS surgery. An ideal protocol for future studies has been established, including a recommendation that the injected dose of FDG should be ≥80MBq, used within two hours of injection and whilst the probe can be applied within the surgical cavity and on the excised specimen it is recommended to be used on the excised specimen.

This research was able to demonstrate the PET probe has a high accuracy when used to determine the status of the surgical margin in DCIS surgery. The probe performed better than all identified technologies when compared by accuracy, sensitivity, specificity and time to apply and return a result. The implications is, when additional margins are taken based on the probe findings, the rate of second operations will be reduced having improved quality of life, health service management and healthcare cost implications. Potentially this will reduce the rate of women experience a subsequent breast cancer event, thus reducing the invasive ductal carcinoma of the breast rate. Further research is required where additional shavings are taken based on the probe results, in a multi-centre study with a larger sample size, to further test the capability of the probe. This future research should include a substantial follow-up of a minimum of ten years to determine the effect of the probe on subsequent breast cancer event rates. An economic analysis is also recommended.

TABLE OF CONTENTS

LIST OF FIGURES

Page

LIST OF TABLES

Page

ABBREVIATIONS

@	at
&	and
ABBI	advanced breast biopsy instrument
AIHW	Australian Institute of Health and Welfare
ANZBCTG	Australian and New Zealand Breast Cancer Trails Group
ASR	age-standardised incidence rate
BAC	Breast Assessment Centre
BCE	breast cancer event
BCT	breast conserving therapy
BMI	body mass index
CI	confidence interval
CIS	carcinoma in situ
cm	centimetres
CNB/CNA	core needle biopsy/aspiration
CPS	counts per second
DCIS	ductal carcinoma in situ
EORTC	European Organization for Research and Treatment of Cancer
ER	oestrogen receptor
F-18	fluorine-18
FCH	^{18}F-fluoromethylcholine
FDG	^{18}F-fluorodeoxyglucose
FNB/FNA/FNAB	fine needle biopsy/aspiration
FN	false negative
FP	false positive
FUP	follow-up
FWHM	full width at half maximum
g	grams
HER2	human epidermal growth factor receptor-2
HRT	hormone replacement therapy
I-131	iodine-131
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
ID	identification number

IDC	invasive ductal carcinoma
IDSM	intraoperative digital specimen mammography
ILC	invasive lobular carcinoma
IMA	intraoperative margin assessment
IMI	IntraMedical Imaging
Int.	intermediate
kBq	kilobecquerel
keV	kiloelectronvolt
LCIS	lobular carcinoma in situ
LSO	lutetium oxyorthosilicate
MBq	megabecquerel
MeV	megaelectron volt
mg	milligrams
MIBB	minimally invasive breast biopsy
ml	millilitres
mm	millimetre
mmol/l	millimoles per litre
MRI	magnetic resonance imaging
mSv	millisievert
NA	not applicable
NBCA	National Breast Cancer Audit
NBCC	National Breast Cancer Centre
No.	number
NOS	not otherwise specified
NPV	negative predictive value
NR	not reported
NS	not specified
NSABP	National Surgical Adjuvant Breast and Bowel Project
OCT	optical coherence tomography
OR	odds ratio
PAH	polycyclic aromatic hydrocarbons
PET	positron emission tomography
PET-CT	positron emission tomography – computer tomography
PPV	positive predictive value
PR	progesterone receptor

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QAS	quality assessment score
QAT	quality assessment tool
RACS	Royal Australasian College of Surgeons
RAPID	Radiopharmaceutical Production and Development Centre
RFS	radiofrequency spectroscopy probe
ROI	region of interest
RPH	Royal Perth Hospital
RR	relative risk
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
SR	specimen radiography
SSM	standard specimen mammography
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUV	standardised uptake value
TTB	tumour to background
μl	microliter
μm	micrometre
USA	United States of America
VNPI	Van Nuys prognostic index
WA	Western Australia
WLE	wide local excision

CHAPTER 1 INTRODUCTION

1.1 Introduction

Ductal carcinoma in situ (DCIS) is characterised as neoplastic cells confined to the mammary duct system of the breast. Whilst DCIS remains within, or extends along these ducts, it is still a non-invasive tumour. However it has the potential to spread outside of the ducts into the surrounding tissue and become invasive ductal carcinoma.[1] It is important to ensure all the DCIS has been removed during the first operation as approximately half of reported invasions are found at or close to the original DCIS site. The literature varies between 5 to 72% of cases require a second operation to obtain adequate margins which impacts on the patient quality of life and health service management.[2-4] Adequate excision of DCIS during the first operation may also reduce the number of cases that progress to invasive ductal carcinoma of the breast.

1.2 Statement of the problem

In breast conserving therapy (BCT) for DCIS the literature has reported failure to achieve adequate margins can result in the need for a second operation and there is a significant rate of subsequent breast cancer events, specifically recurrence or invasion.[4]

1.3 Research question

The main research question is whether a preoperative radiopharmaceutical injection and the use of an intraoperative positron emission tomography (PET) probe can accurately (≥80%) determine the margin status during BCT surgery for DCIS. To test this hypothesis, this study was developed in a staged approach: (1) literature review to identify the accuracy of existing intraoperative margin assessment (IMA) methods, (2) epidemiological study of DCIS in Western Australia (WA), (3) radiopharmaceutical testing, (4) laboratory testing and phantom study for the PET probe, and (5) clinical testing of the PET probe in surgery.

1.4 Research aim and objectives

The National Breast Cancer Centre (NBCC) recognises that further research in DCIS is needed in the area of treatment. An intraoperative device that is able to accurately assess the extent of DCIS remaining within the surgical margin during the first operation, thus allowing additional shavings to be taken where necessary, can potentially reduce the need for a second operation and the risk of a subsequent breast cancer event/s. This validation study aimed to identify a suitable radiopharmaceutical tracer for DCIS and determine the accuracy (≥80%) of a PET probe to evaluate the margin status during BCT for DCIS.

The five objectives of this thesis are outlined below.

(1) Systematic literature review:

1. Identify published academic literature, using a systematic method, that reports the use of an intraoperative method to determine margin status in BCT;
2. Identify the level of concordance in margin assessment between reported IMA methods and standard assessment; and
3. Determine the accuracy of such methods.

(2) Epidemiological study:

1. Identify the characteristics of women who have been diagnosed with DCIS in WA between January 1996 and December 2005;
2. Determine the rate of second operations and breast cancer events (BCE) (recurrence or invasion) in the study population; and
3. Identify risk factors for a breast cancer event in the study population.

(3) Radiopharmaceutical testing:

1. Determine if both ^{18}F-fluorodeoxyglucose (FDG) PET and ^{18}F-fluoromethylcholine (FCH) PET can detect newly diagnosed DCIS;
2. Identify the tumour to background (TTB) ratio for each radiopharmaceutical in DCIS; and
3. Determine the best radiopharmaceutical to use with the PET probe.

(4) Laboratory testing and phantom study:

1. Identify the sensitivity and linearity, specific activity, spatial resolution, source detector distance and depth response of the PET probe in a laboratory setting, and
2. Determine the ideal level of activity correlating the probe response with PET standardised uptake value (SUV).

(5) Clinical testing:

1. Determine if the use of a PET probe can accurately assess the surgical margins intraoperatively in women undergoing BCT for DCIS,
2. Determine if there is an association between PET probe findings and histological factors such as DCIS size, nuclear grade or necrosis,
3. Compare the results of this study with those identified in the systematic literature review, and
4. Determine the level of radiation exposure for the surgeon excising and handling the excised tissue.

1.5 Definition of terms

For the purpose of this thesis, the following definitions are used.

Investigator: the PhD candidate.

Ductal carcinoma in situ (DCIS): the confinement of neoplastic cells within the mammary duct system of the breast.

Second operation: the re-excision of DCIS where inadequate margins were obtained during the first operation. This is undertaken within four months of the first operation.

Surgical margin: the edge or rim of the tissue within the breast from where the tumour has been removed. On the excised tissue the surgical margin is the outside edges of the tissue. There are therefore six possible surgical margins: superior (top), inferior (bottom), medial (towards the middle), lateral (towards the side), superficial (towards the surface) and deep (away from the surface).

Clearance of margins: The distance between the edge of the tumour and the edge of the excised tissue to determine the width of normal tissue

Breast cancer event: any recurrence of DCIS within the same breast as the primary DCIS diagnosis, defined as a morphology behaviour code of '2', or invasive ductal carcinoma, defined as a morphology behaviour code of '3', that occurred more than four months after the diagnosis of DCIS.

Shavings: when the surgeon removes an additional thin strip of tissue during surgery after the tumour has been excised. This is performed when the surgeon believes an adequate margin has not been achieved with the removal of the tumour.

Radiopharmaceutical: a pharmaceutical or nuclide that contains a radioactive compound.

1.6 Significance of the study

The significance of this study was the validation of the PET probe in accurately determining the margin status both within the surgical cavity and on the excised tissue during breast conserving surgery for DCIS. Where further shavings are taken based in a positive PET probe result, it would reduce the need for a second operation. By more accurately assessing the margins and as such ensuring all of the DCIS had been removed from the breast during the first operation, this would reduce the risk of a subsequent breast cancer event. Potentially this could reduce the rate of invasive breast cancer where DCIS is detected.

1.7 Limitations of the study

As this was a validation study, no additional shavings were taken during the DCIS operation. Although the accuracy of the probe was determined, the impact of the probe on the second operation rate and rate of subsequent breast cancer events cannot be quantified.

1.8 Thesis organisation

This thesis has been organised into the following chapters.

Chapter 2: Ductal carcinoma in situ.

This chapter provides the reader with a brief introduction to DCIS. It includes an overview of the anatomy of the breast, the histology of DCIS, incidence rates, risk factors, detection, diagnosis, treatment, breast cancer event rates and the importance of adequate surgical margins. This chapter is designed to provide the non-clinically orientated reader with sufficient knowledge to understand the implications of residual DCIS and current treatment methods.

Chapter 3: Literature review: intraoperative assessment of surgical margins for breast cancer.

A systematic literature review was undertaken on intraoperative margin assessment methods to identify the accuracy of existing methods in breast cancer surgery. The results of this study were used as a basis of comparison with the PET probe.

Chapter 4: Epidemiology of ductal carcinoma in situ in Western Australia 1996 – 2005.

Whilst chapter 2 provides the clinical background to this study, chapter 4 provides the epidemiological evidence to support this study. The chapter discusses the rate of DCIS in WA, the rate of second operations and the rate of subsequent BCEs. This chapter supports the need for IMA technology in WA in the surgical treatment of DCIS.

Chapter 5: Comparison of radiopharmaceuticals in the detection of ductal carcinoma in situ with positron emission tomography.

There has been little information available on the use of PET imaging for DCIS. Therefore it is unknown which radiopharmaceutical tracer is suitable to use with the PET probe. This chapter compares FDG against FCH in two case studies to determine how well each is taken up by DCIS.

Chapter 6: Positron emission tomography (PET) probe laboratory testing and phantom study.

As there has also been minimal published research on how the PET probe functions and the most appropriate protocol to use in surgery, a number of laboratory tests were performed to identify the sensitivity and linearity, specific activity, spatial resolution,

source detector and depth response of the probe. A phantom study was also developed to ascertain the appropriate injected dose to use in surgery. This chapter concludes with the best protocol to use in surgery.

Chapter 7: Intraoperative positron emission tomography (PET) probe for margin assessment of DCIS.

This chapter discusses the results and findings from using the PET probe in BCT for DCIS. It outlines the accuracy, sensitivity and specificity of the probe, determines if histological factors impact on this accuracy, compares the results against the other studies identified in chapter 3 and examines the radiation exposure for the surgeon.

Chapter 8: Conclusion and recommendations.

This final chapter discusses the findings from the present study and the tentative conclusions drawn. Recommendations for future research are identified at the conclusion of this thesis.

1.9 References

1. National Breast and Ovarian Cancer Centre. Understanding ductal carcinoma in situ., 2010. Surry Hills, NSW: National Breast and Ovarian Cancer Centre.

2. National Breast Cancer Centre. The clinical management of ductal carcinoma in situ, lobular carcinoma in situ and atypical hyperplasia of the breast, 2003. Camperdown, NSW: National Breast Cancer Centre.

3. Kricker A, Armstrong B. Surgery and outcomes of ductal carcinoma in situ of the breast: a population-based study in Australia. European Journal of Cancer. 2004; 40(16):2396-2402.

4. Dillon MF, Mc Dermott EW, O'Doherty A, Quinn CM, Hill AD, O'Higgins N. Factors affecting successful breast conservation for ductal carcinoma in situ. Annals of Surgical Oncology. 2007; 14(5):1618-28.

CHAPTER 2 DUCTAL CARCINOMA IN SITU

2.1 Introduction

Ductal carcinoma in situ (DCIS) is a heterogeneous disease characterised as a proliferation of neoplastic cells confined to the mammary duct system of the breast. Normal breasts contain lobules, and ducts that take the milk from the lobules to the nipple. These are surrounded by a fibrofatty tissue. DCIS initially develops within these ducts and has the potential to extend along these ducts. When these neoplastic cells spread outside the ducts into the tissue, the lesion becomes invasive ductal carcinoma.[1]

This chapter aims to provide a detailed background about DCIS. The anatomy and pathophysiology of DCIS is outlined, including the natural history of the disease. The risk factors of DCIS, including age, family history and reproductive factors, are examined. The incidence of DCIS in Australia will be discussed in this chapter, but the epidemiology of the disease in Western Australia (WA) shall be examined and discussed in detail in Chapter 4. Methods of detecting and diagnosing DCIS are reviewed, including explanations for recommended methods of detection and diagnosis. The treatment methods and Australian treatment guidelines are examined and predictors of subsequent breast cancer events (BCE) (recurrence or invasion) outlined. At the conclusion of this chapter the reader should have an adequate understanding of DCIS and an introduction to the problem of this research study: the difficulties in ensuring adequate margins have been achieved and the implications of not ensuring complete excision of the DCIS during surgery.

2.2 Abbreviations

Below is a list of abbreviations used in this chapter:

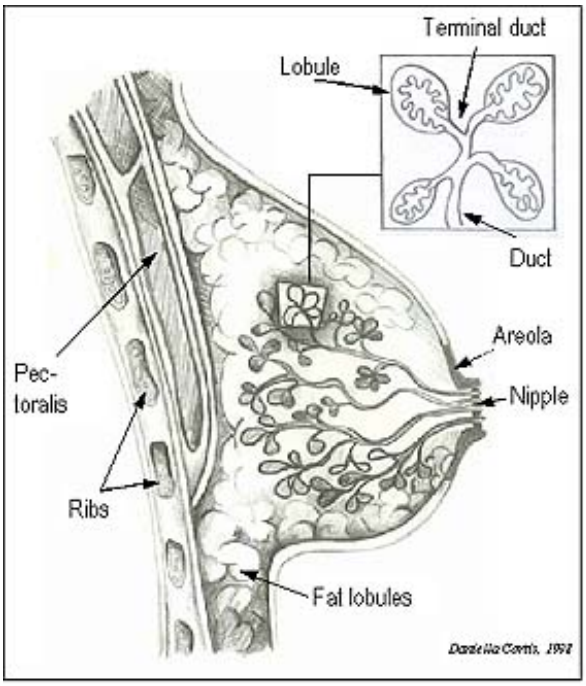
ABBI	advanced breast biopsy instrument
ANZBCTG	Australian and New Zealand Breast Cancer Trial Group
BCE	breast cancer event
BCT	breast conserving therapy
CI	confidence interval
CNB/CNA	core needle biopsy/aspiration
DCIS	ductal carcinoma in situ

EORTC	European Organization for Research and Treatment of Cancer
ER	oestrogen receptor
FNB/FNA/FNAB	fine needle biopsy/aspiration
HRT	hormone replacement therapy
mg	milligrams
MIBB	minimally invasive breast biopsy
MRI	magnetic resonance imaging
NBCA	National Breast Cancer Audit
NBCC	National Breast Cancer Centre
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	odds ratio
PAH	polycyclic aromatic hydrocarbons
RACS	Royal Australasian College of Surgeons
RR	relative risk
VNPI	Van Nuys prognostic index
WA	Western Australia
WLE	wide local excision

2.3 Breast anatomy

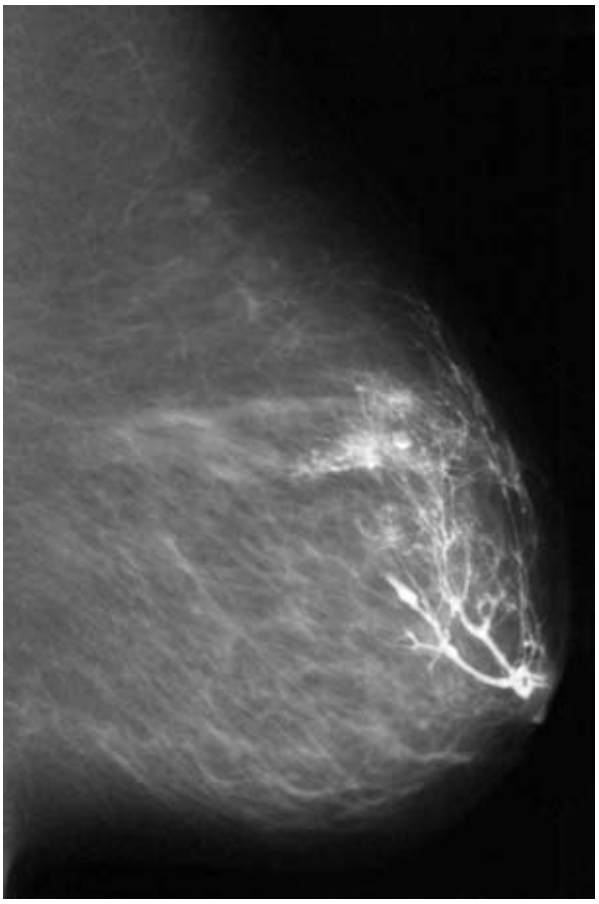
The breasts are a number of sebaceous glands within the superficial fascia of the anterior wall of the chest, weighing on average 200-300 grams and comprised of 20% glandular tissue and 80% fat and connective tissue.[2] Within the breast and extending from the nipple in a radial manner are 15-20 lobes, each containing one collecting duct measuring 2-8mm in size. Within each lobe are 20-40 lobules, each containing 10-100 alveoli.[2] The anatomical positioning of these ducts and their lobe is important when assessing the location and extent of breast disease. Figure 2.1 shows a sagittal cross-section of the breast, including a cross-section sketch of a lobe. Figure 2.2 shows a galactogram image of the breast, which highlights the ductal system.

Figure 2.1: Sagittal cross-section of the breast



Source: http://www.bci.org.au/public/guides/breast.jpg

Figure 2.2: Ductal structure of the breast including ducts



Source: http://www.radiologyinfo.org/en/photocat/gallery3.cfm?pid=1&image=brst-xr-galacto1.jpg&pg=galactogram

Lymphatic fluid drains to the axillary nodes (approximately 75% of drainage) or to the internal mammary nodes and skin lymphatics.[2] The axillary contains 30-60 lymph nodes that are anatomically found in one of three levels that determine the sequential lymphatic draining and potential metastasis pathway. Commencing at level 1 nodes, these are located lateral to the pectoralis minor muscles. Draining is then to the level 2 nodes located beneath the pectoralis minor muscles, then to level 3 nodes located medial to the pectoralis minor muscles.[2]

2.4 Histopathology

The key histological feature of DCIS of the breast is that it contains malignant cells that do not have the capacity to invade the basement membrane or to metastasise outside of the breast. Instead the malignant cells can spread along the duct system. DCIS develops when dysplastic cells within the ducts of the breast become malignant cells. Generally only one duct is involved, but multiple ducts may contain the malignant cells thereby involving several quadrants, known as multifocal disease. Unfortunately there is a high level of inter-observer variability amongst pathologists when examining breast tissue, largely due to the small samples obtained through biopsy and the continuum of change from normal epithelium to DCIS.[3-5] DCIS accounts for approximately 15-30% of mammographically detected breast cancers.[5-8]

2.4.1 Architecture

Historically, DCIS was classified according to architectural pattern. There are five general architectural growth patterns of DCIS:[2]

1. Comedo: rod-shaped or branching epithelial cells that are rapidly proliferating. This is the most common form detected by mammography, in approximately 50% of cases.
2. Solid: disorderly proliferation of epithelial cells.
3. Cribriform: sieve-like or geometric lacy. Most common form to be detected symptomatically.
4. (Micro) Papillary: papillary projections into the lumen of the epithelial cells. More often multisectional.
5. Mixed type

In many cases pathologists see a mixture of architectural patterns. Other types of DCIS have been identified, such as neuroendocrine, cystic hypersecretory, small cell solid,

encysted papillary DCIS and clinging variants, but these are rarer subtypes and infrequently reported.[9]

2.4.2 Grading

It has been agreed that classification based on architecture alone has poor reproducibility amongst even experienced pathologists.[9, 10] Today, DCIS is generally classified by cytonuclear grade of the nuclei, as low, intermediate or high grade disease. This is grouped based on the architecture and size of the cells and nuclear abnormalities seen by the pathologist, as outlined in Table 2.1.

Table 2.1: Pathological classification of ductal carcinoma in situ

High grade	Intermediate grade	Low grade
• Large cells with profuse cytoplasm, • Marked nuclear pleomorphism, • Increased mitosis, • Often central comedo-type necrosis in the lumen, • Typically a solid architecture with rod-shaped calcifications but can be (micro)papillary or cribriform, • Nuclear membranes are irregular, chromatin coarse and often multiple prominent nucleoli, • Cellular polarization is infrequent.	• Moderately sized cells, • Usually solid architecture, (micro)papillary or cribriform, • Nuclear polarization is usually at a moderate degree, with a degree of atypia and nuclear uniformity between the two grades, • Some evidence of cellular polarization and mitosis, • Single cell necrosis are infrequent, • Psammoma-like or amorphous calcification.	• Small, uniform cells, • Often cribiform or (micro)papillary architecture, • Round calcifications often seen, • Smooth nuclear membrane, fine chromatin, and unremarkable nucleoli, • Indication of cellular polarization, with the cellular apex oriented towards the intercellular spaces, • Infrequent mitoses, • Central necrosis and psammoma-body like calcifications can be seen.

Sources: Dervan (2001)[5]; Pinder & Provenzano (2010)[6]

Using the grading system allows greater reproducibility in diagnostic results by pathologists.[7,9,11] Other systems have been proposed but most pathologists use nuclear grade as a basis. A general consensus has been reached that DCIS should be classified using nuclear grade, necrosis, cellular polarization and architecture.[9]

It has been noted that DCIS follows a continuous spectrum from low to high grade, with an increase in growth pattern.[12] The growth pattern of DCIS appears to correlate with

the nuclear grade, whereby high grade DCIS shows continuous growth along the ducts and low grade DCIS are composed of discontinuous foci.[7, 9] High grade DCIS has a higher risk of recurrence, which impacts on the management plan for the patient.[9, 11, 13]

2.4.3 Natural history

The natural history of DCIS is not fully understood, with many studies based on historical information or case studies of low grade DCIS. A sub-study analysed the data for 28 women diagnosed with small, non-comedo DCIS who did not undergo any treatment, with 25-35 years follow-up data.[14, 15] The purpose of the longitudinal study was to understand the natural history of low grade, noncomedo DCIS, commencing in the 1970s with follow-up in 1982, 1995 and 2005. The study found eleven (39.3%) cases developed ipsilateral (same breast) invasive breast cancer, all located at the original biopsy site. The majority of cases progressed to invasive carcinoma within 15 years of the initial biopsy. The study concluded that untreated low grade, noncomedo DCIS will eventually progress to invasive breast carcinoma in approximately a third of cases within 15 years.[15] Given these findings, the risk of progression for high grade DCIS is much higher, with studies reporting approximately 50% of high grade DCIS cases will progress to invasive breast carcinoma.[15-17]

2.4.4 Other histological factors

It is difficult to reliably predict the biological behaviour of DCIS.[7] One possible predictor of outcome is specific genetic alterations. Identification of any biological factors, such as histological or genetic factors that could accurately predict the likelihood of progression to invasive breast cancer, would allow better tailoring of treatment for the initial DCIS diagnosis.[7] Similar to invasive breast cancer, amplification of several specific chromosomal regions are involved with the development of the cancer and usually one or more oncogenes are identified.[7] 10-25% of invasive breast cancers have identified amplified regions. Research has suggested the same chromosomal regions are amplified in DCIS with comparable frequencies.[7] The three oncogenes that have been identified in DCIS are HER-2, cyclin D1 and C-MYC. Amplification of several other chromosomal regions have been identified. Genetic studies have inferred that high and low grade DCIS have different alterations.[10] Another predictor is hormonal status, with oestrogen receptor (ER) negative cell clusters having a higher expressing frequency of multiple growth related genes than ER positive cell

clusters. This suggests greater potential for a subsequent BCE (recurrence or invasion) in the same breast.[11, 18]

2.5 Incidence

Between 1993 and 1998, the incidence of DCIS in Australia increased by over 80%.[19] This may be due to an increase in the number of women having screening mammograms and improved data collection. The most recent Australian data reported there were 13,749 new cases of DCIS diagnosed in Australia between 1995 and 2005, with 1,558 new cases diagnosed in 2005.[20]

In WA only 10 cases of DCIS without invasion were diagnosed in 1982, yet there were 120 cases diagnosed in 1997 for reasons described above.[21] Since 2000, the number of cases has remained steadily around 200.[21]

The incidence of DCIS compared to invasive breast cancer varies by state and mammography services, between 1:4 to 1:10.[19] Incidence peaks at an earlier age, with the mean age in Australia of 59 years.[19] More than a third of new DCIS cases in 2005 were women in the 50-59 years age group.[20]

2.6 Risk factors

There has been no research to successfully identify the cause of DCIS. Research has identified a number of associated risks, which are similar to those for invasive breast cancer.

2.6.1 Family history and age

Similar to invasive breast cancer, family history has a strong association with DCIS.[22-25] In a large population-based case-control study, a family history of breast cancer was identified as the greatest risk factor for developing DCIS with an odds ratio (OR) of 1.48, with other studies reporting an OR up to 2.4.[22, 24] A first-degree family member who was diagnosed at a young age with breast or ovarian cancer further increased this risk. Research has identified the link between the presence of the BRCA1 and BRCA2 alleles and an increased risk of invasive breast-ovarian cancer, yet this has not been extended to DCIS. This may be due to in situ cancers being unstable genetically with

alterations shared with synchronous invasive cancer.[26] There was also an inverse relationship between family history of breast cancer and age of onset, with an OR 2.4 for cases diagnosed under 50 years of age versus 1.4 for cases diagnosed 50 years or older.[23] Women under 45 years of age, with a first-degree family member with a history of breast cancer, have the highest risk factor (relative risk [RR] = 2.50).[23]

2.6.2 Reproductive factors

A number of reproductive factors have been associated with DCIS, including older age at time of first full term pregnancy, or fewer full-term pregnancies or nulligravida (never been pregnant).[22-25, 27] The risk was halved in women who had four or more full-term pregnancies when compared to women with a single birth.[23] Women who were nulligravida had a RR of 2.31. Later menarche reduced the risk of DCIS whilst an older age at menopause increased the risk of DCIS, supporting the argument that long uninterrupted periods of exposure to oestrogen and progesterone can increase the risk of developing DCIS.[22, 25] However, research has found there is no significant increase in risk of DCIS when assessing postmenopausal serum levels of sex hormones (estradiol, estrone, testosterone, androstenedione, DHEAS and SHBG).[28] Within mammary tissue the degree of ER expression peaks during the DCIS stage and hormone dependence is diminished.[29]

Most studies have found no association between the use of oral contraceptives or the use of hormone replacement therapy (HRT) and an increased risk of DCIS, with the OR 0.92 and 1.22 respectively.[22] Longnecker found an OR of 1.47 for use of HRT after excluding cases with an imputed age at menopause, but the 95% confidence interval (CI) was very wide (0.82-2.63). When adjusted for frequency of mammography and number of physician visits, there was no difference in risk to the control group. A similar result was found in the group who had ever used oestrogen replacement therapies.[25] Only two studies suggested a positive association between HRT and DCIS, but there were significant flaws in study design or statistical results and therefore these results cannot be accepted. The first study identified a statistically significant relationship (p=0.0004), yet there is no mention of adjusting for any confounding factors and the primary aim of this research was to examine the association between alcohol consumption and DCIS.[30] The second study identified a RR of 1.51 for DCIS in the oestrogen-only HRT use group, but the p value was not statistically significant (p=0.1).[31]

2.6.3 Body and breast density

Although obesity has been associated with an increased risk of invasive breast cancer, no such association has been found with DCIS.[23] In fact, research has found that a body mass index of 25 kg/m^2 or higher was associated with a decreased risk of DCIS (OR=0.4-0.66).[24, 25] Breast density has been identified as a risk factor for DCIS.[32] Measured as the percentage density and size of dense area, mammographic breast density was found to have an OR of 2.86 when the mean percentage density was over 50% (p=0.001). The OR became 1.70 where the mean breast dense area was 30-44.9cm^2, and 2.59 where over 45cm^2 (p=0.0026).[32] However, the factors that affect breast density are unknown and could be the actual risk factors for DCIS.

2.6.4 Social factors

Although there is little evidence linking diet to DCIS, research has linked diet to early menarche, which has been shown above to increase the risk of DCIS.[29] Vitamin D stores (or plasma 25-hydroxyvitamin D [25-OHD] levels) decrease the invasive breast cancer risk, but a significant association was not observed in DCIS.[33]

The association with alcohol consumption and cigarette smoking has been extensively established for invasive breast cancer but these risk factors are debatable for DCIS. Whilst a number of studies [22, 23, 30, 31] found no association between either risk factor and DCIS, some websites still list these as risk factors (MayoClinic, DCIS Info and Macmillan Cancer Support). Polycyclic aromatic hydrocarbons (PAH) may play a role in the development of breast cancer.[34] PAH are a class of chemical carcinogens found in the environment due to fossil fuel combustion, tobacco smoke and foods including charred or broiled meats. A study that measured PAH-DNA adducts in both diagnosed women and controls found that after controlling for known risk factors PAH-DNA adducts was significantly associated with breast cancer (OR=4.43).[34] But the research also identified that neither smoking status (including passive smoking) nor diet were significantly associated with PAH-DNA adducts or breast cancer status. The study did not provide separate DCIS data but did include DCIS cases in the analysis.

2.6.5 Other factors

'Environmental factors' are also listed as risk factors on a number of websites yet are not detailed as to what these are. An extensive literature search could not locate any published article to support this potential association, other than the occasional reference to it being a risk factor.

Another area of debate is the association between a history of atypical hyperplasia of the breast (benign breast disease) and DCIS, and a history of breast biopsy and DCIS. A breast biopsy does not necessarily imply a positive result. However, a history of any breast disease could result in more frequent surveillance, thereby increasing the likelihood of early detection. The risk of invasive breast cancer following a diagnosis of benign breast disease is well documented, attributed to the natural history of the disease.[22, 23, 25]

The measles virus was identified in 64% of invasive breast cancer tumours excised as part of a study.[35] All specimens which contained a DCIS component showed the measles virus. The research found that a lower histological grade ($p=0.011$), overexpression of the tumour protein p53 ($p=0.03$) and younger age ($p=0.041$) were significantly associated with the presence of the measles virus. Due to the presence of the measles virus antigen in these three subgroups of breast cancer, including DCIS, it appeared to be a factor in the development of breast cancer. In turn this provides further support for immunization programs in order to reduce the risk of developing breast cancer.

However it should be remarked that women without any apparent risk factors can still develop DCIS. Therefore further research is required.

2.7 Detection

A number of methods can be used to detect DCIS, but mammography is the most widely used. Very uncommonly, DCIS can be palpated either by self-breast or clinical examination.

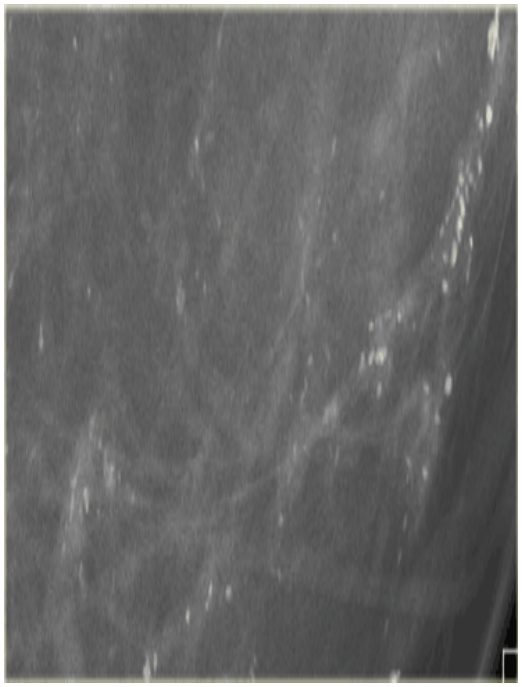
2.7.1 Mammography

Mammography uses low-dose x-rays to create an image of the breast. Most modern mammograms are digital, or known as full-field digital mammography, which converts the x-ray into electrical signals using solid-state detectors. These can then be viewed on a computer. Computer-aided detection is where specialist computer software is able to detect abnormalities such as abnormal mass, density or calcification. Mammography works by placing the breast into the unit, which is then compressed and held in place with a paddle so images can be obtained of only the breast tissue from different angles. Radiation is then passed through the tissue in short bursts, allowing the x-ray to be captured.[36] DCIS is usually identified through routine mammograms by the presence of (micro)calcification/s.

Figure 2.3 shows DCIS on a mammogram. During a mammography, lesions detected are classified as:[36]

1. Benign.
2. Probably benign.
3. Indeterminate/equivocal findings.
4. Suspicious findings of malignancy.
5. Malignant findings.

Figure 2.3: Ductal carcinoma in situ detected by mammogram



Source: http://www.radiologyassistant.nl/en/p4793bfde0ed53

The accuracy of mammography has been well reported in the literature, ranging from 55.0% to 95.0%.[37-41] Large screening programs occur in many countries, and the cost-benefits of mammography compared to other modalities make it the ideal screening tool for breast diseases.

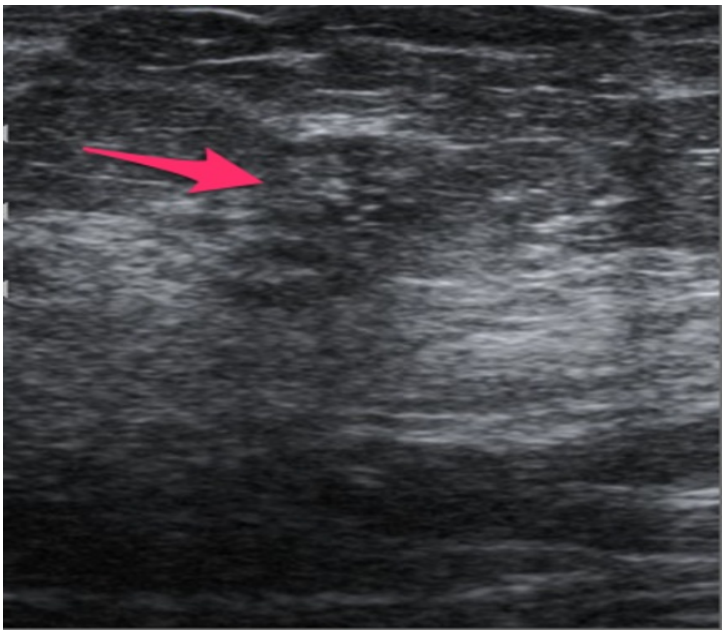
While mammography is an adequate tool in detecting the calcification associated with DCIS, mammograms tend to underestimate the actual pathological extent of DCIS.[19, 42] A review of hospital mammograms for diagnosed DCIS cases showed that the extent of DCIS on the mammogram was inaccurate by more than 10mm compared to the actual pathological extent of DCIS in 43% (89/205) of cases.[43] This has been validated by other research.[44]

2.7.2 Ultrasound

Ultrasound, also known as ultrasound scanning or sonography, uses high-frequency sound waves to produce images of the inside of the body. Using a transducer, or small probe, and ultrasound gel, the transducer sends soundwaves into the body and receives the echoing waves. The transducer is able to detect small changes in the sound's direction and pitch, capturing real-time images on a monitor. A Doppler ultrasound can also be used to measure the blood flow, speed and direction through vessels. This is useful with breast changes to determine if an abnormal area has any blood flow. The advantage of this modality is it does not produce any radiation and the patient can lie comfortably on their back whilst undergoing the procedure.[45]

Whilst invasive breast carcinoma can be seen clearly on ultrasound, DCIS can be difficult to distinguish, as shown in Figure 2.4.[39] Ultrasound should be used to supplement mammography findings.[38]

Figure 2.4: Ductal carcinoma in situ detected by ultrasound

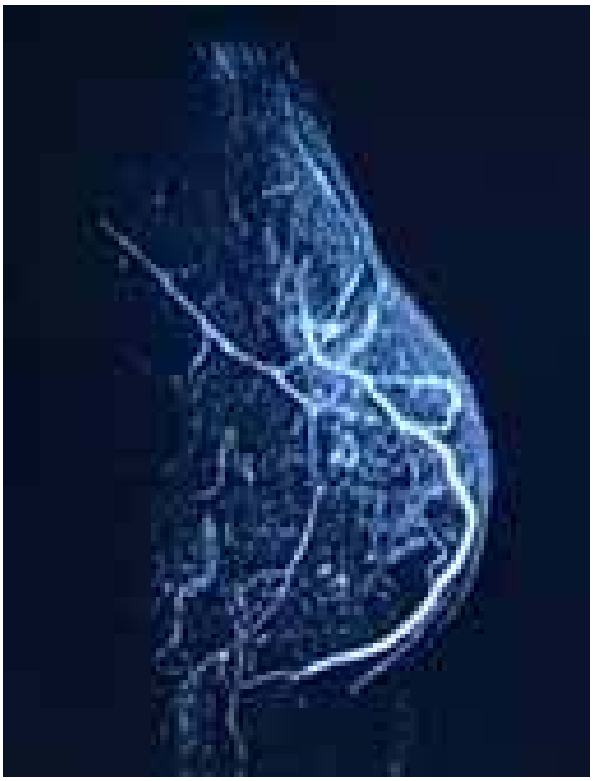


Source: http://radiopaedia.org/cases/dcis-ultrasound-image-correlation

2.7.3 Magnetic resonance imaging

Magnetic resonance imaging (MRI) uses magnetic field, radio frequency pulses to produce the image of the inside of the body. The traditional MRI unit is a large donut-shaped tube surrounded by a circular magnet, with a movable bed which passes through the centre. Some are cylinder-shaped that the patient moves into, whilst others are open MRI units, where the unit is open on the sides and the magnet does not completely surround the patient. The unit works by passing an electrical current through wire coils, sending and receiving radio waves to produce a signal. A computer program then processes these signals into a series of images, which results in thin slices of the area of interest. For a breast MRI the patient is required to lie face down on a platform which has been designed to accommodate the breasts and allow them to hang. A contrast, gadolinium, which is used to enhance images, is injected intravenously.[46] Figure 2.5 shows the contrast in the duct system during a MRI.

Figure 2.5: Ductal carcinoma in situ detected by magnetic resonance imaging



Source: http://www.radiologyinfo.org/en/info.cfm?pg=breastmr

Current data indicates that MRI has a high sensitivity in detecting DCIS, in particular high grade DCIS, and dynamic contrast-enhanced MRI is considered to have the highest sensitivity.[41] The reported accuracy of MRI in detecting DCIS ranges from 77%-96%.[39, 41, 47] However, there is a need for larger sample size studies to support use of MRI. Currently, it is recommended to use MRI to supplement mammography in the staging of breast disease, particularly those who are at high risk.[47] Indeed, a combination of mammography, clinical examination and MRI greatly increases the sensitivity of DCIS diagnosis, with 100% accuracy reported.[39]

2.7.4 Breath analysis

Recently researchers in WA have been testing a novel device to identify women who are unlikely to have malignant breast cancer, through the analysis of volatile organic compounds in a woman's breath. Volatile organic compounds are known markers of the oxidative stress associated with breast cancer, which leads to lipid peroxidation in cell membranes. This generates a number of alkanes which can then be detected by analysing the breath. Pilot data has identified a negative predictive value of 99.93% but also revealed that co-morbidities such as infectious or inflammatory conditions could also cause the oxidative stress.[48] Subsequent studies found the sensitivity of the test to

be 78.5% and specificity 88.3%.[49] Further research with larger sample sizes are required and should include DCIS only cases to establish the accuracy of this technology in this subgroup.

2.7.5 Other detection techniques

There are other new techniques under investigation, such as magnetic resonance elastography, ultrasound elastography, ductoscopy and ductal lavage, and optical imaging.[38, 44, 47]

2.8 Diagnosis

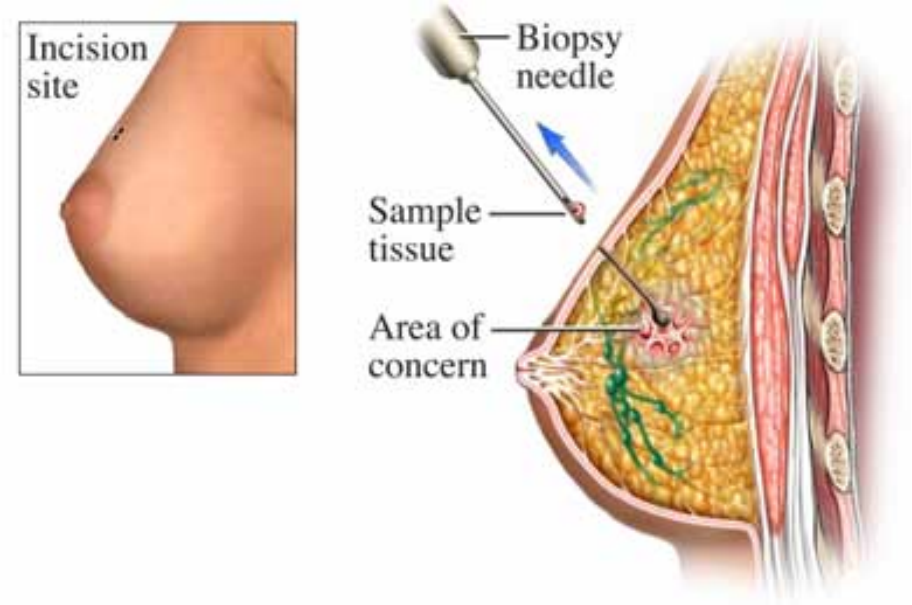
Diagnosis can only be confirmed through a biopsy (removal of a small sample of tissue to be microscopically examined by a pathologist to determine the cytological processes of the tissue). Usually a biopsy is performed for diagnosis before the surgeon considers removing the lesion. A biopsy can be collected through a number of methods. Typically a fine or core needle biopsy is used to remove the sample for pathological examination.

2.8.1 Fine needle biopsy/aspiration

A fine needle biopsy or aspiration (FNB or FNA or FNAB) is where the surgeon uses a very thin needle, which is attached to a syringe, to aspirate a small sample of tissue from the area of interest. The needle is finer than those used to withdraw blood for testing.[50]

If the area can be palpated, the surgeon may be able to guide the needle directly into the site. But with DCIS the site usually cannot be felt and the surgeon will need to be guided. This can occur through two methods. In ultrasound-guided FNB the surgeon uses ultrasound to guide them to the DCIS. Alternatively stereotactic FNB uses mammogram images from two different angles to guide the surgeon to the DCIS.[50] Figure 2.6 shows a fine needle biopsy of the breast.

Figure 2.6: Fine needle biopsy of the breast



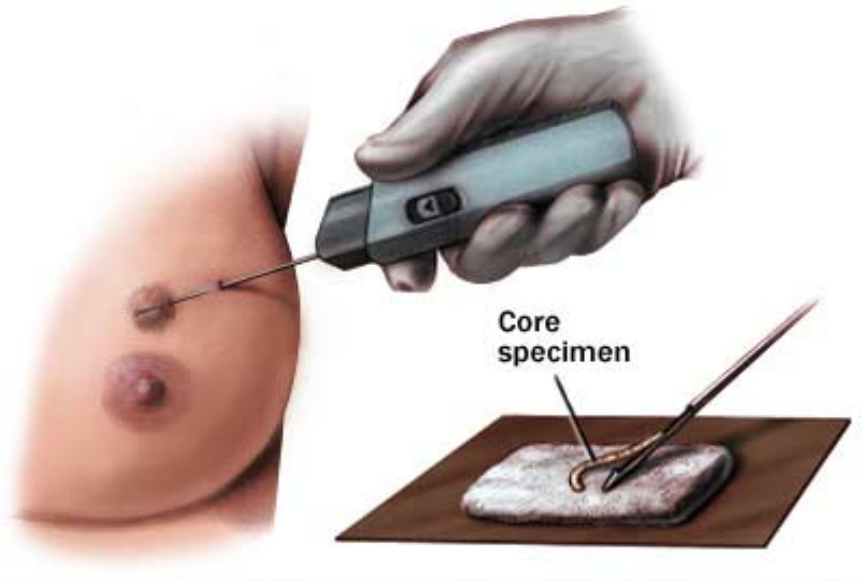
Source: http://www.beliefnet.com/healthandhealing/getcontent.aspx?cid=14777

There is minimal pain incurred by such a thin needle. The limitation of this technique is only the sample being removed is tested. There is a risk that the DCIS is missed or when the full lesion is removed, pathology may identify a different result to the biopsy. Fortunately using this technique minimises the risk of such occurrences.

2.8.2 Core needle biopsy/aspiration

A core needle biopsy or aspiration (CNB or CNA) is the same as a FNB but the needle used is larger and hollow. It then removes small cores of the tissue of interest (i.e. usually a number of cores are removed for examination), as shown in Figure 2.7. As the needle is larger and more samples are taken the results are likely to be more accurate, but it can induce some pain and bruising to the breast. Like a FNB, ultrasound-guided or stereotactic methods can be used to guide the surgeon.[50]

Figure 2.7: Core needle biopsy of the breast



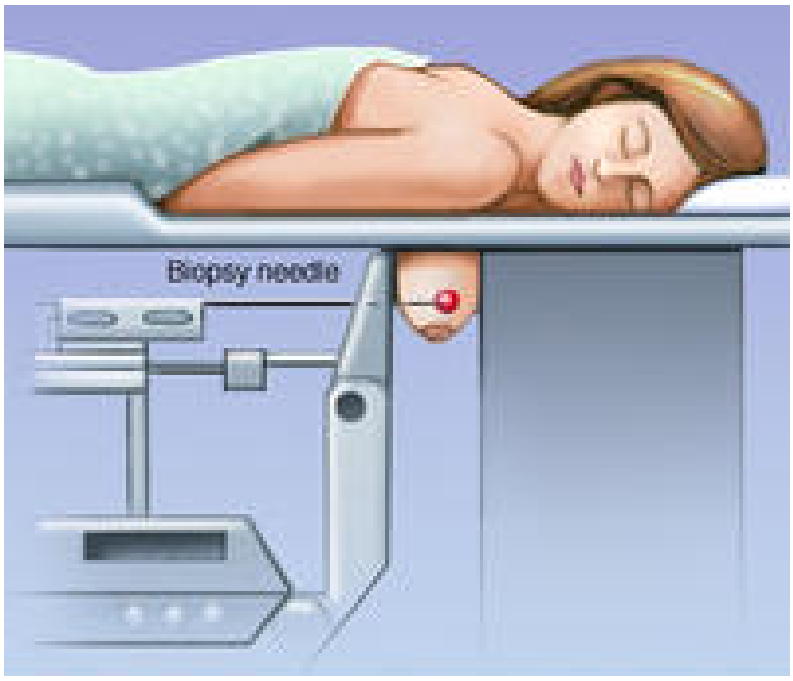
Source: http://www.mayoclinic.com/health/medical/IM00066

A Mammotome® or Automated Tissue Excision and Collection® system is a vacuum or suction assisted CNB. The probe is guided using the technique described above, but then, using a vacuum or suction, a cylinder of tissue is drawn into the probe and a rotating knife cuts the tissue from the breast. Multiple samples can be removed using this technique, allowing a greater quantity for pathological testing.[50]

2.8.3 Advanced breast biopsy instrument

An advanced breast biopsy instrument (ABBI) is a device used for diagnostic biopsy of breast lesions. During an ABBI procedure the patient is lying face down, with the breast under investigation brought through an aperture on the table and pressure is applied to the breast similar to a mammogram. Stereotactic views are taken for localisation. Once the patient has been transferred to the stereotactic table, the ABBI is applied, extending a guide needle to position a T-bar for targeting. Further stereotactic views are taken to ensure correct placement. An oscillating blade (part of the ABBI) is then inserted beyond the target and the specimen is excised using an electrocautery-powered snare.[51] Figure 2.8 shows the positioning of the patient and probe during an ABBI procedure.

Figure 2.8: Advanced breast biopsy instrument



Source: http://www.mayoclinic.com/health/medical/IM04058

A minimally invasive breast biopsy (MIBB) is the same procedure as the ABBI, except it is a suction-assisted instrument and is designed similar to the mammotome.

2.8.4 Other techniques

Other techniques include an open (surgical) biopsy, either incisional or excisional, or a wire localisation.

2.9 Treatment

The primary treatment for DCIS is surgical excision, but other treatments are described below. The risk of not treating DCIS has been discussed above in section 2.4.3. The ten year survival rate is reported as 95-99%, depending on the extent of the treatment received.[8, 52-54]

2.9.1 Surgery

Once a patient has been diagnosed with DCIS, the surgeon will decide whether to recommend surgical excision and what type of surgery is most suitable for the patient, based on size, focality and extent of DCIS foci, presence of invasion and family history.

The National Breast Cancer Centre (NBCC) states that complete surgical excision with the best cosmetic results should be the aim for surgical treatment of DCIS.[19] Therefore the decision between a wide local excision (WLE), a quandrantectomy or a mastectomy is an important one. Breast conserving therapy (BCT), through either a WLE or lumpectomy, is where a wide area around the lesion is removed. A quadrantectomy is where a quadrant or quarter of the breast tissue is removed. And a mastectomy is where the whole breast is removed, either simple, radical or sparing (nipple and/or skin). For most DCIS patients primary surgical treatment will be BCT rather than a mastectomy, but the size of the DCIS, location, grade and surgeon/patient preference will determine the method used.[19]

The role of the pathologist is to ensure all the DCIS has been removed. They will measure the distance between the edge of the DCIS and the edge of the specimen to determine the extent of health tissue, or clearance of the margins. The recommended width varies by country but most require a 5-10mm distance between the DCIS and the margins of the specimen to ascertain whether there is clearance of the margins. Where the width is smaller, the surgeon must determine whether to excise more breast tissue in case any DCIS remains in the breast.

The literature has indicated that 14 – 39% of women with a diagnosis of DCIS who were treated by biopsy alone, without any further surgical intervention, developed invasive breast cancer (follow-up 4.4 – 21 years).[19, 55] The standardised incidence ratio for subsequent invasion after completely excised DCIS varies between 4.5 to 11.7 (RR=1.13-1.84) and the majority of invasions occurred in the ipsilateral (same) breast.[56]

The NBCC reported 84% of patients were free from disease after being treated by surgery alone after 4 years, as compared to 91% for BCT and radiation therapy and 98% by mastectomy.[56] The survival for women treated for DCIS with BCT alone after 15 years was 94%.

There is some concern that DCIS cases may be over-treated.[8, 52] For primary surgical method, it has been reported as many as 58.7% of cases are treated by mastectomy, largely due to high grade DCIS.[54, 57-60] The subsequent BCE rate following BCT has been reported as 3.9-10.5% compared to 0.35-2% following mastectomy.[52, 54, 61, 62]

2.9.2 Radiation therapy

There is still much debate as to whether to use radiation therapy following surgery for DCIS.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 study evaluated the use of radiation therapy following breast conserving therapy in 790 patients (recruited from 1985 to the late 1990s in the United States) diagnosed with DCIS.[63, 64] Patients were randomised to either no further treatment (follow-up only) or to receive 50 Gy radiation therapy at 2Gy per week with no boost. Randomisation was stratified by age, method of detection, histological subtype and axillary dissection, with an even balance between the control and study group. The inclusion of radiation therapy in the management of invasive ductal cancer and DCIS resulted in a 1.8-fold reduction in risk of a subsequent BCE in both groups (45%; RR=0.56). There was a similar distribution between primary surgical methods of BCT and mastectomy. [63, 64] However, the study found no reduction or impact on breast cancer mortality (RR=1.12).

The European Organization for Research and Treatment of Cancer (EORTC) conducted a randomised phase III trial of radiation therapy following breast conserving therapy.[64] This study found a 55% (RR=0.46) reduction in risk of a BCE but similar to the NSABP B-17 study, there was no impact on mortality (RR=0.33).

The Australian & New Zealand Breast Cancer Trial Group (ANZBCTG) collaborated with the CRC Breast Cancer Trials Group (United Kingdom DCIS Trial) and the Scottish Cancer Trials Breast Group in a large randomised trial between May 1990 and August 1998.[65] A total of 1030 women were randomised to receive or not to receive

radiation therapy. The study found radiation therapy reduced the rate of subsequent BCEs by 61%.

Although all of the above studies found statistically significant reductions in risk of recurrence, these typically only represented less than 10% of women diagnosed. Other research has demonstrated that any treatment of DCIS reduces the BCE rate by 10%.[66-68]

Another study examining the impact of radiation therapy on recurrence included margin width as a correlating factor.[69] With a sample size of 469 cases, the study concluded that radiation therapy did not lower the rate of recurrence where the margins were 10mm or more. There was also no statistically significant benefit of radiation therapy where margins were 1mm-10mm. Statistically significant benefits for post-operative radiation therapy was only observed in patients who have a margin width of 1 mm or less. This finding was supported by the NSABP, the EORTC and other studies.[15, 70-72]

2.9.3 Tamoxifen

The NSABP B-24 study examined the use of tamoxifen (10mg twice daily) for five years following BCT and radiation therapy.[11] Tamoxifen is an oestrogen antagonistic drug used to treat breast cancer following primary treatment (for example, surgery, chemotherapy and/or radiotherapy).[11] Local recurrence was 8% in the tamoxifen group after seven years compared to 11% in the control group (p=0.02). This was not significant in DCIS recurrence but was for invasion. There was an increase in prevalence in endometrial cancer (0.8% versus 0.3%) in the study group compared to the control group, and thromboembolic events (2% versus 1%), but no benefit was seen in women over 50 years of age, cases with complete excision or where histology showed no necrosis. The study found no effect on breast cancer mortality. Analysis of ER positive cases that benefit from tamoxifen was limited to this subgroup.[11]

In the ANZBCTG study, 1,576 patients participated in the tamoxifen arm of the study, to either receive tamoxifen or not receive tamoxifen (control). Patients received BCT and no radiation therapy. Results showed an 18% reduction in BCE in the tamoxifen group, but was not statistically significant (p=0.13). Although tamoxifen did not affect invasive events, there was a 33% reduction in local recurrence (p=0.02).[65]

It appears that the greatest reduction of risk occurs in women aged under 50 years who were ER positive. The benefits of using tamoxifen in this group must be weighed against the increased risk of incidental events (endometrial cancer, thromboembolic events) for the management of DCIS.

2.9.4 Van Nuys prognostic index

The original Van Nuys prognostic index (VNPI) categorises DCIS cases based on nuclear grade, size and margin clearance. Low grade nuclei (1) is where nuclei diameter is 1-1.5 times that of red blood cells with diffuse chromatin and inapparent nucleoli, no necrosis. Intermediate grade nuclei (2) is where nuclei diameter is 1-2 times that of red blood cells with coarse chromatin and infrequent nucleoli, necrosis present. High grade nuclei (3) is where nuclei diameter is greater than two red blood cells with vesicular chromatin and one or more nucleoli, with or without necrosis.[12, 58] Size is grouped as less than 15mm (1), 16-40mm (2) and greater than 40mm (3). Clearance of the margins is grouped as greater than 10mm (1), 1-9mm (2) and less than 1mm margin (3). The sum of the three scores is the VNPI, from 3 to 9. Based on this score, the recommended treatment can be identified: 3-4 = BCT, 5-7 = BCT and radiation therapy and 8-9 = mastectomy. In 2003 a fourth prognostic factor of age was introduced to the modified VNPI: greater than 60 years (1), 40-60 years (2) and less than 40 years (3).[58] This resulted in a score from 4-12 with recommended treatment as: 4-6 = BCT, 7 – 9 = BCT and radiation therapy and 10-12 = mastectomy.[58 73]

A retrospective study reviewed 104 patients applying the modified VNPI to determine if they would have received a different management plan and the impact of the VNPI on BCEs.[58] Applying the VNPI, the study found that 58.6% of patients had been undertreated, with 35.3% experiencing a BCE. Only 7.7% of patients were over-treated, with 1.3% of cases experiencing a BCE. Overall, there was an 11.5% rate of BCEs, with more than half involving invasion (58%). The study supported the VNPI to ensure patients were not over-treated, that high-risk patients received adequate treatment and radiation therapy was only used appropriately.

A British study applied the VNPI (not modified since age had no effect on recurrence in the study population) retrospectively to 215 DCIS cases treated with BCT alone (except nine patients who received radiation therapy). This allowed the analysis of recurrence rates in each VNPI category. Those who scored a VNPI of 3-4 had a low recurrence rate

(0%, p=0.002). An intermediate score of 5-7 had a 21.5% recurrence rate (p=0.002) and a high score of 8-9 had a 32.1% recurrence rate (p=0.002). The report supported the VNPI as an accurate predictor of recurrence and the need for increased treatment of high risk patients.[74]

2.10 Treatment guidelines

In Australia, a set of evidence-based clinical practice guidelines, *The Clinical Management of DCIS, Lobular Carcinoma In Situ and Atypical Hyperplasia of the Breast*, was published by the NBCC.[19] Table 2.2 is the summary of recommendations taken directly from the guidelines. Breast Surgeons of Australia and New Zealand Inc. conducted a National Breast Cancer Audit (NBCA) to ascertain adherence to the guidelines, in which participation is mandatory for all surgeons wishing to maintain full membership status with the Royal Australasian College of Surgeons (RACS) Breast Section.[75] An analysis of the audit data entered between 1998 and 2004 showed close adherence to the guidelines in Australia.

Table 2.2: Summary of the recommendations from "The Clinical Management of DCIS, Lobular Carcinoma In Situ and Atypical Hyperplasia of the Breast". [19]

SUMMARY OF RECOMMENDATIONS
DIAGNOSIS OF DCIS
Image-guided core biopsy is the recommended diagnostic method for DCIS.
PSYCHOSOCIAL SUPPORT
Women should be offered appropriate support and information about their diagnosis and treatment to enhance their emotional wellbeing and physical recovery.
SURGERY
It is essential to ensure that clear margins are obtained when DCIS is excised. If the margins are involved, further excision is required. Axillary dissection should not be performed in the management of DCIS unless invasion is suspected.
ADJUVANT RADIOTHERAPY
The addition of radiotherapy after complete local excision reduces the risk of subsequent invasive breast cancer and recurrence of DCIS for all pathological subgroups of patients. For women with good prognostic features, the overall clinical benefit of adjuvant radiotherapy may be small. In these circumstances, the woman may choose to omit radiotherapy. Women with high-grade DCIS with necrosis, close margins and larger lesions have a relatively high risk of recurrence with conservative surgery alone, and adjuvant radiotherapy is therefore recommended.
RISK OF RECURRENCE
The risk of recurrence of DCIS or subsequent invasive breast cancer following complete local excision, with or without radiotherapy, will vary depending on identified predictive factors, such as nuclear grade, size, presence or absence of necrosis, margin width and other prognostic factors. All these factors should be considered when discussing the risk of recurrence and management options with the woman.

Source: taken directly from page 7 of the NBCC publication [19]

2.11 Recurrence and invasion

An Australian study found the five year probability of invasion following a diagnosis of DCIS was 4.36% and ten year probability was 8.27%.[20] It is estimated half of subsequent BCEs are invasive disease, usually at the original excision site.[10] The literature identified the following predictors for future recurrence or invasion:[7, 10, 76-78]

- Primary surgical method (BCT versus mastectomy);
- Involved or close margins;
- Less than 40 years of age;
- Large lesion size;
- Poorly differentiated DCIS;
- High nuclear grade;
- Architectural growth pattern;
- Presence of necrosis;
- Symptomatic detection.

Margin status emerged as the most important predictor of a BCE, followed by age and size.[71, 79-82]

2.12 Margins

It has been generally agreed that BCE often occur at the previous excision site and that this could be due to inadequate margins at initial excision.[10,16,70,83] A study that identified that 96% of recurrences following complete resection of DCIS were at or near the initial surgical site concluded that there was inadequate resection of the primary DCIS.[84] The study recruited patients in which pathology indicated clear margins, to undergo further excision within days of the initial surgery to increase the margin of safety. In these re-excised tissue samples, 48% had residual DCIS. The study concluded that inadequate initial excision of the DCIS was the leading cause of recurrence and invasion.[84]

Therefore, complete excision is vital in the treatment of DCIS. Yet there is no universally agreed margin width for complete clearance. Research has demonstrated that a margin less than 1mm increases the risk of a BCE.[10,72,83,85-87] Most surgeons define adequate clearance as a margin width of 2mm (with radiation therapy) to 10mm

or more, with many reported surgeons and countries requiring at least a 5mm margin and preference for a 10mm margin.[10,73,82,85,86,88, 89]

Inadequate margin width can result in a patient requiring a second operation, also referred to as re-excision. The second operation rate can vary between and within countries, from 5-72%, with most reporting a 20-25% re-excision rate.[19,54,85] A local Royal Perth Hospital review identified there was a higher rate of second operations in patients with high-grade DCIS or aged less than 50 years following an initial WLE. In both of these groups, over 50% of patients required a second operation.[43]

Surgeons rely on mammographic images when determining the extent of tissue to remove during surgery. It is very difficult to accurately identify from mammography how much should be excised to ensure clearance of the margins.[7, 10] The size of DCIS on mammography is underestimated, though this can be variable by the architecture of the DCIS. It has been reported 80-85% of cases underestimation is by less than 20mm.[10] Another study found more than 40% of cases were underestimated by mammography by more than 10mm.[85]

There have been a number of intraoperative methods for the assessment of surgical margins developed, and these will be reviewed in Chapter 3.

2.13 Conclusion

Although DCIS is a pre-invasive carcinoma, it has a strong association with invasive ductal carcinoma. Even where there is a complete excision of DCIS as determined by pathology, there is still a risk of a subsequent BCE, lending researchers to question if complete excision has been truly achieved. Mammography remains the gold standard for detecting DCIS, but advances in other technologies have seen an increase in the use of MRI in high risk cases. BCT is the recommended treatment method for DCIS as it is minimal treatment for a pre-invasive condition. However mastectomy is still widely used, particularly for high grade DCIS. Radiotherapy has shown to decrease the risk of BCEs when used in high grade cases. It is important to ensure patients are free of DCIS whilst minimising the number of procedures and achieving satisfactory cosmetic appearance of the breast. Therefore an effective method is required to identify that margins are free of disease during the initial operation.

2.14 References

1. National Breast and Ovarian Cancer Centre. Understanding ductal carcinoma in situ., 2010. Surry Hills, NSW: National Breast and Ovarian Cancer Centre.
2. Hall JA, Knaus JV. An atlas of breast disease. Boca Raton: The Parthenon Publishing Group; 2003.
3. Rosai J. Borderline epithelial lesions of the breast. American Journal of Surgical Pathology. 1991; 15(3):209-21.
4. Masood S. Is it time to retire the term of "In Situ Carcinoma" and use the term of "Borderline Breast Disease?". The Breast Journal. 2010; 16(6):571-572.
5. Dervan P. Understanding breast cancer. North Carolina: McFarland & Company, Inc. Publishers; 2001.
6. Pinder SE, Provenzano E. Pathology: ductal carcinoma in situ and lesions of uncertain malignant potential. In: Mitchell M, editor. Breast Cancer. Cambridge: Cambridge University Press; 2010. p. 127 - 145.
7. van de Vijver MJ. Biological variables and prognosis of DCIS. The Breast. 2005; 14(6):509-519.
8. Kumar S, Sacchini V. The surgical management of ductal carcinoma in situ. Breast Journal. 2010; 16 Suppl 1:S49-52.
9. Harris G, Pinder S, Ellis I. Ductal carcinoma in situ: diagnosis and classification. Current Diagnostic Pathology. 2004; 10(3):204-210.
10. Pinder SE. Ductal carcinoma in situ (DCIS): pathological features, differential diagnosis, prognostic factors and specimen evaluation. Modern Pathology. 2010; 23 Suppl 2:S8-13.
11. Mokbel K, Cutuli B. Heterogeneity of ductal carcinoma in situ and its effects on management. The Lancet Oncology. 2006; 7(9):756-765.
12. Silverstein MJ, Poller DN, Waisman JR, Coburn WJ, Barth A, Gierson ED, et al. Prognostic classification of breast ductal carcinoma-in-situ. The Lancet. 1995; 345(8958):1154-1157.
13. Zakhour H, Wells C. Diagnostic cytopathology of the breast. London: Harcourt Publishers Ltd.; 1999.
14. Page D, Dupont W, Rogers L, Jensen R, Schuyler P. Continued local recurrence of carcinoma 15-25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated only by biopsy. Cancer. 1995; 76:1197 - 1200.
15. Sanders ME, Schuyler PA, Dupont WD, Page DL. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. Cancer. 2005; 103(12):2481-2484.
16. Pinder S, Ellis I. The diagnosis and management of pre-invasive breast disease: ductal carcinoma in situ (DCIS) and atypical ductal hyperplasia (ADH) - current definitions and classification. Breast Cancer Research. 2003; 5(5):254 - 257.
17. Ketcham A, Moffat F. Vexed surgeons, perplexed patients, and breast cancer which may not be be cancer. Cancer. 1990; 65:387 - 393.

18. Man YG, Zhang Y, Shen T, Zeng X, Tauler J, Mulshine JL, et al. cDNA expression profiling reveals elevated gene expression in cell clusters overlying focally disrupted myoepithelial cell layers: implications for breast tumor invasion. Breast Cancer Research and Treatment. 2005; 89(2):199-208.

19. National Breast Cancer Centre. The clinical management of ductal carcinoma in situ, lobular carcinoma in situ and atypical hyperplasia of the breast, 2003. Camperdown, NSW: National Breast Cancer Centre.

20. Australian Institute of Health and Welfare, National Breast and Ovarian Cancer Centre. Risk of invasive breast cancer in women diagnosed with ductal carcinoma in situ in Australia between 1995 and 2005, 2010. Canberra, ACT: Australian Institute of Health and Welfare.

21. WA Cancer Registry. Health data collections, 2004. Perth: Department of Health Western Australia.

22. Claus EBE, Stowe MM, Carter DD. Breast carcinoma in situ: risk factors and screening patterns. Journal of the National Cancer Institute. 2001; 93(23):1811-1817.

23. Weiss HA, Brinton LA, Brogan D, Coates RJ, Gammon MD, Malone KE, et al. Epidemiology of in situ and invasive breast cancer in women aged under 45. British Journal of Cancer. 1996; 73(10):1298–1305.

24. Kerlikowske K, Barclay J, Grady D, Sickles EA, Ernster V. Comparison of risk factors for ductal carcinoma in situ and invasive breast cancer. Journal of the National Cancer Institute. 1997; 89(1):76-82.

25. Longnecker M, Bernstein L, Paganini-Hill A, Enger S, Ross R. Risk factors for in situ breast cancer. Cancer Epidemiology, Biomarkers & Prevention. 1996; 5:961 - 965.

26. Ellsworth DL, Ellsworth RE, Liebman MN, Hooke JA, Shriver CD. Genomic instability in histologically normal breast tissues: implications for carcinogenesis. Lancet Oncology. 2004; 5(12):753-8.

27. Ma H, Henderson K, Sullivan-Halley J, Duan L, Marshall S, Ursin G, et al. Pregnancy-related factors and the risk of breast carcinoma in situ and invasive breast cancer among postmenopausal women in the California Teachers Study cohort. Breast Cancer Research. 2010; 12(3):R35.

28. Zeleniuch-Jacquotte A, Gu Y, Shore RE, Koenig KL, Arslan AA, Kato I, et al. Postmenopausal levels of sex hormones and risk of breast carcinoma in situ: Results of a prospective study. International Journal of Cancer. 2005; 114(2):323-327.

29. Stoll BA. Adiposity as a risk determinant for postmenopausal breast cancer. International Journal of Obesity and related Metabolic Disorders. 2000; 24(5):527-33.

30. Kabat GC, Kim M, Shikany JM, Rodgers AK, Wactawski-Wende J, Lane D, et al. Alcohol consumption and risk of ductal carcinoma in situ of the breast in a cohort of postmenopausal women. Cancer Epidemiology Biomarkers & Prevention. 2010; 19(8):2066-2072.

31. Reeves GK, Pirie K, Green J, Bull D, Beral V. Comparison of the effects of genetic and environmental risk factors on in situ and invasive ductal breast cancer. International Journal of Cancer. 2012; 131(4):930-937.

32. Gill JK, Maskarinec G, Pagano I, Kolonel LN. The association of mammographic density with ductal carcinoma in situ of the breast: the Multiethnic Cohort. Breast Cancer Research. 2006; 8(3):R30.

33. Crew KD, Gammon MD, Steck SE, Hershman DL, Cremers S, Dworakowski E, et al. Association between plasma 25-hydroxyvitamin D and breast cancer risk. Cancer Prevention Research. 2009; 2(6):598-604.

34. Rundle A, Tang D, Hibshoosh H, Estabrook A, Schnabel F, Cao W, et al. The relationship between genetic damage from polycyclic aromatic hydrocarbons in breast tissue and breast cancer. Carcinogenesis. 2000; 21(7):1281-9.

35. Ariad SS, Milk NN, Bolotin AA, Gopas JJ, Sion-Vardy NN, Benharoch DD. Measles virus antigens in breast cancer. Anticancer research. 2011; 31(3):913-920.

36. RadiologyInfo. Mammography. 2012 [cited 21 December 2013]. Available from: http://www.radiologyinfo.org/en/info.cfm?pg=mammo.

37. Ernster VL, Ballard-Barbash R, Barlow WE, Zheng Y, Weaver DL, Cutter G, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. Journal of the National Cancer Institute. 2002; 94(20):1546-54.

38. Yang WT, Tse GMK. Sonographic, mammographic, and histopathologic correlation of symptomatic ductal carcinoma in situ. American Journal of Roentgenology. 2004; 182(1):101-110.

39. Berg WA, Gutierrez L, NessAiver MS, Carter WB, Bhargavan M, Lewis RS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology. 2004; 233(3):830-849.

40. The JS, Schilling KJ, Hoffmeister JW, Friedmann E, McGinnis R, Holcomb RG. Detection of breast cancer with full-field digital mammography and computer-aided detection. 2009; American Journal of Roentgenology. 192(2):337-40.

41. Yamada T, Mori N, Watanabe M, Kimijima I, Okumoto T, Seiji K, et al. Radiologic-pathologic correlation of ductal carcinoma in situ. Radiographics. 2010; 30(5):1183-1198.

42. Cardenose G. Breast imaging companion, 1997. Philadelphia: Lippincott-Raven Publishers.

43. Willsher P, Wylie L, Bettenay F, Anderson J, Saunders C, Metcalf C, et al. 4th Scientific Meeting of the Australasian Society for Breast Disease. How accurate is the mammogram in determining the extent of DCIS?, 2004 The Breast.

44. Chakrabarti J, Evans AJ, James J, Ellis IO, Pinder SE, Macmillan RD. Accuracy of mammography in predicting histological extent of ductal carcinoma in situ (DCIS). European Journal of Surgical Oncology. 2006; 32(10):1089-92.

45. RadiologyInfo. Breast Ultrasound. 2012 [cited 21 December 2013]. Available from: http://www.radiologyinfo.org/en/info.cfm?pg=breastus.

46. RadiologyInfo. MRI of the Breast. 2012 [cited 21 December 2013]. Available from: http://www.radiologyinfo.org/en/info.cfm?pg=breastmr.

47. Shiraishi A, Kurosaki Y, Maehara T, Suzuki M, Kurosumi M. Extension of ductal carcinoma in situ: histopathological association with MR imaging and mammography. Magnetic Resonance in Medical Sciences. 2003; 2(4):159-63.

48. Singh V, Saunders C, Wylie L, Bourke A. New diagnostic techniques for breast cancer detection. Future Oncol. 2008; 4(4):501-13.

49. Phillips M, Cataneo RN, Saunders C, Hope P, Schmitt P, Wai J. Volatile biomarkers in the breath of women with breast cancer. Journal of Breath Research. 2010; 4(2).

50. American Cancer Society. Types of biopsy procedures. 2012 [cited 21 December]. Available from:

http://www.cancer.org/treatment/understandingyourdiagnosis/examsandtestdescriptions/forwomenfacingabreastbiopsy/breast-biopsy-biopsy-types.

51. Wong AY, Salisbury E, Bilous M. Recent developments in stereotactic breast biopsy methodologies: an update for the surgical pathologist. Advances in Anatomical Pathology. 2000; 7(1):26-35.

52. Morrow M, O'Sullivan MJ. The dilemma of DCIS. The Breast. 2007; 16(Supplement 2):59-62.

53. Vapiwala N, Harris E, Hwang WT, Solin LJ. Long-term outcome for mammographically detected ductal carcinoma in situ managed with breast conservation treatment: prognostic significance of reexcision. Cancer Journal. 2006; 12(1):25-32.

54. Kricker A, Armstrong B. Surgery and outcomes of ductal carcinoma in situ of the breast: a population-based study in Australia. European Journal of Cancer. 2004; 40(16):2396-2402.

55. Meijnen P, Gilhuijs KG, Rutgers EJ. The effect of margins on the clinical management of ductal carcinoma in situ of the breast. Journal of Surgical Oncology. 2008; 98(8):579-84.

56. National Breast Cancer Centre. Ductal carcinoma in situ, 2004. Camperdown: National Breast Cancer Centre.

57. Meijnen P, Peterse JL, Oldenburg HSA, Woerdeman LAE, Rutgers EJT. Changing patterns in diagnosis and treatment of ductal carcinoma in situ of the breast. European Journal of Surgical Oncology. 2005; 31(8):833-839.

58. Asjoe FT, Altintas S, Huizing MT, Colpaert C, Marck EV, Vermorken JB, et al. The value of the Van Nuys Prognostic Index in ductal carcinoma in situ of the breast: a retrospective analysis. Breast Journal. 2007; 13(4):359-67.

59. Shugg D, White VM, Kitchen PR, Pruden M, Collins JP, Hill DJ. Surgical management of ductal carcinoma in situ in Australia in 1995. Australian and New Zealand Journal of Surgery. 2002; 72(10):708-15.

60. Verkooijen HM, Fioretta G, De Wolf C, Vlastos G, Kurtz J, Borisch B, et al. Management of women with ductal carcinoma in situ of the breast: a population-based study. Annals of Oncology. 2002; 13(8):1236-45.

61. Sakorafas GH, Farley DR. Optimal management of ductal carcinoma in situ of the breast. Surgical Oncology. 2003; 12(4):221-40.

62. Hughes LL, Wang M, Page DL, Gray R, Solin LJ, Davidson NE, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. Journal of Clinical Oncology. 2009; 27(32):5319-24.

63. Estévez LG, Álvarez I, Seguí MÁ, Muñoz M, Margelí M, Miró C, et al. Current perspectives of treatment of ductal carcinoma in situ. Cancer Treatment Reviews. 2010; 36(7):507-517.

64. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. Journal of the National Cancer Institute. 2010; 102(3):170-8.

65. Australian and New Zealand Breast Cancer Trials Group. Protocol ANZ 9002: DCIS. In: 2003 Annual Scientific Report. Newcastle; 2003. p. 125 - 131.

66. Warren JL, Weaver DL, Bocklage T, Key CR, Platz CE, Cronin KA, et al. The frequency of ipsilateral second tumors after breast-conserving surgery for DCIS: a population based analysis. Cancer. 2005; 104(9):1840-8.

67. Li CI, Malone KE, Saltzman BS, Daling JR. Risk of invasive breast carcinoma among women diagnosed with ductal carcinoma in situ and lobular carcinoma in situ, 1988-2001. Cancer. 2006; 106(10):2104-12.

68. Smith BD, Gross CP, Smith GL, Galusha DH, Bekelman JE, Haffty BG. Effectiveness of radiation therapy for older women with early breast cancer. Journal of the National Cancer Institute. 2006; 98(10):681-90.

69. Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. New England Journal of Medicine. 1999; 340(19):1455-1461.

70. Fisher ER, Costantino J, Fisher B, Palekar AS, Redmond C, Mamounas E. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17. Intraductal carcinoma (ductal carcinoma in situ). The National Surgical Adjuvant Breast and Bowel Project Collaborating Investigators. Cancer. 1995; 75(6):1310-9.

71. Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. Journal of Clinical Oncology. 2001; 19(8):2263-71.

72. Neuschatz AC, DiPetrillo T, Safaii H, Lowther D, Landa M, Wazer DE. Margin width as a determinant of local control with and without radiation therapy for ductal carcinoma in situ (DCIS) of the breast. International Journal of Cancer. 2001; 96 Suppl:97-104.

73. Silverstein MJ, Buchanan C. Ductal carcinoma in situ: USC/Van Nuys Prognostic Index and the impact of margin status. The Breast. 2003; 12(6):457-471.

74. Gilleard O, Goodman A, Cooper M, Davies M, Dunn J. The significance of the Van Nuys prognostic index in the management of ductal carcinoma in situ. World Journal of Surgical Oncology. 2008; 6:61.

75. White V, Pruden M, Kitchen P, Villanueva E, Erbas B. The impact of publication of Australian treatment recommendations for DCIS on clinical practice: A population-based, "before-after" study. European Journal of Surgical Oncology. 2010; 36(10):949-956.

76. Pinder SE, Duggan C, Ellis IO, Cuzick J, Forbes JF, Bishop H, et al. A new pathological system for grading DCIS with improved prediction of local

recurrence: results from the UKCCCR/ANZ DCIS trial. British Journal of Cancer. 2010; 103(1):94-100.

77. Innos K, Horn-Ross PL. Risk of second primary breast cancers among women with ductal carcinoma in situ of the breast. Breast Cancer Research and Treatment. 2008; 111(3):531-40.

78. Shamliyan T, Wang SY, Virnig BA, Tuttle TM, Kane RL. Association between patient and tumor characteristics with clinical outcomes in women with ductal carcinoma in situ. Journal of the National Cancer Institute Monographs. 2010; 2010(41):121-9.

79. Schouten van der Velden AP, Peeters PH, Koot VC, Hennipman A. Local recurrences after conservative treatment of ductal carcinoma-in-situ of the breast without radiotherapy: the effect of age. Annals of Surgical Oncology. 2006; 13(7):990-8.

80. Weng EY, Juillard GJ, Parker RG, Chang HR, Gornbein JA. Outcomes and factors impacting local recurrence of ductal carcinoma in situ. Cancer. 2000; 88(7):1643-9.

81. Douglas-Jones AG, Logan J, Morgan JM, Johnson R, Williams R. Effect of margins of excision on recurrence after local excision of ductal carcinoma in situ of the breast. Journal of Clinical Pathology. 2002; 55(8):581-6.

82. Kerlikowske K, Molinaro A, Cha I, Ljung BM, Ernster VL, Stewart K, et al. Characteristics associated with recurrence among women with ductal carcinoma in situ treated by lumpectomy. Journal of the National Cancer Institute. 2003; 95(22):1692-702.

83. Sigal-Zafrani B, Lewis JS, Clough KB, Vincent-Salomon A, Fourquet A, Meunier M, et al. Histological margin assessment for breast ductal carcinoma in situ: precision and implications. Modern Pathology. 2004; 17(1):81-8.

84. Silverstein MJ, Figueira Fo A, Novais-Dias E, Salvador-Silva HA, Barros A. The dilemma of appropriate therapy for DCIS. The Van Nuys Breast Centre expereince. 8th International Congress on Senology (Breast Diseases); 1995; Rio de Janeiro, Brazil: Elsevier; 8-12 May 1994. p. 165 - 169.

85. Dillon MF, Mc Dermott EW, O'Doherty A, Quinn CM, Hill AD, O'Higgins N. Factors affecting successful breast conservation for ductal carcinoma in situ. Annals of Surgical Oncology. 2007; 14(5):1618-28.

86. Neuschatz AC, DiPetrillo T, Steinhoff M, Safaii H, Yunes M, Landa M, et al. The value of breast lumpectomy margin assessment as a predictor of residual tumor burden in ductal carcinoma in situ of the breast. Cancer. 2002; 94(7):1917-24.

87. Cheng LL, Al-Kaisi NKN, Gordon NHN, Liu AYA, Gebrail FF, Shenk RRR. Relationship between the size and margin status of ductal carcinoma in situ of the breast and residual disease. Journal of the National Cancer Institute. 1997; 89(18):1356-1360.

88. Macdonald HR, Silverstein MJ, Lee LA, Ye W, Sanghavi P, Holmes DR, et al. Margin width as the sole determinant of local recurrence after breast conservation in patients with ductal carcinoma in situ of the breast. The American Journal of Surgery. 2006; 192(4):420-422.

89. MacDonald HR, Silverstein MJ, Mabry H, Moorthy B, Ye W, Epstein MS, et al. Local control in ductal carcinoma in situ treated by excision alone: incremental

benefit of larger margins. The American Journal of Surgery. 2005; 190(4):521-525.

CHAPTER 3 LITERATURE REVIEW: INTRAOPERATIVE ASSESSMENT OF SURGICAL MARGINS FOR BREAST CANCER

3.1 Introduction

There is a strong association between ductal carcinoma in situ (DCIS) and invasive ductal carcinoma. Ensuring clear margins during the resection of DCIS is part of the recommendations made by the National Breast Cancer Centre's (NBCC) evidence-based clinical practice guidelines.[1] Research has reported that 20-25% of patients treated for DCIS using breast conserving therapy (BCT) will require a second operation to obtain clear margins, with second operation rates as high as 72% being reported.[1-3] Optimal surgical margin distance varies between and within countries, with most reporting between 2mm and 10mm as the optimal minimal margin width.[3-5] BCT is the preferred surgical method for patients who are not at high risk, therefore surgeons need to accurately assess the extent of disease and margin status during surgery to reduce the need for a second operation. A method that is able to provide the surgeon with accurate information intraoperatively about margin status would potentially reduce the need for a second operation. An intraoperative margin assessment (IMA) method is defined for the purpose of this chapter as a non-invasive method applied to the excised tissue or within the surgical cavity to produce results about margin status during surgery to enable further tissue shavings to be taken. The gold standard assessment will be defined as pathology (histology or cytology), performed postoperatively, and hereby referred to as the standard assessment. Results from this review will be useful to compare against the positron emission tomography (PET) probe results in Chapter 7.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines have been used to structure the format and reporting of this systematic literature review.[6] Articles were selected and analysed to identify reported IMA methods in BCT. Since there are only a few reports on IMA in surgery for DCIS of the breast, this review included all breast cancer articles. The objectives of this review were: (1) identify published academic literature, using a systematic method, that reports the use of an IMA method to determine margin status in breast conserving therapy (BCT); (2) identify the level of concordance in margin assessment between reported IMA methods and standard assessment; and (3) determine the accuracy of such methods.

3.2 Abbreviations

Below is a list of abbreviations used in this chapter:

BCT	breast conserving therapy
cm	centimetres
DCIS	ductal carcinoma in situ
IDC	invasive ductal carcinoma
IDSM	intraoperative digital specimen mammography
ILC	invasive lobular carcinoma
IMA	intraoperative margin assessment
LCIS	lobular carcinoma in situ
mm	millimetre
NBCC	National Breast Cancer Centre
No.	number
NPV	negative predictive value
NR	not reported
OCT	optical coherence tomography
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QAS	quality assessment score
QAT	quality assessment tool
RFS	radiofrequency spectroscopy probe
SD	standard deviation
SR	specimen radiography
SSM	standard specimen mammography
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
USA	United States of America

3.3 Methods

The methods and format used for this systematic review follow the PRISMA format.[6]

3.3.1 Eligibility criteria

The inclusion criteria for articles were those which:

1. examined breast cancer,
2. undertook an intraoperative assessment of the surgical margins with the intention of immediate feedback on the status (with or without further excision),
3. human studies only,
4. available in English,
5. scholarly journal articles with full text available, and
6. published between January 2000 and May 2013.

Articles were excluded from consideration if they:

1. examined phantom (laboratory) or animal data,
2. used an additional shavings method to increase surgical margins,
3. examined lesion size, lesion localisation or guidance or specimen orientation without margin assessment,
4. examined various cancers outside of the breast,
5. examined the predictors of successful margin clearance.

3.3.2 Information sources

The databases Proquest, Medline, PubMed and Science Direct were searched from January 2000 to May 2013. The reference lists of selected journal articles were not reviewed in line with the PRISMA approach adopted.

3.3.3 Search strategy

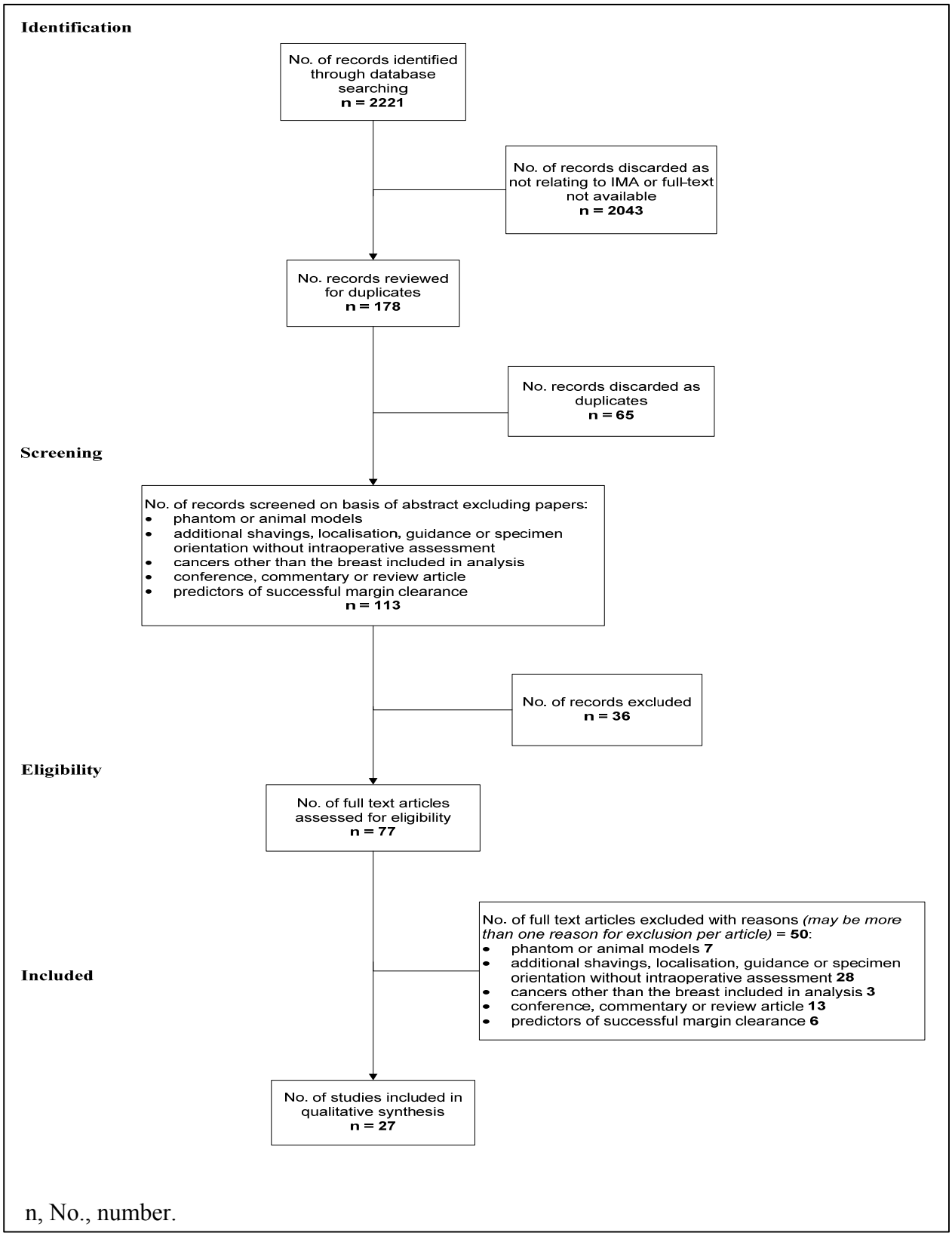
A search was undertaken on 3 June 2013 using the following strategy:

Keywords = ‘breast’ AND ‘surgery’ AND ‘intraoperative’.

3.3.4 Study selection

The process for study selection is presented in Figure 3.1.

Figure 3.1: Flow diagram of article selection strategy.



n, No., number.

In the first stage articles were selected using the search strategy outlined in section 3.3.3 on the databases listed in section 3.3.2. Article titles were reviewed by order of publication date (newest to oldest), blinding for author, journal, institution and country where the research was conducted, starting with all Proquest results, followed by Medline, PubMed and lastly Science Direct. Articles were discarded if the title indicated the study was not an intraoperative assessment of margin status for breast cancer in BCT. Potential titles were then compared to already selected articles for duplication and discarded if appropriate. Next, the abstracts of selected papers were assessed against the eligibility criteria listed in section 3.3.1.

Finally, full text articles were then assessed against the eligibility criteria listed in section 3.3.1, blinding for author, journal, institution and country where the research was conducted. Reason for rejection was documented and later tallied.

Included papers were tabulated and assessed for quality, as described in section 3.3.5.

3.3.5 Assessment of article quality

A quality assessment tool (QAT) (Appendix A) to assess the strength of each article was developed based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort, case-control and cross-sectional studies (combined).[7] Weighting was applied for each area based on the level of importance to give an overall quality assessment score (QAS) out of 20. The tool was tested by three reviewers on the first ten articles. Each reviewer had a minimum five years clinical experience. All reviewers discussed the tool before each reviewer completed their review individually. The tool was then reviewed by the reviewers to discuss the findings for the first ten articles. The tool was then applied to all articles by the investigator.

3.3.6 Data collection process

Each article was reviewed in its entirety by one reviewer and data items were highlighted, because this is a systematic review and not a meta-analysis with quantitative synthesis. No further data was obtained or confirmed from authors/investigators. These data were then extracted into the tables displayed in Section 3.4.

3.3.7 Data items

The following issues were itemised:

- Method – the method used for intraoperative assessment,
- Whether the IMA method was used in the surgical cavity, on the excised specimen or both,
- Study method – retrospective review (chart review), prospective observational (where the IMA method was used but no further shavings were taken based on results) or prospective experimental (where further shavings were taken based on the IMA results),
- Cases recruited, number used in data analysis and number of lesions examined,
- Recruitment period,
- Country,
- Number of hospital sites and surgeons used – to determine the level of potential variability within the results,
- Age of subjects – to determine if all studies were using similar age populations,
- Histological type, histological grade and tumour size - to determine if all studies were using similar pathological populations,
- The optimal margin size the study used – what margin size the study considered to be positive or close and what was classified as negative. This would impact on accuracy interpretation,
- Final intraoperative margin status – the percentage of cases determined to be positive by the IMA method,
- Final pathology margin status - the percentage of cases determined to be positive by standard assessment (pathology). This was not always compared to the above as further shavings may have been taken after IMA (need to take the study methodology into account),
- Procedure classified success – by the author of the article, with level of significance between IMA method and pathology where available,
- Second operation required – the percentage of patients who required a second operation. This does not include additional shavings in the first operation,
- Average difference in operation time for study method,
- Statistical measures: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy percentages.

3.3.8 Risk of bias in individual studies

The risk of bias was assessed as part of the article quality assessment and reflected in the QAS and not separately.

3.3.9 Summary measures

The principal summary measures to meet the objectives of this review were:

- IMA methods,
- Level of significance between the IMA methods and standard assessment,
- Accuracy of the IMA method, or if unavailable the sensitivity and specificity, and
- Second operation rates, taking optimal margin size and study methodology into account.

3.3.10 Data analysis

The data were analysed to determine the accuracy, sensitivity, specificity, PPV and NPV, taking the study design, study method, sample size into account. Where the accuracy, sensitivity and specificity were not provided, the number of positive and negative cases by IMA and pathology was reported. As studies varied by optimal margin size and a complete dataset was not provided in a number of studies, a meta-analysis was not performed and risk of bias across studies was not calculated.

3.4 Results

3.4.1 Study selection

The study selection process is outlined in Figure 3.1. There were 27 studies included in this review.

3.4.2 Quality assessment scores

The QAT was applied to the first ten articles by three independent reviewers to test the tool, and results for each article were compared between reviewers. Overall scores varied by on average 0.1/20 (range of differences 0-1.25) with an intraclass correlation coefficient of 0.998. It was concluded the tool could adequately assess the quality of each article and the investigator was consistent with applying the QAT. Consequently, the remaining 17 articles were assessed by the investigator only.

The results from the article quality assessment are shown in Table 3.1.

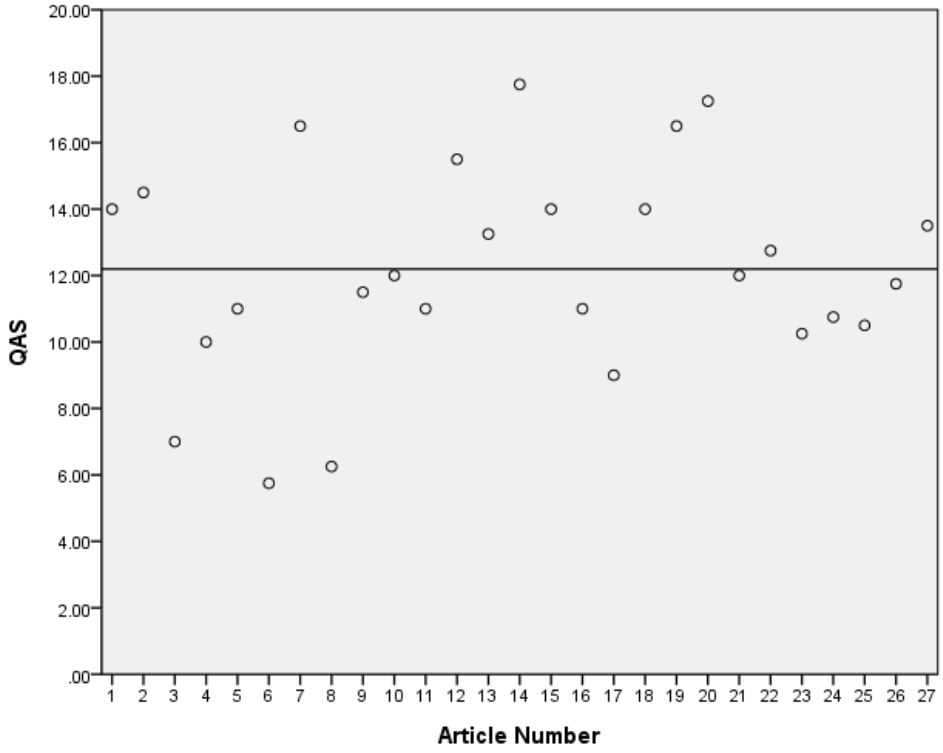
Table 3.1: Article quality assessment

Article No.	First Author	Year	QAS
1	Kim [8]	2013	14
2	Ramos [9]	2012	14.5
3	Rivera [10]	2012	7
4	Jorns [11]	2012	10
5	Sabel [12]	2012	11
6	Thill [13]	2011	5.75
7	Olsha [14]	2011	16.5
8	Martin [15]	2011	6.25
9	Doyle [16]	2011	11.5
10	Sumiyoshi [17]	2010	12
11	Nguyen [18]	2009	11
12	James [19]	2009	15.5
13	Dener [20]	2009	13.25
14	Weber [21]	2008	17.75
15	Allweis [22]	2008	14
16	Paredes [23]	2008	11
17	Duarte [24]	2007	9
18	Karni [25]	2007	14
19	Olson [26]	2007	16.5
20	Cabioglu [27]	2007	17.25
21	Kaufman [28]	2007	12
22	Fleming [29]	2004	12.75
23	McCormick [30]	2004	10.25
24	Chagpar [31]	2003	10.75
25	Rahusen [32]	2002	10.5
26	Creager [33]	2002	11.75
27	Moore [34]	2001	13.5

No., number; QAS, quality assessment score

The mean score was 12.19 (standard deviation [SD] 3.13, range 5.75-17.75). A plot of the variation between QAS is shown in Figure 3.2. The x-axis is in reverse chronological order and the plot indicates the quality of articles has decreased since 2009. The average QAS for articles published before 2009 averaged 12.93 compared to since 2009 averaging 11.40.

Figure 3.2: Plot of quality assessment scores (QAS) from article quality assessment.



Most studies varied greatly on how they presented their results and this impacted on the overall QAS reported above. Studies were rated higher where they clearly identified the methodology used, including how subjects were recruited and randomised (where applicable), the study method, how results were documented, whether further excision would be undertaken based on IMA results in the first operation, the final pathology result (preferably compared to IMA results in a matrix), statistical measures, the rate of second operations required and the additional operating time required to undertake the IMA.

3.4.3 Study characteristics

Most studies used the IMA on the excised specimen (74.1%; 20/27), with 5 (18.5%) studies examining the excised specimen and within the surgical cavity and only two (7.4%) studies examining in the surgical cavity but not the excised specimen.

Table 3.2 summarises and defines the IMA methods reported and the number of articles which assessed this method.

Table 3.2: Intraoperative margin assessment methods reported by studies

IMA Method	No. studies	Principle
Ultrasound	6	Uses soundwaves and receives the echoing waves
Frozen section	5	The excised tissue is frozen rapidly and then sliced for staining and microscopic examination
Radiofrequency spectroscopy probe (RFS)	4	Uses radiofrequency to measure the energy in molecules
Imprint or touch smear cytology	3	Where the margin or edge of the excised tissue is applied directly onto the slide for examination
Gamma camera & probe	2	Using low emitting energy isotopes to measure gamma emissions
Gross tissue inspection & specimen radiography	2	The excised tissue is examined by the eye and under a x-ray
Intraoperative digital specimen mammography (IDSM)	2	Using radiofrequency pulses directly on the excised issue intraoperatively
2-view standard specimen mammography (SSM)	1	Different to the above as typically captured in a radiography department and on film
Macroscopic margin assessment	1	Where the excised tissue is examined by the eye
Optical coherence tomography (OCT)	1	Uses near-infrared light

IMA, intraoperative margin; No., number.

The main characteristics of the studies are presented in Table 3.3. A third (9/27) of the studies recruited subjects prospectively but did not act on results from IMA (prospective observational). Eleven (40.7%) studies recruited prospectively and acted on IMA results (prospective experimental) whereas the remaining 7 (25.9%) studies were retrospective chart reviews. Optimal margin width ranged from ≥0mm to ≥5mm (not reported in four studies), with five studies using ≥0mm, seven studies using ≥1mm, seven using ≥2mm and four using ≥5mm.

Table 3.3: Study characteristics

Article No.	IMA method (cavity or specimen)	Study method	Optimal margins	Cases recruited	Final sample size	No. Lesions	Recruitment period	Country	No. of hospital sites	No. of surgeons	Age mean or median in years (SD)
1	Intraoperative digital specimen mammography (specimen)	Retrospective review	>1mm	214	201 total: 96 study;105 control (specimen radiography [SR])	201	Dec 07 – Mar 11	Canada	1	2	Study 59.5 (9.6) Control 59.6 (10.1)
2	Ultrasound (cavity & specimen)	Prospective observational	>2mm	223	223 total (no controls)	225	Jan 07 – Dec 11	Spain	1	Not reported	59.5 (11.1)
3	Radiofrequency spectroscopy probe (specimen)	Prospective experimental	>1mm	664	596 total: 298 study; 298 control (SR)	Not reported	Not reported	USA	21	Not reported	Not reported
4	Frozen section (specimen)	Prospective experimental	DCIS >3mm IDC >2mm	369	369 total: 181 study; 188 control (SR)	369	Aug 08 – July 10	USA	1	Not reported	Study 58.1 (11.6) Control 57.6 (12.2)
5	Frozen section (specimen)	Retrospective review	>2mm	549	549 total: 278 study; 271 control (SR)	Not reported	Jan 09 – Apr 10	USA	1	Not reported	Study 56.8 Control 58.0
6	Radiofrequency spectroscopy probe (cavity)	Prospective observational	>5mm	27	22 total (no controls)	Not reported	Sept 09 – May 10	Germany	3	Not reported	Not reported
7	Ultrasound (specimen)	Prospective experimental	>2mm	53	45 total (no controls)	48	Jun 08 – Feb 10	Israel	1	1	Not reported
8	Imprint cytology (specimen)	Prospective observational	>0mm	47	29 total (no controls)	29	Not reported	USA	1	Not reported	Not reported
9	Ultrasound (cavity & specimen)	Prospective observational	Not reported	17	17 total (no controls)	31	Not reported	USA	1	1	Not reported
10	Touch smear cytology (specimen)	Prospective experimental	>0mm	160	160 total (no controls)	160	2005 – 2008	Japan	1	Not reported	58.1
11	Optical coherence tomography (specimen)	Prospective observational	>2mm	37	33 total: 18 study; 15 control (SR)	33	Not reported	USA	1	Not reported	Study 66 Control 62
12	Ultrasound (specimen)	Prospective observational	>1mm	155	155 total: 96 study; 59 control (mammographic needle localisation)	Not reported	2003 - 2007	USA	1	Not reported	Study 59 Control 56
13	Frozen section (specimen)	Prospective observational	>2mm	186	186 total (no controls)	190	1997 - 2007	Turkey	1	4	49
14	Frozen section (specimen)	Retrospective review	>1mm	111	111 total: 78 study; 33 control (SR)	115	Jan 90 – Dec 04	Switzerland	1	Not reported	Study 59.6 Control 57.5

15	Radiofrequency spectroscopy probe (specimen)	Prospective experimental	>1mm	300	293 total: 143 study; 150 control (SR or pathology)	Not reported	Nov 06 – Nov 07	Israel	11	Not reported	Study 59 Control 60
16	Gamma camera & probe (cavity & specimen)	Prospective observational	>5mm	42	42 total (no controls)	Not reported	Not reported	Spain	1	Not reported	59 (7.8)
17	Gamma probe (cavity)	Prospective experimental	>0mm	23	23 total (no controls)	23	Jan 05 – Dec 05	Brazil	1	Not reported	51.3 (11.7)
18	Radiofrequency spectroscopy probe (specimen)	Prospective observational	>1mm	68	57 total (no controls)	Not reported	Feb 2005 – Dec 2005	Israel	2	Not reported	Not reported
19	Frozen section (specimen)	Retrospective review	Not reported	290	290 total (no controls)	292	1993 – May 2005	USA	1	Not reported	56
20	Gross tissue inspection & specimen radiography (specimen)	Retrospective review	>2mm	264	251 total (no controls)	251	Jan 94 – Dec 96	USA	1	Not reported	IDC 60 DCIS 58
21	Intraoperative digital specimen mammography (specimen)	Prospective experimental	Not reported	79	79 total: Study group was own control (standard specimen mammography)	85	Apr 04 – May 05	USA	1	Not reported	Not reported
22	Macroscopic margin assessment (specimen)	Prospective experimental	≥5mm	220	220 total (no controls)	220	Not reported	Ireland	1	Not reported	59
23	2-view standard specimen mammography (specimen)	Prospective experimental	Not reported	97	93 total (no controls)	93	2000 – 2001	USA	1	Not reported	Not reported
24	Gross tissue inspection & specimen radiography (specimen)	Retrospective review	>5mm	109	109 total (no controls)	109	Jul 99 – Jul 02	USA	1	Not reported	55 (10)
25	Ultrasound (cavity & specimen)	Prospective experimental	≥1mm	49	49 total: 27 study; 22 control (wire-guided excision)	Not reported	Jun 98 – Jul 01	Netherlands	2	Not reported	Not reported
26	Imprint cytology (specimen)	Retrospective review	>0mm	137	137 total	141	May 97 – May 01	USA	1	Not reported	58
27	Ultrasound (specimen)	Prospective experimental	>0mm	51	51 total: 27 study; 24 control (SR)	Not reported	Dec 98 – Oct 00	USA	Not reported	Not reported	Not reported

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; IMA, intraoperative margin assessment; mm, millimetre; No., number; SD, standard deviation; SR, specimen radiography; USA, United States of America

Half (14/27) of the studies were undertaken in the United States of America (USA) and the majority of studies (21/27) were undertaken at only one site. Few studies (3/27) reported the number of surgeons or users of the IMA method, which does not allow comment on the risk of inter-operator variability.

The mean age of participants, where reported, were similar among studies, ranging from 55 to 60 years. The histological factors of type, grade and tumour size were extracted to assess whether study populations were comparable. Tables 3.4, 3.5 and 3.6 summarise these results. The type of breast cancer was reported in 22 studies, with the majority studies including cases of invasive ductal carcinoma (IDC). Three studies recruited only DCIS cases. More than 50% of cases reported by Doyle and colleagues[16] were 'benign/other' cases, but their study reported DCIS/invasive cases separately. This study also had a very small sample size.

All studies reported the majority of cases as grade II, while there were some variations in distribution of grade I and grade III. Sumiyoshi[17] (article 10) was the exception, reporting 43.75% of cases as grade 1. This study had a good sample size and a majority (78.75%) of cases were invasive ductal carcinoma. The greatest variation in study characteristics was found in tumour size, as reported in fifteen studies. The majority of these studies (12/15) reported a mean tumour size between 1 to 2cm.

Table 3.4: Number (and percentage) of each histological type in reported studies

Article No.	Study Group	DCIS No. (%)	LCIS No. (%)	IDC No. (%) [with DCIS No. (%)]	ILC No. (%)	Mixed ID/LC No. (%)	Benign/other No. (%)
1	Study	16 (17.6)	0	64 (70.3) [46 (50.6)]	0	0	11 (12.1)
	Control	30 (27.3)	0	63 (57.3) [45 (40.9)]	0	0	17 (15.5)
2	Study	0	0	191 (84.9)	25 (11.1)	0	9 (4.0)
3	Study & Control	NR	NR	NR	NR	NR	NR
4	Study	50 (27.6)	0	101 (55.8)	14 (7.7)	11 (6.1)	5 (2.8)
	Control	39 (20.7)	0	115 (61.2)	23 (12.2)	6 (3.2)	5 (2.7)
5	Study	67 (24.1)	0	140 (50.4) [4 (1.4)]	26 (9.4)	29 (10.4)	16 (5.8)
	Control	56 (20.7)	0	140 (51.7) [5 (1.8)]	30 (11.1)	22 (8.1)	23 (8.5)
6	Study	22 (100)	0	0	0	0	0
7	Study	0	0	38 (84.4) [22(48.9)]	5 (11.1)	1 (2.2)	1 (2.2)
8	Study	9 (31.0)	0	18 (62.1)	2 (6.9)	0	0
9	Study	5 (16.1)	2 (6.5)	5 (16.1) [3 (9.7)]	1 (3.2)	0	18 (58.1)
10	Study	7 (4.4)	0	126 (78.8)	0	0	27 (16.9)
11	Study & Control	15 (48.4)	1 (3.2)	11 (35.5)	0	0	4 (12.9)
12	Study	96 (100)	0	0	0	0	0
	Control	59 (100)	0	0	0	0	0
13	Study	0	0	170 (89.5)	16 (8.4)	4 (2.1)	0
14	Study	12 (11.8)	12 (11.8)	68 (66.7) [37 (36.3)]	0	0	10 (9.8)
	Control	21 (48.8)	1 (2.3)	14 (32.6) [9 (20.9)]	0	0	7 (16.3)
15	Study	(12)	0	(37)	(5)	(46)	0
	Control	(8)	0	(38)	(6)	(48)	0
16	Study	4 (9.5)	1 (2.4)	29 (69.1)	3 (7.1)	1 (2.4)	4 (9.5)
17	Study	0	0	23 (100)	0	0	0
18	Study	NR	NR	NR	NR	NR	NR
19	Study	33 (11.3)	0	214 (73.3)	17 (5.8)	1 (0.3)	27 (9.3)
20	Study	64 (24.2)	0	166 (62.9)	14 (5.3)	0	20 (7.6)
21	Study	29 (34.1)	0	47 (55.3) [4 (4.7)]	2 (2.4)	0	7 (8.2)
22	Study	0	0	156 (70.9)	29 (13.2)	12 (5.5)	23 (10.5)
23	Study	NR	NR	NR	NR	NR	NR
24	Study	109 (100)	0	0	0	0	0
25	Study & Control	NR	NR	NR	NR	NR	NR
26	Study	23 (16.3)	0	106 (75.2)	6 (4.3)	6 (4.3)	0
27	Study & Control	NR	NR	NR	NR	NR	NR

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; NR, not reported..

Table 3.5: Number (and percentage) of each histological grade in reported studies

Article No.	Study Group	Grade I (low) No. (%)	Grade II (intermediate) No. (%)	Grade III (high) No. (%)
1	Study	28 (35.4)	34 (43.0)	17 (21.5)
	Control	33 (35.1)	43 (45.7)	18 (19.2)
2	Study	81 (36.0)	98 (43.6)	46 (20.4)
3	Study & Control	NR	NR	NR
4	Study	30 (22.9)	55 (42.0)	46 (35.1)
	Control	44 (29.5)	69 (46.3)	36 (24.2)
5	Study	66 (25.8)	107 (41.8)	83 (32.4)
	Control	70 (27.0)	109 (42.1)	80 (30.9)
6	Study	NR	NR	NR
7	Study	NR	NR	NR
8	Study	NR	NR	NR
9	Study	NR	NR	NR
10	Study	70 (43.8)	50 (31.3)	40 (25.0)
11	Study	NR	NR	NR
12	Study	9 (9.4)	53 (55.2)	34 (35.4)
	Control	5 (8.5)	33 (55.9)	21 (35.6)
13	Study	26 (13.7)	123 (64.7)	41 (21.6)
14	Study & Control	NR	NR	NR
15	Study	(18.0)	(48.0)	(34.0)
	Control	(15.0)	(44.0)	(41.0)
16	Study	NR	NR	NR
17	Study	NR	NR	NR
18	Study	NR	NR	NR
19	Study	NR	NR	NR
20	Study	75 (26.4)	173 (60.9)	36 (12.7)
21	Study	NR	NR	NR
22	Study	NR	NR	NR
23	Study	NR	NR	NR
24	Study	10 (9.2)	55 (50.5)	44 (40.4)
25	Study & Control	NR	NR	NR
26	Study	NR	NR	NR
27	Study & Control	NR	NR	NR

No., Number; NR, not reported.

Table 3.6: Tumour size characteristics in reported studies

Article No.	Study Group	Mean size (cm)	SD (cm)	Range (cm)
1	Study & Control	NR	NR	NR
2	Study	1.21	0.57	NR
3	Study & Control	NR	NR	NR
4	Study	1.16	0.99	NR
	Control	1.11	1.10	NR
5	Study	Invasive = 1.76	NR	Invasive 0.2 – 9.0
		DCIS = 1.06		DCIS = 0.1 – 6.5
	Control	Invasive = 1.84	NR	Invasive 0.2 – 10.5
		DCIS = 1.14		DCIS = 0.1 – 6
6	Study	NR	NR	NR
7	Study	1.9	NR	0.5 – 4.8
8	Study	NR	NR	NR
9	Study	NR	NR	1 - 5
10	Study	2.48	0.7	NR
11	Study	NR	NR	NR
12	Study	1.07	NR	0.0 – 10.2
	Control	1.23	NR	0.05 - 10
13	Study	2.2	NR	0.4 - 5
14	Study & Control	NR	NR	NR
15	Study	1.87	NR	NR
	Control	1.71	NR	NR
16	Study	NR	NR	NR
17	Study	4.05	1.05	2 – 6.1
18	Study	NR	NR	NR
19	Study	1.5	NR	NR
20	Study	Invasive = 1.4	NR	Invasive 0.1 – 3.9
		DCIS = 0.6		DCIS = 0.1 – 3.0
21	Study	NR	NR	NR
22	Study	1.5	NR	NR
23	Study	NR	NR	NR
24	Study	1.2	NR	0.2 – 8.0
25	Study	1.34	NR	0.5 – 2.5
	Control	1.36	NR	0.4 – 2.3
26	Study	1.7	NR	0.2 – 5.3
27	Study & Control	NR	NR	NR

cm, centimetres; DCIS, ductal carcinoma in situ; No., Number; NR, not reported; SD, standard deviation.

3.5 Summary measure results and discussion

The studies were classified and then analysed based on their methodology (retrospective review, prospective observational or prospective experimental).

Table 3.7 and 3.8 displays the summary measures for the eleven prospective experimental studies. Based on the reported level of concordance, where the IMA method was compared to the standard assessment status, the radiofrequency

spectroscopy (RFS) probe performed well ($p<0.0001$ Rivera[10] [article 3]; $p=0.044$ Allweis[22] [article 15]). The 2-view standard specimen mammography (SSM) and the macroscopic margin assessment technique, which had the largest optimal margin distance of $\geq$5mm, reported the lowest second operation rates of 5% and 7.3%, respectively. The reporting of additional operation time was not reliable as some studies compared against a standard procedure whereas others reported against another study method. According to the reported times, the intraoperative digital specimen mammography (IDSM) (Kaufman[28] [article 21]) reduced operation times by on average 19 minutes when compared to SSM, but this is not a standard procedure in many countries. The 2-view SSM (McCormick[30] [article 23]) reported an average 15 minute increase in operation time when compared to the standard procedure. This time could be added to the findings of Kaufman[28] (article 21). Ultrasound was also reported to reduce operation times (Moore[34] [article 27]: 15 minutes; Rahusen[32] [article 25]: 1 minute). Frozen section increased operation times on average by 27 minutes. The introduction of any additional intraoperative methods will increase operation times and needs to be weighed against the reduction in the second operation rate. On this basis, ultrasound (Moore[34] [article 27]) performed best with a second operation rate of 13.7%, a decrease of an average 15 minutes in operation time and statistically significant level of concordance ($p<0.05$). However, ultrasound has its own limitations, with a decreased accuracy in assessing multifocal disease and calcifications.

Table 3.7: Summary measures margin status, success, second operation rate and time for prospective experimental studies

Article No.	IMA method	Optimal margins	Intraoperative margin status[(a)]	Pathological margin status[(b)]	Procedure classified success	Second operation required	Average difference in operation time for study method
3	Radiofrequency spectroscopy probe	>1mm	NR	NR	Yes p<0.00	Study 14.1% Control 29.9%	NR
4	Frozen section	DCIS >3mm IDC >2mm	Study 59.3% positive	NR	Yes	Study 19.3% Control 55.3% (p=0.096)	+ 27 minutes
7	Ultrasound	>2mm	15.5% positive	24.4% positive	Yes	4.4%	NR
10	Touch smear cytology	>0mm	11.25% positive	12.5% positive	Yes	NR	NR
15	Radiofrequency spectroscopy probe	>1mm	NR	Study 40% positive Control 59% positive	Yes p=0.04	Study 12.6% Control 18.6% (p=0.098)	NR
17	Gamma probe	>0mm	NR	21.1% positive	No p=0.23	NR	NR
21	Intraoperative digital specimen mammography (IDSM)	NR	IDSM = 29% positive SSM = 23% positive	28.2% positive	Yes - no significant difference between IDSM & SSM	NR	- 19 minutes when compared to SSM
22	Macroscopic margin assessment	≥5mm	36.81% positive	9.1% positive	Yes	7.3%	NR
23	2-view standard specimen mammography (SSM)	NR	17.2% positive	11.8% positive	Yes	5%	+15 minutes
25	Ultrasound	≥1mm	NR	Study 11% positive Control 45% positive	Yes p=0.01	NR	-1 minute
27	Ultrasound	>0mm	NR	Study 3.5% positive Control 29% positive	Yes p<0.05	13.7%	-15 minutes

(a) – margin status classified by the IMA method and includes close, defined as less than the optimal margin distance

(b) Margin status classified by pathology and includes close, defined as less than the optimal margin distance

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; IDSM, intraoperative digital specimen mammography; IMA, intraoperative margin assessment; No., number; NR, not reported; SSM, standard specimen mammography.

Table 3.8: Summary measures of sensitivity, specificity, positive predictive value, negative predictive value and accuracy for prospective experimental studies

Article No.	IMA method	Optimal margins	Sensitivity	Specificity	PPV	NPV	Accuracy
3	Radiofrequency spectroscopy probe	≥1mm	NR	NR	NR	NR	NR
4	Frozen section	DCIS ≥3mm IDC ≥2mm	91.1%	100%	100%	97.9%	98.3%
7	Ultrasound	≥2mm	25%	95%	27%	95%	NR
10	Touch smear cytology	>0mm	70%	97.1%	77.78%	95.8%	93.8%
15	Radiofrequency spectroscopy probe	≥1mm	NR	NR	NR	NR	NR
17	Gamma probe	>0mm	NR	NR	NR	NR	NR
21	Intraoperative digital specimen mammography	NR	IDSM = 36% SSM = 31%	IDSM = 71% SSM = 74%	IDSM = 50% SSM = 38%	IDSM = 84% SSM = 90%	NR
22	Macroscopic margin assessment	≥5mm	73%	88%	NR	NR	NR
23	2-view standard specimen mammography	NR	54.6%	87.8%	37.5%	93.5%	NR
25	Ultrasound	≥1mm	NR	NR	NR	NR	NR
27	Ultrasound	>0mm	NR	NR	NR	NR	NR

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; IMA, intraoperative margin assessment; No., number; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

The overall accuracy of IMA in prospective experimental studies was only reported in two studies: frozen section (Jorns[11] [article 4]) reported a 98.3% accuracy and touch smear cytology (Sumiyoshi[17] [article 10]) reported a 93.8% accuracy. Sensitivity and specificity rates were reported in half of the prospective experimental studies, with frozen section (Jorns[11] [article 4]) reporting the highest sensitivity (91.1%) and specificity (100%). This study had an adequate sample size (369 patients) and was conducted recently (concluding in July 2010), but reported an additional average operation time of 27 minutes. Interestingly the other two studies which reported good sensitivity and specificity rates were also intraoperative pathological assessments. Touch smear cytology (Sumiyoshi[17] [article 10]) reported a 70% sensitivity and 97.1% specificity rate with a sample size of 160 patients. Touch smear cytology only assesses the direct (or outside) margins of the specimen and will not identify any residual disease within 5mm of the surface of the margin. Macroscopic margin assessment (Fleming[29] [article 22]) reported a sensitivity and specificity of 73% and 88% respectively, with a

sample size of 220 patients. This study also used a larger optimal margin width of ≥5mm. It is hypothesised that if the optimal margin width was reduced for comparison against the other studies with an optimal margin width of ≥1mm and ≥2mm, the sensitivity and specificity would be improved.

Tables 3.9 and 3.10 provide the summary measures for the 16 prospective observational studies and retrospective chart reviews. Based on the reported level of concordance, a number of IMA methods performed well. Ultrasound showed no significant difference to standard assessment in two studies (Doyle[16] [article 9] and James[19] [article 12], both $p<0.05$), which supported the findings of the two prospective experimental studies (Rahusen[32] [article 25]: $p=0.0007$; Moore[34] [article 27]: $p<0.05$). IDSM reported a statistically significant level of concordance ($p=0.012$) in a retrospective review (Kim[8] [article 1]), that also supported the findings of the prospective experimental study (Kaufman[28] [article 21]) which found no difference between IDSM and SSM. All three IMA pathological methods reported a statistically significant level of concordance: the combined use of gross tissue inspection and specimen radiology (SR) ($p<0.001$) (method not used in any prospective experimental studies), imprint cytology ($p<0.001$) (touch smear cytology in the prospective experimental study designs did not report the level of concordance) and frozen section ($p=0.002$) (frozen section in the prospective experimental study designs did not report the level of concordance).

Table 3.9: Summary measures of margin status, success, second operation rate and time for prospective observational and retrospective studies

Article No.	IMA method	Optimal margins	Intraoperative margin status [(a)]	Pathological margin status[(b)]	Procedure classified success	Second operation required	Average difference in operation time for study method[(c)]
1	Intraoperative digital specimen mammography	>1mm	Study 38.0% positive Control 63.8% positive	Study 21.8% positive Control 47.6% positive	Yes p=0.01	Study 14.6%; Control 17.1% (p=0.64)	-2 minutes
2	Ultrasound	>2mm	Study 45.7% positive	Study 13.3% positive	Yes	Study 4%	NR
5	Frozen section	>2mm	NR	Study 6% positive Control 10% positive	Yes	Study 11%; Control 25% (p<0.001)	+30 minutes
6	Radiofrequency spectroscopy probe	>5mm	NR	NR	Yes	Study 18% Historical 38.8%	NR
8	Imprint cytology	>0mm	NR	NR	Yes p<0.001	NR	+20-25 minutes (min 10 minutes)
9	Ultrasound	NR	NR	NR	Yes Ductal carcinoma peak density p<0.05	NR	NR
11	Optical coherence tomography	>2mm	55% positive	45% positive	Yes	NR	NR
12	Ultrasound	>1mm	NR	Study 33.3% positive Control 39.0% positive	Yes	Study 20.8%; Control 30.5% (p=0.184)	NR
13	Frozen section	>2mm	NR	16% positive	Yes	16%	+25 minutes
14	Frozen section	>1mm	Study 46.3% positive Control 51.4% positive	Study 12.5% positive Control 20.0% positive	Yes p=0.002	Study 12.5%; Control 37.1% (p=0.002)	NR
16	Gamma camera & probe	>5mm	NR	Centred 39% positive Non-centred 57.9% positive	NR	NR	+5 minutes
18	Radiofrequency spectroscopy probe	>1mm	33.3% positive	38.6% positive	Yes	NR	+7.37 minutes
19	Frozen section	NR	24% positive	11.3% positive	Yes	11.4%	NR
20	Gross tissue inspection & specimen radiography	>2mm	Invasive = 35.5% positive DCIS = 18.75% positive	Invasive = 17% positive DCIS = 28.1% positive	Yes	8.7%	NR
24	Gross tissue inspection & SR	>5mm	54.1% positive	24% positive	Yes p=0.00005	22% (p=0.029)	NR
26	Imprint cytology	>0mm	21.9% positive	10.9% positive	Yes	NR	+ 20 minutes

(a) Margin status as determined by IMA method, including close margins, defined as less than the optimal margin distance

(b) Margin status as determined by pathology, including close margins, defined as less than the optimal margin distance

(c) Compared to standard assessment unless specified otherwise

IMA, intraoperative margin assessment; No., number; NR, not reported; SR, specimen radiography.

Table 3.10: Summary measures of sensitivity, specificity, positive predictive value, negative predictive value and accuracy for prospective observational and retrospective studies

Article No.	IMA method	Optimal margins	Sensitivity	Specificity	PPV	NPV	Accuracy
1	Intraoperative digital specimen mammography	≥1mm	NR	NR	NR	NR	NR
2	Ultrasound	≥2mm	80%	86.6%	23.3%	95.1%	99.6%
5	Frozen section	≥2mm	NR	NR	NR	NR	94%
6	Radiofrequency spectroscopy probe	≥5mm	NR	NR	NR	NR	73% (2mm 86%)
8	Imprint cytology	>0mm	85% (71.4% in DCIS)	100%	NR	NR	89.7% (77.8% in DCIS)
9	Ultrasound	Not reported	100%	74%	NR	NR	NR
11	Optical coherence tomography	≥2mm	100%	82%	82%	100%	90%
12	Ultrasound	≥1mm	NR	NR	NR	NR	NR
13	Frozen section	≥2mm	NR	NR	NR	NR	NR
14	Frozen section	≥1mm	80%	87.5%	86.5%	81.4%	83.8%
16	Gamma camera & probe	≥5mm	NR	NR	NR	NR	60%
18	Radiofrequency spectroscopy probe	≥1mm	71%	68%	NR	NR	NR
19	Frozen section	Not reported	73.1%	99.6%	91.9%	98.3%	98.0%
20	Gross tissue inspection & specimen radiography	≥2mm	91.7%	77.8%	NR	NR	87.4%
24	Gross tissue inspection & specimen radiography	≥5mm	NR	NR	NR	NR	NR
26	Imprint cytology	>0mm	80%	85%	40%	97%	85%

IMA, intraoperative assessment; No., number; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

When examining second operation rates, frozen section reported the largest difference between study and control rates (Sabel[12] [article 5]: $p<0.001$; Weber[21] [article 14]: $p=0.002$). Gross tissue inspection with SR (Chagpar[31] [article 24]) also reported a significant difference ($p=0.029$). There was no significant difference in second operation rate reported for IDSM (Kim[8] [article 1]) or ultrasound (James[19] [article 12]). Comparing second operation percentages to the prospective experimental studies, ultrasound (Ramos[9] [article 2]) was the only study that reported comparable results to

the prospective experimental studies, thus confirming the value of excising more tissue during the first operation based on IMA findings.

Only six studies reported the variations in operation times when an IMA method was introduced. IDSM (Kim[8] [article 1]), as with the prospective experimental studies, reported a decrease in operation time by 2 minutes. Similar to the prospective experimental study, this was compared to SSM, although it is not the standard protocol in many countries. The gamma camera and probe increased operation times on average by 5 minutes. Studies using frozen section reported an increase in operating time ranging from 20 to 30 minutes, supporting the finding of the prospective experimental study reported in Jorns[11] [article 4] that this method considerably extends operation times.

Accounting for level of concordance, second operation rates and operation time, where all data measures were reported, IDSM (Kim[8] [article 1]) performed the best with a second operation rate of 14.6% (no significant difference), a decrease of an average 2 minutes (plus approximately 15 minutes against SSM) in operation time and a statistically significant level of concordance (p=0.012). Ultrasound (James[19] [article 12]) also performed well, with a second operation rate of 20.8% (no significant difference), and no significant difference against standard assessment (average operation times not reported).

Overall, accuracy of IMA in prospective observational studies and retrospective chart reviews was well reported. Ultrasound (Ramos[9] [article 2]) reported the highest level of accuracy (99.6%), followed by frozen section (Olson[26] [article 19]: 98.02%; Sabel[12] [article 5]: 94%) and optical coherence tomography (Nguyen[18] [article 11]: 90%). Imprint cytology (Martin[15] [article 8]) reported a sensitivity of 85% (71.4% in DCIS) and specificity of 100%. The study only had 29 patients, added 20 to 25 minutes to operation time and similar to touch smear. It could only assess the direct margins but not any residual disease within 5mm of the surface. The other imprint cytology study reported a sensitivity and specificity of 80% and 85% respectively. Optical coherence tomography (OCT) (Nguyen[18] [article 11]) reported a sensitivity of 100% and specificity of 82%, but again the study only involved a small sample size (33 patients) and did not report average operation times. Ultrasound (Doyle[16] [article 9]) reported a sensitivity and specificity of 100% and 74%, with a second study (Ramos[9] [article 2])

reporting 80% and 86.6% respectively. Whilst the first study (Doyle[16] [article 9]) only had a small sample size (17 patients) the second (Ramos[9] [article 2]) had a sample size of 223 patients. Neither reported the additional surgical time taken to apply the ultrasound to the specimen and in the cavity.

Only four studies reported follow-up data, so this information was not analysed.

Where accuracy was reported, it was compared against the optimal margin width, average operation time and QAS. The second operation rate was not included in this comparison as it varied depending on whether additional shavings were taken during the first operation based on the IMA findings. The results are collated and presented in Table 3.11.

Table 3.11: Comparison of optimal margin width, accuracy, average difference in operation time, sample size and quality assessment score (QAS)

Article No.	IMA method	Optimal margins	Accuracy	Average difference in operation time for study method	Sample size	QAS
2	Ultrasound	≥2mm	99.6%	Not reported	223	14.5
4	Frozen section	DCIS ≥3mm IDC ≥2mm	98.3%	+ 27 minutes	369	10
19	Frozen section	Not reported	98.02%	Not reported	290	16.5
5	Frozen section	≥2mm	94%	+30 minutes	549	11
10	Touch smear cytology	>0mm	93.8%	Not reported	160	12
11	Optical coherence tomography	≥2mm	90%	Not reported	33	11
8	Imprint cytology	>0mm	89.7% (77.8% in DCIS)	+20-25 minutes (min 10 minutes)	29	6.25
20	Gross tissue inspection & specimen radiography	≥2mm	87.4%	Not reported	251	17.25
26	Imprint cytology	>0mm	85%	+ 20 minutes	137	11.75
14	Frozen section	≥1mm	83.8%	Not reported	111	17.75
6	Radiofrequency spectroscopy probe	≥5mm	73% (2mm 86%)	Not reported	22	5.75
16	Gamma camera & probe	≥5mm	60%	+5 minutes	42	11

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; IMA, intraoperative assessment; mm, millimetre; No., number; QAS, quality assessment score.

Of the 12 studies that reported accuracy, four of the top five studies were intraoperative pathology methods: frozen section and touch smear cytology (93.8 – 98.3% accuracy). Ultrasound (Ramos[9] [article 2]) reported the highest accuracy (99.6%) for a ≥2mm optimal margin width. Although average operation time was not reported, it is hypothesised that ultrasound would be quicker to apply and return results (in the operating theatre) than frozen section or touch smear cytology, yet it does not perform as well with multifocal cancers or calcifications. Only one RFS probe study (Thill[13]

[article 6]) reported the accuracy (73% at ≥5mm, 86% at ≥ 2mm), however, the study only examined 22 cases and did not score highly in the QAS. Only two studies that reported the use of a radiopharmaceutical guided probe (Paredes[23] [article 16] and Duarte[24] [article 17]) but neither scored highly in the QAS, had small sample sizes and only one article reported the accuracy of this device (Paredes[23] [article 16]: 60%).

3.6 Discussion

Breast cancer was the most commonly diagnosed cancer among females in Australia in 2012, and the second leading cause of death by cancer.[35] During 2006-10 the 5 year survival rate for breast cancer in females was 89%.[36] It is the sixth leading cause of burden of disease for females and expected to contribute more years of life lost (40,800) than years of health life lost to disability (20,500).[36] Local recurrence following BCT for DCIS has been reported as 3.9-10.5% and invasive breast cancer 5-22%, with positive or close margins being a risk factor. 2,[4,37-41] With approximately 25% of women requiring a second operation to ensure clear margins, a method of accurately assessing margins intraoperative would potentially reduce the number of second operations required as well as the recurrence rate.

In general, intraoperative pathological methods performed well according to the systematic review. Accuracy for frozen section were reported between 83.8-98.3%, touch smear and imprint cytology between 85%-93.8% and gross tissue inspection combined with specimen radiology was 87.4%, all with large sample sizes used.[11-12,15,17,21,26-27,33] The sensitivity rates in the frozen section studies reported here (73.1%-91.1%) are slightly higher than that reported in other literature (65-80%). The specificity rates reported here appear to be consistent with those reported in the literature (87.5-100%).[21,42,43] Also, the imprint cytology sensitivity rates reported here (70-85%) are similar to those reported in the literature (72-100%), while specificity appeared to be consistent with those reported in the literature (85-100%).[43-45]

Although the sensitivity, specificity and accuracy of pathological IMA methods are high, these methods add significant time to operation time, often between 20-30 minutes on average. This additional time has a number of adverse implications including additional costs, the number of cases that can be treated per day, additional time under anaesthetic and loss of productivity time for theatre staff whilst waiting for results to be

returned. In addition touch smear and imprint cytology methods only assess the direct surgical margin and do not identify where there may be residual disease up to 5mm under the surface.

Among the other methods, ultrasound was the only IMA that returned notable results. At a ≥2mm optimal margin width, a 99.6% accuracy had been reported using a large sample size (223 patients), with only a 4% second operation rate.[9] The positive concordance between ultrasound and standard procedures was supported by the literature analysed.[14,16,19,32,34] Ultrasound is often used to guide surgery but there has been little report in terms of accuracy, sensitivity and specificity to assess the surgical margins. The sensitivity rates reported here ranged from 25 to 100% and specificity ranged from 74 to 95%. A study by Jeong had reported a sensitivity of 80% and specificity of 90%, which is within the range reported here.[46] Ultrasound can be used in the operating theatre and, when applied by a trained operator, it can produce results immediately, allowing the decision to take further shavings with minimal impact on operating times. However it should be noted that one study did report a poor sensitivity (25%), with a PPV of 27%, when using ultrasound on the excised specimen.[14] Also ultrasound is known not to perform well where there is calcifications or multifocal disease, limiting its applicability in DCIS surgery greatly.

A RFS probe offers an alternative to ultrasound, by examining the electromagnetic signature of the tissue in the operating theatre. Four articles reported the use of a RF spectroscopy probe in breast surgery, two with large samples (Rivera[10] [article 3]: 596 patients; Allweis[22] [article 15]: 293 patients) from multicentre studies.[10,13,22,25] All four articles reported a statistically significant level of concordance ($p<0.05$) but only two studies provided statistical measures of performance, both with small sample sizes. Thill[13] (article 6) reported an accuracy of 86% when the optimal margin width was ≥2mm and Karni[25] (article 18) reported a sensitivity and specificity of 71% and 68%, respectively. This was lower than the reported sensitivity and specificity in the literature ranging from 70 to 100% and 70 to 87% respectively.[47] Although these devices do not greatly increase operating time and provide immediate feedback, the sensitivity and accuracy reported here are lower than pathological IMA methods, and second operation rates did not vary significantly from controls in prospective experimental studies. Statistical measures of sensitivity, specificity and accuracy for the larger studies should

be provided to determine if the above rates were affected by the small sample sizes and to ascertain whether the device has an important role in IMA in breast surgery.

Three studies reported the use of intraoperative mammography technology.[8,28,30] Two studies applied IDSM,[8, 28] compared to standard SR or mammography, whilst the third used 2-view SSM.[30] Whilst all three studies reported concordance with standard procedures (Kim[8] [article 1]: p=0.012), only one study reported a small second operation rate (McCormick[30] [article 23]: 5%). There was no significant difference in second operation rates in article 1 (Kim[8]), however it was a retrospective chart review. Both Kaufman[28] [article 21] and McCormick[30] [article 23] reported poor sensitivity rates (36% and 54.55% respectively), while no accuracy rates were provided for either study. Use of this device took approximately the same time, or slightly longer, as a hand held ultrasound or RFS probe, yet it reduced the second operation rate in only one study with a poor sensitivity, which could result in the excision of more tissue than necessary. Further research with larger sample sizes is required and confirmed against standard procedures to identify the actual additional operation time required.

Lastly, for OCT, only one study examined the use of such interferometry technology.[18] The study reported 90% accuracy, with sensitivity, specificity, PPV and NPV of 100%, 82%, 82% and 100% respectively. Additional operation time and the second operation rate were not reported. Whilst a number of publications[48-49] have emerged examining the potential use of this technology in surgery, specifically breast surgery, data on accuracy, sensitivity or specificity rates in breast surgery to compare were lacking. Further research reporting on these statistical measures is required before making any recommendations.

The limitation of this systematic review is it does not include a meta-analysis of pooled data. Articles were reviewed in reverse chronological order and therefore there was a learning effect. Articles were analysed and presented individually and this approach did not impact on findings.

3.7 Positron Emission Tomography probe

An IMA method that did not appear in this review is the positron emission tomography (PET) probe. There is little research dedicated to examining the use of this technology is breast cancer, with most papers either animal models or report the use of the probe in

surgery for many different cancers. PET works by injecting a radionuclide that targets specific tissue characteristics. ^{18}F-fluorodeoxyglucose (FDG) is a positron-emitting analog of glucose, which is seen to have higher metabolism in tumour cells. As gamma rays can travel several centimetres into tissue, whereas positrons only travel millimetres, a handheld dual PET probe capable of detecting positron rays can identify tissue with greater accuracy during surgery following injection of FDG.[50, 51] The PET probe works as a combined gamma and beta probe. The central scintillator detects both positron (beta) and gamma rays whilst the surrounding scintillator detects just gamma rays, allowing the unit to subtract one count from the other to obtain generate only the positron count.[50, 51] The main limitation for PET probes is the uptake of FDG by the heart, liver, bladder and brain. The heart is the main concern in breast cancer surgery due to its close proximity to the breast tissue potentially returning false positive count rates.

Raylman and colleagues[52] examined the use of a PET probe in rats implanted with mammary tumours. They found uptake of FDG in this model to only be in the bladder, liver and brain. Bladder uptake can be reduced in humans by encouraging the patient to void before surgery. The study reported good uptake of FDG by mammary tumour tissue and recommended the use of a smaller probe when applying to smaller tumours. The probe was able to differentiate between normal and tumour tissue and results between the probe results and pathology correlated well, with a good sensitivity (percentage not reported). The findings in this study are supported by another animal study, using a mouse model.[53] They found the PET probe was able to detect positron rays at a close range to the site of interest and concluded the PET probe may have a higher sensitivity compared to the gamma probe. Both studies recommended further research using the PET probe in breast surgery, including the timing from FDG injection and using the probe intraoperatively.

The ability of the PET probe to detect small tumours was supported by Essner and colleagues.[50, 54] However their studies did not include breast cancer cases. Two other studies applied the probe in breast surgery cases, but it was only applied to the lymph nodes.[55, 56] Molina and colleagues[57] used the PET probe on three patients with a past history of breast cancer. All patients were intravenously injected with 10-12 mCi of FDG 3-4 hours prior to the procedure. The probe was able to accurately identify the

recurrent breast lesions in all three cases, but the study only used the probe for lesion localisation and not margin assessment.

The only study to examine primary breast tumours was undertaken by Piert and colleagues.[58] The study included one case of invasive ductal breast cancer. The patient was intravenously injected with 41.1 MBq of FDG and the probe was used 105 minutes after injection. The site of interest was identified by the PET probe, however the probe was only used for tumour localisation and not margin assessment. The study also concluded the performance of the probe depended on the uptake and metabolism of the injected radionuclide, the technical performance of the probe, the time between injection and using the probe and the size of the probe. They also concluded that the radiation burden to theatre staff is less that that associated with high-energy gamma probes.

A literature search did not identify any studies where the PET probe was used to assess surgical margins in breast cancer cases. The potential application of the PET probe in this context was identified as necessary for future research in three other articles not mentioned above.[59-61] Utilisation of a PET probe may allow more accurate delineation of normal from abnormal tissue and may accurately assess surgical margins, particularly in DCIS BCT. Further research is required on the suitability of FDG for DCIS, timing between injection and using the probe and suitable injection quantities.

3.8 Conclusion

This review systematically selected and analysed published literature on IMA methods in BCT for breast cancer. Different pathological IMA methods, specifically frozen section and touch smear or imprint cytology, reported high accuracy but they can add 20 to 30 minutes on operation time and thus are less appealing. Whilst the two studies reporting the use of ultrasound showed high accuracy, a third performed poorly. Whilst ultrasound can return results in a short time period compared to pathological assessment methods, it does not perform well where there is associated calcification or multifocal cancers. Further research, particularly using large samples, is required for the application of mammography, radiofrequency spectroscopy, and optical coherence tomography in IMA during BCT. The impact on intraoperative assessment methods in multifocal cancers also needs to be further explored. The PET probe is a novel device

with no research published in this area. Further research is required to determine its application in breast surgery.

3.8 References

1. National Breast Cancer Centre. The clinical management of ductal carcinoma in situ, lobular carcinoma in situ and atypical hyperplasia of the breast, 2003. Camperdown, NSW: National Breast Cancer Centre.
2. Kricker A, Armstrong B. Surgery and outcomes of ductal carcinoma in situ of the breast: a population-based study in Australia. European Journal of Cancer. 2004; 40(16):2396-2402.
3. Dillon MF, Mc Dermott EW, O'Doherty A, Quinn CM, Hill AD, O'Higgins N. Factors affecting successful breast conservation for ductal carcinoma in situ. Annals of Surgical Oncology. 2007; 14(5):1618-28.
4. Pinder SE. Ductal carcinoma in situ (DCIS): pathological features, differential diagnosis, prognostic factors and specimen evaluation. Modern Pathology. 2010; 23 Suppl 2:S8-13.
5. Silverstein MJ, Buchanan C. Ductal carcinoma in situ: USC/Van Nuys Prognostic Index and the impact of margin status. The Breast. 2003; 12(6):457-471.
6. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. International Journal of Surgery. 2010; 8(5):336-341.
7. STROBE Initiative. STROBE statement. 2013 [cited 31 May 2013]. Available from: http://www.strobe-statement.org/
8. Kim SHH, Cornacchi SD, Heller B, Farrokhyar F, Babra M, Lovrics PJ. An evaluation of intraoperative digital specimen mammography versus conventional specimen radiography for the excision of nonpalpable breast lesions. The American Journal of Surgery. 2013; 205(6):703-10.
9. Ramos M, Diaz JC, Ramos T, Ruano R, Aparicio M, Sancho M, et al. Ultrasound-guided excision combined with intraoperative assessment of gross macroscopic margins decreases the rate of reoperations for non-palpable invasive breast cancer. Breast. 2013; 22(4):520-524.
10. Rivera RJ, Holmes DR, Tafra L. Analysis of the impact of intraoperative margin assessment with adjunctive use of MarginProbe versus standard of care on tissue volume removed. International Journal of Surgical Oncology. 2012; 2012:868623.
11. Jorns JM, Visscher D, Sabel M, Breslin T, Healy P, Daignaut S, et al. Intraoperative frozen section analysis of margins in breast conserving surgery significantly decreases reoperative rates: one-year experience at an ambulatory surgical center. American Journal of Clinical Pathology. 2012; 138(5):657-669.
12. Sabel MS, Jorns JM, Wu A, Myers J, Newman LA, Breslin TM. Development of an intraoperative pathology consultation service at a free-standing ambulatory surgical center: clinical and economic impact for patients undergoing breast cancer surgery. The American Journal of Surgery. 2012; 204(1):66-77.
13. Thill M, Röder K, Diedrich K, Dittmer C. Intraoperative assessment of surgical margins during breast conserving surgery of ductal carcinoma in situ by use of radiofrequency spectroscopy. Breast. 2011; 20(6):579-580.

14. Olsha O, Shemesh D, Carmon M, Sibirsky O, Abu Dalo R, Rivkin L, et al. Resection margins in ultrasound-guided breast-conserving surgery. Annals of Surgical Oncology. 2011; 18(2):447-452.

15. Martin DT, Sandoval S, Ta CN, Ruidiaz ME, Cortes-Mateos MJ, Messmer D, et al. Quantitative automated image analysis system with automated debris filtering for the detection of breast carcinoma cells. Acta Cytologica. 2011; 55(3):271-280.

16. Doyle TE, Factor RE, Ellefson CL, Sorensen KM, Ambrose BJ, Goodrich JB, et al. High-frequency ultrasound for intraoperative margin assessments in breast conservation surgery: a feasibility study. BMC Cancer. 2011; 11:444.

17. Sumiyoshi K, Nohara T, Iwamoto M, Tanaka S, Kimura K, Takahashi Y, et al. Usefulness of intraoperative touch smear cytology in breast-conserving surgery. Experimental and Therapeutic Medicine. 2010; 1(4):641-645.

18. Nguyen FT, Zysk AM, Chaney EJ, Kotynek, JG, Oliphant UJ, Bellafiore FJ, et al. Intraoperative evaluation of breast tumor margins with optical coherence tomography. Cancer Research, 2009. 69(22): p. 8790-8796.

19. James TA, Harlow S, Sheehey-Jones J, Hart M, Gaspari C, Stanley M, et al. Intraoperative ultrasound versus mammographic needle localization for ductal carcinoma in situ. Annals of Surgical Oncology. 2009; 16(5):1164-1169.

20. Dener C, Inan A, Sen M, Demirci S. Interoperative frozen section for margin assessment in breast conserving energy. Scandinavian Journal of Surgery. 2009; 98(1):34-40.

21. Weber WP, Engelberger S, Viehl CT, Zanetti-Dallenbach R, Kuster S, Dirnhofer S, et al. Accuracy of frozen section analysis versus specimen radiography during breast-conserving surgery for nonpalpable lesions. World Journal of Surgery. 2008; 32(12):2599-2606.

22. Allweis TM, Kaufman Z, Lelcuk S, Pappo I, Karni T, Schneebaum S, et al. A prospective, randomized, controlled, multicenter study of a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. American Journal of Surgery. 2008; 196(4):483-489.

23. Paredes P, Vidal-Sicart S, Zanon G, Roe N, Rubi S, Lafuente S, et al. Radioguided occult lesion localisation in breast cancer using an intraoperative portable gamma camera: first results. European Journal of Nuclear Medicine and Molecular Imaging. 2008; 35(2):230-5.

24. Duarte GM, Cabello C, Torresan RZ, Alvarenga M, Telles GH, Bianchessi ST, et al. Radioguided Intraoperative Margins Evaluation (RIME): preliminary results of a new technique to aid breast cancer resection. European Journal of Surgical Oncology. 2007; 33(10):1150-7.

25. Karni T, Pappo I, Sandbank J, Lavon O, Kent V, Spector R, et al. A device for real-time, intraoperative margin assessment in breast-conservation surgery. American Journal of Surgery. 2007; 194(4):467-73.

26. Olson TP, Harter J, Muñoz A, Mahvi DM, Breslin T. Frozen section analysis for intraoperative margin assessment during breast-conserving surgery results in low rates of re-excision and local recurrence. Annals of Surgical Oncology. 2007; 14(10):2953-2960.

27. Cabioglu N, Hunt KK, Sahin AA, Kuerer HM, Babiera GV, Singletary SE, et al. Role for intraoperative margin assessment in patients undergoing breast-conserving surgery. Annals of Surgical Oncology. 2007; 14(4):1458-71.

28. Kaufman CS, Jacobson L, Bachman BA, Kaufman LB, Mahon C, Gambrell L-J, et al. Intraoperative digital specimen mammography: rapid, accurate results expedite surgery. Annals of Surgical Oncology. 2007; 14(4):1478-1485.

29. Fleming FJ, Hill ADK, Mc Dermott EW, O'Doherty A, O'Higgins NJ, Quinn CM. Intraoperative margin assessment and re-excision rate in breast conserving surgery. European Journal of Surgical Oncology. 2004; 30(3):233-237.

30. McCormick JT, Keleher AJ, Tikhomirov VB, Budway RJ, Caushaj PF. Analysis of the use of specimen mammography in breast conservation therapy. American Journal of Surgery. 2004; 188(4):433-436.

31. Chagpar A, Yen T, Sahin A, Hunt KK, Whitman GJ, Ames FC, et al. Intraoperative margin assessment reduces reexcision rates in patients with ductal carcinoma in situ treated with breast-conserving surgery. American Journal of Surgery. 2003; 186(4):371-377.

32. Rahusen FD, Bremers AJ, Fabry HF, J, van Amerongen AH, Boom RP, Meijers S, et al. Ultrasound-guided lumpectomy of nonpalpable breast cancer versus wire-guided resection: a randomized clinical trial. Annals of Surgical Oncology. 2002; 9(10):994-8.

33. Creager AJ, Shaw JA, Young PR, Geisinger KR. Intraoperative evaluation of lumpectomy margins by imprint cytology with histologic correlation: a community hospital experience. Archives of Pathology & Laboratory Medicine. 2002; 126(7):846-8.

34. Moore MM, Whitney LA, Cerilli L, Imbrie JZ, Bunch M, Simpson VB, et al. Intraoperative ultrasound is associated with clear lumpectomy margins for palpable infiltrating ductal breast cancer. Annals of Surgery. 2001; 233(6):761-768.

35. Australian Institute of Health and Welfare & Australasian Association of Cancer Registries. Cancer in Australia: an overview, 2012 Issue Cat. no. CAN 70, 2012. Canberra: AIHW.

36. Australian Institute of Health and Welfare & Cancer Australia. Breast cancer in Australia: an overview Issue Cat. no. CAN 67, 2012. Canberra: AIHW.

37. Morrow M, O'Sullivan MJ. The dilemma of DCIS. The Breast. 2007; 16(Supplement 2):59-62.

38. Sakorafas GH, Farley DR. Optimal management of ductal carcinoma in situ of the breast. Surgical Oncology. 2003; 12(4):221-40.

39. Hughes LL, Wang M, Page DL, Gray R, Solin LJ, Davidson NE, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. Journal of Clinical Oncology. 2009; 27(32):5319-24.

40. Huston TL, Simmons RM. Locally recurrent breast cancer after conservation therapy. American Journal of Surgery. 2005; 189(2):229-35.

41. Sigal-Zafrani B, Lewis JS, Clough KB, Vincent-Salomon A, Fourquet A, Meunier M, et al. Histological margin assessment for breast ductal carcinoma in situ: precision and implications. Modern Pathology. 2004; 17(1):81-8.

42. Cendan JC, Coco D, Copeland EM, 3rd. Accuracy of intraoperative frozen-section analysis of breast cancer lumpectomy-bed margins. Journal of the American College of Surgeons. 2005; 201(2):194-8.

43. Esbona K, Li Z, Wilke LG. Intraoperative imprint cytology and frozen section pathology for margin assessment in breast conservation surgery: a systematic review. Annals of Surgical Oncology. 2012; 19(10):3236-3245.

44. Klimberg VS, Harms S, Korourian S. Assessing margin status. Surgical Oncology. 1999; 8(2):77-84.

45. D'Halluin F, Tas P, Rouquette S, Bendavid C, Foucher F, Meshba H, et al. Intra-operative touch preparation cytology following lumpectomy for breast cancer: a series of 400 procedures. Breast. 2009; 18(4):248-53.

46. Jeong JW, Shin DC, Do SH, Blanco C, Klipfel NE, Holmes DR, et al. Differentiation of cancerous lesions in excised human breast specimens using multiband attenuation profiles from ultrasonic transmission tomography. Journal of Ultrasound in Medicine. 2008; 27(3):435-51.

47. Thill M. MarginProbe(®): intraoperative margin assessment during breast conserving surgery by using radiofrequency spectroscopy. Expert Review of Medical Devices. 2013; 10(3):301-315.

48. Curatolo A, McLaughlin RA, Quirk BC, Kirk RW, Bourke AG, Wood BA, et al., Ultrasound-guided optical coherence tomography needle probe for the assessment of breast cancer tumor margins. American Journal of Roentgenology, 2012. 199(4): p. W520-W522.

49. Boppart, S.A, Luo, W, Marks, DL, Singletary, KW. Optical coherence tomography: feasibility for basic research and image-guided surgery of breast cancer. Breast Cancer Research and Treatment, 2004. 84(2): p. 85-97.

50. Essner R, Daghighian F, Giuliano AE. Advances in FDG PET probes in surgical oncology. Cancer J. 2002; 8(2):100-8.

51. Daghighian F, Mazziotta JC, Hoffman EJ, Shenderov P, Eshaghian B, Siegel S, et al. Intraoperative beta probe: a device for detecting tissue labeled with positron or electron emitting isotopes during surgery. Med Phys. 1994; 21(1):153-7.

52. Raylman RR, Fisher SJ, Brown RS, Ethier SP, Wahl RL. Fluorine-18-fluorodeoxyglucose-guided breast cancer surgery with a positron-sensitive probe: validation in preclinical studies. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 1995; 36(10):1869-1874.

53. Strong VE, Galanis CJ, Riedl CC, Longo VA, Daghighian F, Humm JL, et al. Portable PET probes are a novel tool for intraoperative localization of tumor deposits. Annals of Surgical Innovation and Research. 2009; 3:2-2.

54. Essner R, Hsueh EC, Haigh PI, Glass EC, Huynh Y, Daghighian F. Application of an [18F]Fluorodeoxyglucose-Sensitive Probe for the Intraoperative Detection of Malignancy. Journal of Surgical Research. 2001; 96(1):120-126.

55. Gulec SA, Hoenie E, Hostetter R, Schwartzentruber D. PET probe-guided surgery: applications and clinical protocol. World J Surg Oncol. 2007; 5:65.

56. Gulec SA, Daghighian F, Essner R. PET-Probe: evaluation of technical performance and clinical utility of a handheld high-energy gamma probe in

oncologic surgery. Annals of Surgical Oncology. 2006. July 24 (e-pub http://www.ncbi.nlm.nih.gov/pubmed/16865592).

57. Molina MA, Goodwin WJ, Moffat FL, Serafini AN, Sfakianakis GN, Avisar E. Intra-operative use of PET probe for localization of FDG avid lesions. Cancer Imaging. 2009; 9:59-62.

58. Piert M, Burian M, Meisetschläger G, Stein H, Ziegler S, Nährig J, et al. Positron detection for the intraoperative localisation of cancer deposits. European Journal of Nuclear Medicine and Molecular Imaging. 2007; 34(10):1534-1544.

59. Wahl RL. Current status of PET in breast cancer imaging, staging, and therapy. Semin Roentgenol. 2001; 36(3):250-60.

60. Pleijhuis RG, Graafland M, de Vries J, Bart J, de Jong JS, van Dam GM. Obtaining adequate surgical margins in breast-conserving therapy for patients with early-stage breast cancer: current modalities and future directions. Ann Surg Oncol. 2009; 16(10):2717-30.

61. Ravi A, Reilly RM, Holloway CM, Caldwell CB. Feasibility evaluation of radioimmunoguided surgery of breast cancer. Int J Mol Imaging. 2012; 2012:545034.

CHAPTER 4 EPIDEMIOLOGY OF DUCTAL CARCINOMA IN SITU IN WESTERN AUSTRALIA 1996 - 2005

4.1 Introduction

Before attempting to implement an intraoperative margin assessment (IMA) technology to improve the clinical outcomes for women diagnosed with ductal carcinoma in situ (DCIS), it is essential to identify the current status of DCIS in Western Australia (WA). In March 2010 the Australian Institute of Health and Welfare (AIHW) published a report examining the characteristics of Australian women diagnosed with DCIS between 1995 and 2005, including data from BreastScreen Australia for 1996 to 2005.[1] The purpose of this chapter was to compare the WA data against the national results, and to supplement with information available in WA that was not reported in the national report. The objectives of this epidemiological study were to: (1) identify the characteristics of women who have been diagnosed with DCIS in WA between January 1996 and December 2005; (2) determine the rate of second operations and breast cancer events (BCE) (recurrence or invasion) in the study population; and (3) identify risk factors for a breast cancer event in the study population.

4.2 Abbreviations

Below is a list of abbreviations used in this chapter:

AIHW	Australian Institute of Health and Welfare
ASR	age-standardised incidence rate
BCE	breast cancer event
BCT	breast conserving therapy
CI	confidence interval
CIS	carcinoma in situ
DCIS	ductal carcinoma in situ
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
IMA	intraoperative margin assessment
Int.	intermediate
No.	number
NOS	not otherwise specified
OR	odds ratio

RR	relative risk
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
WA	Western Australia

4.3 Methods

Ethical approval from the Human Research Ethics Committee, Curtin University (Appendix B) was sought before the Confidentiality of Health Information Committee for the Department of Health, WA, approved the release of the data for this epidemiological study. De-identified data were extracted from the Cancer Registry of WA and the Hospital Morbidity Database for WA, and provided in two separate Microsoft Excel spreadsheets linked by a cancer registry number. Cases where the first diagnosis in WA between 1 January 1996 and 31 December 2005 with *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification* (ICD-10-AM) classification codes "C50.x" or "D50.x" (breast) and morphology code with a tumour behaviour "/2" were selected. The Cancer Registry of WA did not have complete cases for DCIS until after 1995, which is why the start date is 1996, and examines a ten year period. Data was selected until 2005 to match the national dataset and to allow data collection for a minimum 5 year follow-up (status as of 31 December 2010). Cases were then selected based on the reported morphology. All cancer registries in Australia use a 'four month rule' whereby any record with a diagnosis of DCIS that had a subsequent diagnosis of invasive breast cancer within four months was discarded.[1]

4.3.1 Extracted variables

Extracted variables included:

- Initial diagnosis and subsequent (related) diagnoses,
- Age at time of diagnosis,
- Indigenous status,
- Date and basis of diagnosis,
- Site, morphology, behaviour and grade,
- Surgical method/procedures during admission/s,
- Surgical length of stay,
- Second operation to obtain adequate margins for primary DCIS,
- Breast cancer events (BCE), specifically recurrence and invasion, including date, site, morphology, behaviour, grade and treatment,
- Other treatment data, specifically chemotherapy and radiotherapy,
- Date and cause of death.

4.3.2 Data analysis

The data was cleaned and cross-matched to create one spreadsheet containing the data from the two different databases. This data was then analysed using Statistical Package for the Social Sciences (SPSS) version 21. Incidence means, distribution and frequency were estimated. The probability of developing invasive breast cancer following DCIS was calculated by the Kaplan-Meier method. Odds ratios of a BCE, and specifically invasion, were calculated using a multivariate logistic regression analysis, including variables of age group, grade, first operation type, if a second operation (re-excision) occurred and type, and radiotherapy use.

4.4 Epidemiology of ductal carcinoma in situ in Western Australia

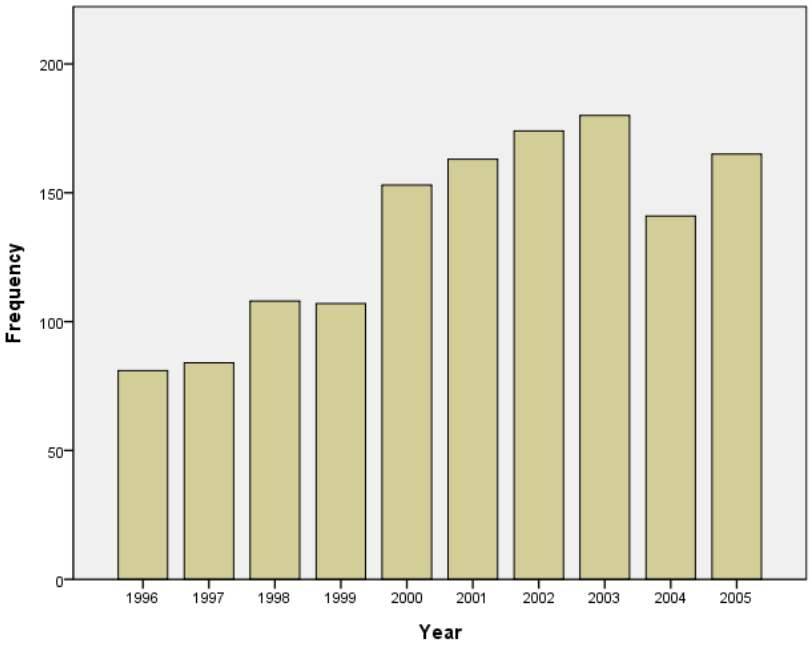
4.4.1 Incidence

Between January 1996 and December 2005 there were 1,356 new DCIS cases diagnosed in WA. The peak increase in incidence rate occurred in 2003 but the largest percentage increase from the previous year was seen in 2000, as shown in Table 4.1 and Figure 4.1. There was an incidence increase on average of 9.6% per year.

Table 4.1: Incidence by year of primary ductal carcinoma in situ, Western Australia 1996 – 2005

Year	Incidence	Percentage of total cohort	Percentage increase from previous year
1996	81	6.0%	
1997	84	6.2%	3.70%
1998	108	8.0%	28.57%
1999	107	7.9%	-0.93%
2000	153	11.3%	42.99%
2001	163	12.0%	6.54%
2002	174	12.8%	6.75%
2003	180	13.3%	3.45%
2004	141	10.4%	-21.67%
2005	165	12.2%	17.02%

Figure 4.1: Incidence by year of primary ductal carcinoma in situ, Western Australia 1996 – 2005



4.4.2 Age and age-standardised incidence rate

The average age at time of diagnosis for primary DCIS was 58.13 years (95% confidence interval [CI] 57.55, 58.72, standard deviation [SD] 10.93). The range was 20.0 to 95.7 years with a normal distribution (Shapiro-Wilk p=0.000). Figure 4.2 shows the distribution of age in the study population.

Figure 4.2: Distribution of age of primary ductal carcinoma in situ, Western Australia 1996 – 2005

The incidence varied noticeably by age. When examined by age group, the highest number of cases were reported in the 50-59 years, followed by 60-69 years, in every year except 2001 (Table 4.2). These two age groups accounted for more than half of cases each year, with 71.08% (118/166 cases) of cases diagnosed in 2005 aged between 50-69 years.

Table 4.2: Crude incidence by age group of primary ductal carcinoma in situ, Western Australia 1996 – 2005

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	Total
<40	8	5	5	3	4	2	6	8	2	6	49
40 - 49	19	19	18	30	24	34	30	24	25	26	249
50 - 59	23	30	40	40	65	52	57	68	57	66	498
60 - 69	21	21	28	21	40	53	54	59	34	52	383
70 - 79	8	9	10	7	15	18	24	18	15	9	133
≥80	2	0	6	6	5	3	3	4	8	7	44
Total	81	84	107	107	153	162	174	181	141	166	1356

In 2005 the *age-standardised incidence rate* (ASR) was 15.4 cases per 100,000 females, as shown in Table 4.3. Between 1996 and 2005 the ASR increased on average by 5.4%, but in the age groups 50-59 years and 60-69 years the ASR increased by 26.2% and 21.3%, respectively. Figure 4.3 graphically represents the age-standardised rate by year

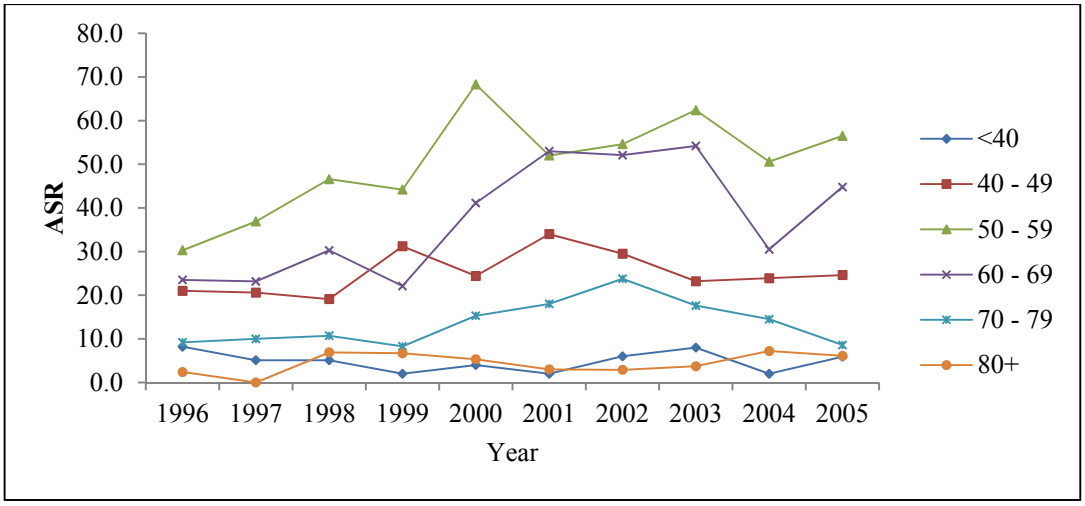
and age group, showing the increase in incidence in the 50-59 years, followed by 60-69 years age group.

Table 4.3: Age-standardised incidence rate of ductal carcinoma in situ, Western Australia 1996 – 2005.

	Age (years)						
	<40	40 - 49	50 - 59	60 - 69	70 - 79	≥80	ASR[(a)]
1996	8.2	21.0	30.3	23.5	9.2	2.4	10.0
1997	5.1	20.6	36.9	23.2	10.0	0.0	10.1
1998	5.1	19.1	46.6	30.3	10.7	6.9	12.5
1999	2.0	31.2	44.2	22.1	8.3	6.7	12.1
2000	4.0	24.4	68.3	41.1	15.3	5.3	16.7
2001	2.0	34.0	52.0	53.0	18.0	3.0	17.1
2002	6.0	29.5	54.6	52.1	23.8	2.9	17.8
2003	8.0	23.2	62.4	54.2	17.6	3.7	17.8
2004	2.0	23.9	50.6	30.5	14.5	7.2	13.6
2005	5.9	24.6	56.5	44.8	8.6	6.1	15.4

(a) Age-standardised incidence rate (ASR). Rates are age-standardised to the Western Australian population at 30 June 2001 and expressed per 100,000 women per year.

Figure 4.3: Age-standardised incidence rate (ASR) by year, age group of primary ductal carcinoma in situ, Western Australia 1996 – 2005



4.4.3 Patient characteristics

Table 4.4 summarises the patient characteristics of DCIS in WA. Only 18/1356 (1.3%) of cases reported they were Aboriginal or Torres Strait Islander. The majority (1298/1356; 95.72%) of cases were diagnosed by histology, with 50/1356 (3.69%) diagnosed by cytology. Whilst more than a third of cases (37.02%) did not specify the site of DCIS, 380/1356 (28.02%) were located in the upper-outer quadrant of the breast.

This percentage was larger than the percentages for the other areas of the breast, albeit statistically non-significant.

With respect to the lateral site of the tumour the side of the breast was approximately evenly distributed between left and right: 50.66% left compared to 45.98% right, 0.15% bilateral and 3.24% not reported. Data was not available for the grade of the DCIS for nearly half the cases (46.09%), but 411/1356 (30.31%) of cases were classified high grade (poorly differentiated), and 208/1356 (15.34%) of cases were classified intermediate grade (moderately differentiated). The majority of cases (94.40%) were classified as intraductal carcinoma noninfiltrating [morphology code 8500].

Table 4.4: Patient characteristics of primary ductal carcinoma in situ, Western Australia 1996 – 2005

		Total	%
Race	Indigenous Australian	18	1.3
	Non-Indigenous	1338	98.7
Basis for diagnosis	Histopathology	1298	95.72
	Cytology	50	3.69
	Not reported	8	0.59
Site of DCIS	Central portion of breast [C501]	62	4.57
	Upper-inner quadrant [C502]	104	7.67
	Lower-inner quadrant [C503]	76	5.60
	Upper-outer quadrant [C504]	380	28.02
	Lower-outer quadrant [C505]	78	5.75
	Other [C500 or C506]	31	2.28
	Overlapping lesion [C508]	123	9.07
	Unspecified [C509]	502	37.02
Lateral	Left breast	687	50.66
	Right breast	623	45.98
	Bilateral	2	0.15
	Not reported	44	3.24
Grade	1 - Low / Well differentiated	109	8.04
	2 - Int. / Moderately differentiated	208	15.34
	3 - High / Poorly differentiated	411	30.31
	4 - Anaplastic / Undifferentiated'	3	0.22
	9 - Not determined / not stated	625	46.09
Morphology (Behaviour = 2 [in situ])	CIS NOS [8010]	4	0.29
	Cribriform CIS [8201]	10	0.74
	DCIS, solid type [8230]	21	1.55
	Intraductal carcinoma, noninfiltrating NOS [8500]	1280	94.40
	Comedocarcinoma, noninfiltrating [8501]	31	2.29
	Noninfiltrating intraductal papillary adenocarcinoma [8503]	9	0.66
	Noninfiltrating intracystic carcinoma [8504]	1	0.07

%, percentage; CIS, Carcinoma in situ; DCIS, ductal carcinoma in situ; Int., intermediate; NOS, not otherwise specified.

Surgical length of stay data was available for 282 patients, ranging from same day to 9 days, with a mean 2.11 days (95% CI: 1.81, 2.41; SD 2.54) including same day cases, and a mean 3.20 days (95% CI: 2.67, 3.74; SD 3.22) excluding same day cases. Nearly half (140/282) of the cases were same day procedures for treatment of a primary DCIS diagnosis.

4.4.4 Primary operation type and other treatment

Operation type for the surgical treatment of primary DCIS was available for 287 patients, with the remaining cases not reported in the data provided. Breast conserving therapy (BCT) was the most common procedure used for surgical treatment of primary DCIS, with 206/287 (71.8%) of patients treated by this method. Table 4.5 shows the frequency and percentage of surgical methods. A quarter of patients (70/287; 24.4%) elected to undergo mastectomy. Of these, where the nuclear grade was available (43 patients), 31/43 (72.09%) were high grade DCIS, with 11/43 (25.58%) intermediate grade and 1/43 (2.32%) low grade.

A third of patients (469/1356; 34.59%) underwent radiotherapy following surgery. Of these, where the nuclear grade was reported (286 patients), 205/286 (71.68%) of cases were high grade DCIS, 64/286 (22.38%) of cases were classified intermediate grade and 17/286 (5.94%) of cases were low grade. There was only one reported case of chemotherapy following surgery for primary DCIS. This patient underwent BCT and radiotherapy, but the grade was not specified.

Table 4.5: Surgery method for treatment, with histological grade, of primary ductal carcinoma in situ, Western Australia 1996 – 2005

Surgery type	Frequency	Grade	Number	Overall Percentage
Biopsy	11	**1**	6	3.8%
		2	1	
		3	1	
		NS	3	
Breast Conserving Therapy	206	**1**	22	71.8%
		2	35	
		3	70	
		NS	79	
Mastectomy	70	**1**	1	24.4%
		2	11	
		3	31	
		NS	27	

NS, not specified.

4.4.5 Second operation

Following surgery for primary DCIS, 245/1356 (18.07%) of patients required a second operation within six weeks of the initial surgery to obtain adequate margins. Of these, where the nuclear grade was reported (188 patients), 173/188 (92.02%) were high grade (poorly differentiated) DCIS, 13/188 (6.91%) of cases were classified intermediate grade (moderately differentiated) and 2/188 (1.06%) of cases were low or well differentiated. Without the full dataset for primary surgery type it is difficult to obtain statistics of the frequency of second operations following BCT.

4.4.6 Breast cancer events

There were 235/1356 (17.30%) cases reporting a recurrence of DCIS and/or invasion (defined as a BCE) by the 31 December 2010. Of the BCEs 86/1356 (6.34%) of all cases reported a recurrence of DCIS, and 159/1356 (11.72%) of all cases reported invasion, including ten cases that reported invasion following recurrence. The mean follow-up time was 9.44 years (95% CI 9.30-9.59; SD 2.80) and median time was 9.18 years.

BCEs after DCIS diagnosis occurred between 5 months and 14 years and 4 months, with a mean BCE time of 5 years and 3 months (5.23) (95% CI: 4.79-5.67; SD 3.42). The average time since diagnosis of DCIS for recurrence was 4.64 (95% CI 3.92-5.35; SD 3.32) and invasion was 5.36 (95% CI 4.82-5.90; SD 3.45).

The probability of a woman in WA following the diagnosis of DCIS having a BCE is 4.36% (95% CI 4.26-4.46) within 5 years and 8.27% (95% CI 8.08-8.46) within 10 years. The probability of a woman in WA following the diagnosis of DCIS having a diagnosis of invasive breast cancer is 4.55% (95% CI 4.46-4.64) within 5 years and 8.78% (95% CI 8.60-8.96) within 10 years. Figures 4.4 and 4.5 show the increase in probability of a BCE (Figure 4.4) or invasion (Figure 4.5) following a diagnosis of DCIS. Data for patients between 5 to 10 years following diagnosis was only available for 532 (39.23%) patients in the cohort, which may explain the lag observed in Figures 4.4 and 4.5

Figure 4.4: Probability of having a breast cancer event (recurrence or invasion) following diagnosis of ductal carcinoma in situ, Western Australia, 1996 – 2005.

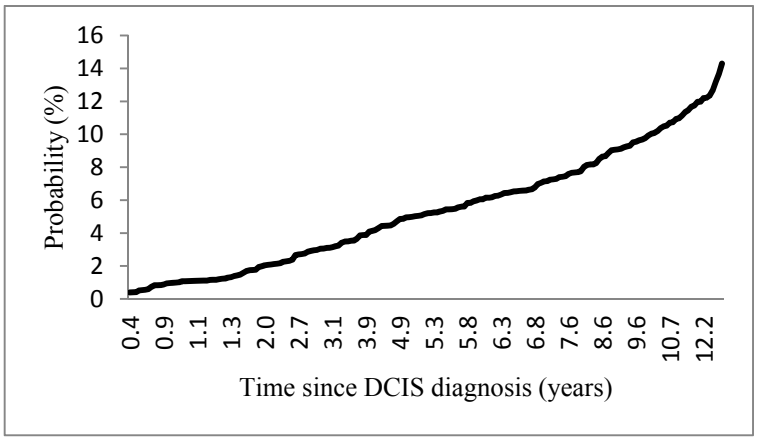
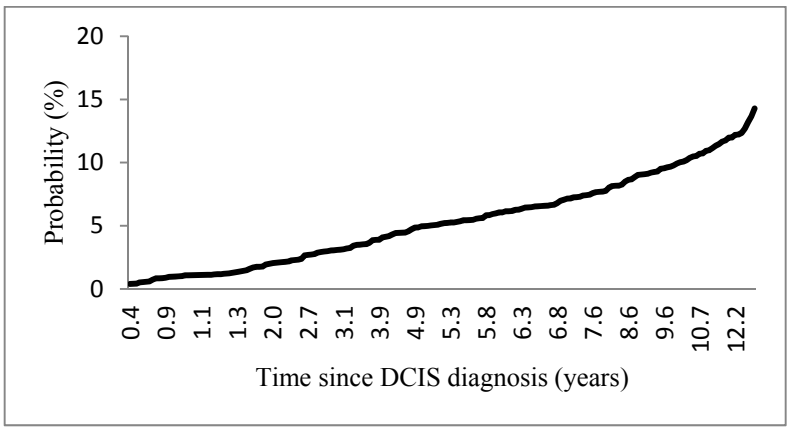


Figure 4.5: Probability of having invasive breast cancer following diagnosis of ductal carcinoma in situ, Western Australia, 1996 – 2005.



4.4.7 Risk factors for a breast cancer event

Known risk factors of age, histological grade, type of primary surgery, whether a second operation was performed to ensure adequate margins, type of second operation performed and the use of radiotherapy were analysed to identify if they were risk factors for a BCE in this study population. There was an increased risk in women under 40 years of age having a subsequent BCE, and specifically invasion, with an adjusted odds ratio (OR) for a BCE of 8.86 ($p<0.001$; 95% CI 4.85-16.19), and an adjusted OR for invasion of 5.45 ($p<0.001$; 95% CI 2.99-9.93). There was also an increased risk in women with grade 3 DCIS having a subsequent BCE, and specifically invasion, with an adjusted OR for a BCE of 1.34 ($p=0.058$; 95% CI 1.00-1.81), and 1.42 ($p=0.049$; 95% CI 1.00-2.01) for invasion.

There was a statistically significant adjusted OR of 16.28 (p<0.001; 95% CI 4.26-62.14) of a BCE where biopsy alone was used instead of excision on the primary DCIS. This was not statistically significant for invasion, with the adjusted OR 2.05 (p=0.363; 95% CI 0.44-9.62), largely due to the small number of cases which underwent biopsy alone. When the data was examined for the difference in risk for excision compared to mastectomy, the difference was not significant (p=0.090).

There was a 9.85-fold (p<0.001; 95% CI 4.94-19.63) increased risk for a BCE in patients who did not have a second operation to excise the primary DCIS, and 7.08-fold (p<0.001; 95% CI 3.47-14.47) increased risk for invasion. The risk of a BCE was decreased for those who had an excision alone for their second operation, however the small sample size must be acknowledged and the increased frequency of high grade DCIS in those who underwent mastectomy compared to low or intermediate grade for those who only had re-excision. There is an increased risk for those who did not undergo postoperative radiotherapy for a BCE (p=0.049) and specifically invasion (p=0.043). Tables 4.6 and 4.7 displays the crude and adjusted ORs for BCEs and specifically invasion.

Table 4.6: Odds ratio for breast cancer event for risk factors in women diagnosed primary ductal carcinoma in situ, Western Australia 1996 – 2005

Risk factor		BCE No. (%)	No BCE No. (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	p*
Age (years) (No.=1356)	< 40	31 (13.2)	18 (1.6)	9.35 (5.13 – 17.03)	8.86 (4.85 – 16.19)	<0.001
	≥ 40	204 (86.8)	1103 (98.4)	1.00	1.00	
Grade (No.=729)	3	73 (55.3)	339 (56.8)	1.46 (1.09 – 1.95)	1.34 (1.00 – 1.81)	0.058
	1 or 2	59 (44.7)	258 (43.2)	1.00	1.00	
Primary surgical type (No.=287)	Biopsy alone	8 (16.7)	3 (1.3)	15.73 (4.00 – 61.83)	16.28 (4.26 – 62.14)	<0.001
	Excision or mastectomy	40 (83.3)	236 (98.7)	1.00	1.00	
Second operation (No.=1356)	No second operation	219 (93.2)	892 (79.6)	3.51 (2.07 – 5.96)	9.85 (4.94 – 19.63)	<0.001
	Second operation	16 (6.8)	229 (20.4)	1.00	1.00	
Second operation type (No.=244)	Re-excision	11 (68.8)	167 (73.2)	0.28 (0.15 – 0.53)	0.86 (0.04 – 0.20)	<0.001
	Mastectomy	5 (31.3)	61 (26.8)	1.00	1.00	
Radiotherapy (No.=1356)	No radiotherapy	167 (71.1)	720 (64.2)	1.37 (1.01 – 1.86)	1.38 (1.00 – 1.90)	0.049
	Radiotherapy	68 (28.9)	401 (35.8)	1.00	1.00	

* Adjusted for age and grade

BCE, breast cancer event; CI, confidence interval; No., number; OR, odds ratio.

Table 4.7: Odds ratio for invasive breast cancer following for risk factors in women diagnosed primary ductal carcinoma in situ, Western Australia 1996 – 2005

Risk factor		Invasion No. (%)	No Invasion No. (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	p*
Age (years) (No.=1356)	< 40	20 (12.6)	29 (2.4)	5.79 (3.19 – 10.52)	5.45 (2.99 – 9.93)	<0.001
	≥ 40	139 (87.4)	1168 (97.6)	1.00	1.00	
Grade (No.=729)	3	50 (58.8)	362 (56.2)	1.53 (1.09 – 2.15)	1.42 (1.00 – 2.01)	0.049
	1 or 2	35 (41.2)	282 (43.8)	1.00	1.00	
Primary surgical type (No.=287)	Biopsy alone	2 (6.7)	9 (3.5)	1.68 (0.36 – 7.85)	2.05 (0.44 – 9.62)	0.363
	Excision or mastectomy	28 (93.3)	248 (96.5)	1.00	1.00	
Second operation (No.=1356)	No second operation	149 (93.7)	962 (80.4)	3.64 (1.89 – 7.01)	7.08 (3.47 – 14.47)	<0.001
	Second operation	10 (6.3)	235 (19.6)	1.00	1.00	
Second operation type (No.=244)	Re-excision	7 (70.0)	171 (73.1)	0.28 (0.13 – 0.60)	0.14 (0.06 – 0.31)	<0.001
	Mastectomy	3 (30.0)	63 (26.9)	1.00	1.00	
Radiotherapy (No.=1356)	No radiotherapy	115 (72.3)	772 (64.5)	1.44 (1.00 – 2.08)	1.48 (1.01 – 2.17)	0.043
	Radiotherapy	44 (27.7)	425 (35.5)	1.00	1.00	

* Adjusted for age and grade

CI, confidence interval; No., number; OR, odds ratio.

4.4.8 Mortality

There were 76 patients reported as deceased by 31 December 2010, with cause of death outlined in Table 4.8. Of these ten recorded the cause of death as breast cancer. Therefore there was a 0.74% mortality rate in this study group. Of the ten deceased patient, nine developed invasive ductal breast cancer in the ipsilateral (same) breast as the primary DCIS. The tenth patient developed invasive lobular breast cancer in the ipsilateral (same) breast. Of the other 66 patients who died of other causes, only one case had a reported recurrence (with a cause of death as colorectal cancer), and one had invasive breast cancer (with a cause of death as ovarian cancer).

The time between diagnosis of DCIS and death due to breast cancer was documented for six of the ten patients, ranging from 4.2 years to 5 years, with a mean of 4.48 (SD 0.37) years.

Table 4.8: Cause of death in women diagnosed with primary ductal carcinoma in situ, Western Australia 1996 – 2005

Cause of death	Frequency	Proportion (%)
Malignant neoplasms of breast	10	13.16
Cardiovascular disorders	20	26.32
Malignant neoplasms of digestive organs	8	10.53
Malignant neoplasms of female genital organs	5	6.58
Malignant cancer other	4	5.26
Lung	3	3.95
Non-Hodgkin lymphoma	3	3.95
Malignant neoplasms of urinary tract	2	2.63
Malignant neoplasms of brain	2	2.63
Malignant myeloma	2	2.63
Digestive disorders (not malignant)	2	2.63
Genitourinary disorders	2	2.63
Pneumonia	1	1.32
Not reported	12	15.79
Total	76	100

4.5 Comparison with national data

The purpose of this section was to compare characteristics of DCIS in the WA context against those reported by the AIHW.[1] The national data examined an eleven year period, but Cancer Registry WA data was incomplete for DCIS until after 1995 so only 1995 to 2005 data, which matches the national BreastScreen data timeframe, was examined. The AIHW reported that complete national data for DCIS was not available until 1997, which may explain some differences between the WA and national data for the first two years of our cohort.[2] The WA cohort represented 10.49% of the total national incidence rate during 1996 to 2005. The variations in incidence between years were not the same between WA and nationally, as shows in Table 4.9. The variations by year could not be explained by differences in breast screening, by year, as shown by Table 4.10, however it is acknowledged this is data for BreastScreen WA only and there may have been an increase in mammography use in private services. There was only a 5.67% increase in breast screening through BreastScreen WA during the study period, following the national implementation of the screening program in 1991. Whilst the WA cohort demonstrated an increase in incidence by an average of 9.60% per year, the national cohort only had an incidence increase by average of 7.51% per year.

Table 4.9: Comparison of difference in percentage increase of ductal carcinoma in situ between Western Australia and national data, 1996 - 2005

Year	Percentage increase from previous year	
	Western Australia	National[2]
1997	3.70%	25.24%
1998	28.57%	13.15%
1999	-0.93%	1.78%
2000	42.99%	9.08%
2001	6.54%	10.54%
2002	6.75%	-3.94%
2003	3.45%	3.31%
2004	-21.67%	6.69%
2005	17.02%	1.70%

Table 4.10: Number of women aged 50-69 participating in BreastScreen (Western Australia), 1996-1997 to 2005-2006 (adapted from BreastScreen Australia[3])

Year	Participants[a]	Population[b]	Percentage participating	Percentage increase from previous year
1996 – 1997	845,143	1,645,331	51.37	
1997 – 1998	927,735	1,700,951	54.54	9.77
1998 – 1999	976,182	1,754,254	55.65	5.22
1999 – 2000	1,012,184	1,809,735	55.93	3.69
2000 – 2001	1,064,246	1,868,832	56.95	5.14
2001 – 2002	1,102,642	1,928,878	57.16	3.61
2002 - 2003	1,118,823	1,989,802	56.23	1.47
2003 – 2004	1,144,008	2,051,480	55.77	2.25
2004 – 2005	1,188,955	2,114,036	56.24	3.93
2005 - 2006	1,242,210	2,177,660	57.04	4.48

(a) Participants are the number of women screened through BreastScreen Australia in each 2-year reporting period. The screening periods cover 1 January of the initial year to 31 December of the latter year indicated.

(b) Population is the average of the ABS estimated resident population for women aged 50-69 for the two reporting years

The WA cohort also varied from the national reporting by age. Both cohorts reported low incidence in women under 40 years of age and over 80 years. The national study found the highest incidence in the age group 60-69 years, whereas the WA cohort has the highest incidence in the age group 50-59 years, followed by 60-69 years. The ASR was similar between cohorts except between 2000-2003 when it was higher in WA, as shown in Table 4.11. This is in line with the increase in incidence seen in WA in 2000 but again cannot be explained by breast screening in WA.

Table 4.11: Age-standardised incidence rate of ductal carcinoma in situ in females, Western Australia 1996 – 2005

Year	Age-standardised rate[(a)]	
	Western Australia	National[2]
1996	10.0	10.4
1997	10.1	11.7
1998	12.5	12.8
1999	12.1	12.8
2000	16.7	13.6
2001	17.1	14.7
2002	17.8	13.8
2003	17.8	13.9
2004	13.6	14.5
2005	15.4	14.4

a) Rates are age-standardised to the Western Australian population at 30 June 2001 and expressed per 100,000 women

The probability of having a BCE (recurrence or invasion) following DCIS was not reported in the national data, but the probability of invasion was reported. The WA cohort was only slightly lower than the national cohort, with the five year probability of 4.36% versus 5.30% and ten year probability of 8.27% versus 10.90% in the WA and national cohort, respectively. Whilst cases in WA were tracked and matched by the Cancer Registry as patients move between local health providers, some cases were lost to follow-up if they moved interstate, a limitation not applicable to the national data. The WA cohort also had a smaller sample size which may also explain the difference.

As population data for invasive breast cancer was not available, the overall relative risk (RR) of a woman diagnosed with DCIS developing invasive breast cancer could not be calculated. As with the national study, there was a significant ($p<0.001$) increase in risk of a BCE, and specifically invasion, for women under 40 years. The national study did not examine other risk factors.

4.6 Discussion

A number of countries have published data on the incidence of DCIS. A study in the Netherlands examined newly diagnosed DCIS cases reported between January 1989 and December 2003.[4] In a population of 800 women, they reported 77% of cases underwent BCT for initial surgery, compared to 23% mastectomy. Over half (54%) of the cases were grade 3. Of patients treated with BCT, 40% also received radiotherapy. A study in Canada examined all cases between 1991 to 2000 newly diagnosed through the Ontario

Breast Screening Program.[5] The study examined 727 patients, where 26.3% were treated by mastectomy compared to 73.7% treated with BCT. 23.1% of patients had grade 3 DCIS. Nearly half (49.43%) of the patients treated with BCT also received radiotherapy. An Australian study of all new DCIS cases in 1995 reported 55% of the 415 women were grade 3.[6] Two-thirds (62%) of patients underwent BCT compared to 23% mastectomy. The study surveyed surgeons on reasons for DCIS management decisions and reported 40% of surgeons did not consider radiotherapy as they did not use radiotherapy for DCIS. Only 22% of patients were referred for radiotherapy consultation.

There was an increase in incidence seen in WA in 2000. Literature identifying any difference in pathology reporting could not be identified. This increase may be explained by an improvement in the detection and interpretation by mammography of DCIS given it is within a decade of introduction in WA, an unreported change in pathology reporting or methods for DCIS biopsy, and the smaller increase in mammography use and DCIS incidence in the year prior. An increase in incidence was reported in New South Wales from 1995 to 2000 which was attributed to the introduction of mammography, as was the increase experienced in the Netherlands.[7, 8] An Australian study reported that only half of all DCIS tumours diagnosed in Australia in 1995 were detected through the BreastScreen program so there may have been an increase in mammography use through other providers.[6] The WA cohort also reported an increase in DCIS diagnosis in women 50-69 years during 2000, so an alternative hypothesis is an increase in promotion of mammography to this population prior to 2000 led to an increase in women seeking mammography screening.

Age and grade has been positively associated widely in the literature with a BCE following the diagnosis of DCIS.[9-11] Our study identified there was an 8-fold increased risk for women under 40 years, relative to those over 40 years, to have a subsequent BCE, and 5-fold increased risk where the DCIS was grade 3, relative to grade 1 and grade 2 DCIS.

Given the reported association between DCIS site and site of subsequent BCEs, the need to ensure adequate margins is essential.[12-18] This study identified an increased risk of a subsequent BCE ($p<0.001$), and specifically invasion ($p<0.001$), where a second operation was not performed. Although the WA cohort reported 18.07% of cases

underwent a second operation, which is lower than that reported in the literature, the significant finding suggests under the WA protocol sufficient margins may not be taken during the primary surgery and residual DCIS is remaining in the breast.

The debate around the use of mastectomy for non-invasive breast cancer continues to be reported in the literature. Whilst a lower BCE rate is seen in those who undergo mastectomy, it is viewed by some as overtreatment.[12,19-23] Although in the WA cohort there was a statistically significant increase in risk of a BCE ($p<0.000$) following biopsy alone, the risk was not significant for invasion ($p=0.363$) nor for excision versus mastectomy ($p=0.090$). Only 11 patients in the cohort underwent biopsy alone.

The findings in the WA cohort matched that reported in the literature with regards to the use of radiotherapy following surgery. The risk of a BCE was 1.38-fold for those who did not have postoperative radiotherapy, and 1.48-fold for invasion. The use of radiotherapy between 1996 to 2005 in the WA cohort doubled. Half (50%) of the cases that underwent BCT also received radiotherapy in the WA cohort.

As of 1st June 2001 there were 66,069 Indigenous Australians living in WA, representing 3.47% of the WA population.[24] Our cohort reported only 1.3% of cases were identified as Indigenous Australians but none had a BCE. Despite the apparent underutilisation of health services among Indigenous populations, breast services were the most used cancer services by Indigenous Australians, likely due to the increased awareness of the disease and availability of information.[25] Although no literature on DCIS could be found, a lower incidence and mortality rate for invasive breast cancer is seen in Indigenous versus non-Indigenous populations in Australia.[26, 27] Interestingly whilst most literature supports lower incidence rates in Indigenous populations, a higher mortality rate has been reported in this population. Research has also identified an association between Indigenous status and more aggressive tumours.[28-30] Further research on DCIS in Indigeonous Australians is required.

4.7 Conclusion

A higher age-standardised incidence rate of DCIS has been reported since 2000 in WA. Whilst a lower incidence rate is seen in the under 40 years of age group both at a state and national level, the highest incidence rate is seen in the 50-59 year group in WA,

compared to 60-69 years nationally. The five and ten year probability of a BCE, and specifically invasion, is lower in WA compared to nationally. Risk factors of age, grade, second operation (re-excision) and radiotherapy use were statistically significant associated with a subsequent BCE, and specifically invasion, in WA. The statistical analysis of DCIS in WA supports the need for ensuring adequate margins are excised during the first operation to reduce the number of second operations and the risk of a subsequent BCE. An in-depth study of the effect of screening promotion and disease progression among Indigenous Australians is also recommended.

4.8 References

1. Australian Institute of Health and Welfare, National Breast and Ovarian Cancer Centre. Risk of invasive breast cancer in women diagnosed with ductal carcinoma in situ in Australia between 1995 and 2005, 2010. Canberra, ACT: Australian Institute of Health and Welfare.
2. Australian Institute of Health and Welfare & National Breast and Ovarian Cancer Centre. Breast cancer in Australia: an overview, 2009 Issue Cat. no. CAN 46, 2009. Canberra: AIHW.
3. Australian Institute of Health and Welfare. BreastScreen Australia monitoring report 2009–2010 Issue Cat. no. CAN 68, 2012. Canberra: AIHW.
4. Schouten van der Velden AP, Van Dijck JAAM, Wobbes T. Variations in treatment of ductal carcinoma in situ of the breast: A population-based study in the East Netherlands. European Journal of Surgical Oncology. 2007; 33(4):424-429.
5. Rakovitch E, Pignol JP, Chartier C, Hanna W, Kahn H, Wong J, et al. The management of ductal carcinoma in situ of the breast: a screened population-based analysis. Breast Cancer Research and Treatment. 2007; 101(3):335-47.
6. Shugg D, White VM, Kitchen PR, Pruden M, Collins JP, Hill DJ. Surgical management of ductal carcinoma in situ in Australia in 1995. Australian and New Zealand Journal of Surgery. 2002; 72(10):708-15.
7. Kricker A, Goumas C, Armstrong B. Ductal carcinoma in situ of the breast, a population-based study of epidemiology and pathology. British Journal of Cancer. 2004; 90(7):1382-1385.
8. Meijnen P, Peterse JL, Oldenburg HSA, Woerdeman LAE, Rutgers EJT. Changing patterns in diagnosis and treatment of ductal carcinoma in situ of the breast. European Journal of Surgical Oncology. 2005; 31(8):833-839.
9. Harris G, Pinder S, Ellis I. Ductal carcinoma in situ: diagnosis and classification. Current Diagnostic Pathology. 2004; 10(3):204-210.
10. Mokbel K, Cutuli B. Heterogeneity of ductal carcinoma in situ and its effects on management. The Lancet Oncology. 2006; 7(9):756-765.
11. Silverstein M, Poller D, Waisman J, Colburn W, Barth A, Gierson E, et al. Prognostic classification of breast ductal carcinoma-in-situ. Lancet. 1995; 345(8958):1154 - 1157.
12. Silverstein MJ, Figueira Fo A, Novais-Dias E, Salvador-Silva HA, Barros A. The dilemma of appropriate therapy for DCIS. The Van Nuys Breast Centre expereince. 8th International Congress on Senology (Breast Diseases); 1995; Rio de Janeiro, Brazil: Elsevier; 8-12 May 1994. p. 165 - 169.
13. Sigal-Zafrani B, Lewis JS, Clough KB, Vincent-Salomon A, Fourquet A, Meunier M, et al. Histological margin assessment for breast ductal carcinoma in situ: precision and implications. Modern Pathology. 2004; 17(1):81-8.
14. Fisher ER, Costantino J, Fisher B, Palekar AS, Redmond C, Mamounas E. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17. Intraductal carcinoma (ductal carcinoma in situ). The National Surgical Adjuvant Breast and Bowel Project Collaborating Investigators. Cancer. 1995; 75(6):1310-9.

15. Pinder S, Ellis I. The diagnosis and management of pre-invasive breast disease: Ductal carcinoma in situ (DCIS) and atypical ductal hyperplasia (ADH) - current definitions and classification. Breast Cancer Research. 2003; 5(5):254 - 257.

16. Pinder SE. Ductal carcinoma in situ (DCIS): pathological features, differential diagnosis, prognostic factors and specimen evaluation. Modern Pathology. 2010; 23 Suppl 2:S8-13.

17. Neuschatz AC, DiPetrillo T, Safaii H, Lowther D, Landa M, Wazer DE. Margin width as a determinant of local control with and without radiation therapy for ductal carcinoma in situ (DCIS) of the breast. International Journal of Cancer. 2001; 96 Suppl:97-104.

18. Dillon MF, Mc Dermott EW, O'Doherty A, Quinn CM, Hill AD, O'Higgins N. Factors affecting successful breast conservation for ductal carcinoma in situ. Annals of Surgical Oncology. 2007; 14(5):1618-28.

19. Zelis JJ, Sickle-Santanello BJ, Liang WC, Nims TA. Do not contemplate invasive surgery for ductal carcinoma in situ. The American Journal of Surgery. 2002; 184(4):348-349.

20. Morrow M, O'Sullivan MJ. The dilemma of DCIS. The Breast. 2007; 16(Supplement 2):59-62.

21. Kumar S, Sacchini V. The surgical management of ductal carcinoma in situ. Breast Journal. 2010; 16 Suppl 1:S49-52.

22. Hwang ES. The impact of surgery on ductal carcinoma in situ outcomes: The use of mastectomy. Journal of the National Cancer Institute Monographs. 2010; 2010(41):197-199.

23. Gøtzsche PC. Re: Trends in the treatment of ductal carcinoma in situ of the breast. Journal of the National Cancer Institute. 2004; 96(16):1257.

24. Australian Bureau of Statistics. Population distribution. Aboriginal and Torres Strait Islander Australians Issue Cat. No. 4705.0, 2002. Canberra: Australian Bureau of Statistics;

25. Bernardes CM, Whop LJ, Garvey G, Valery PC. Health service utilization by indigenous cancer patients in Queensland: a descriptive study. International Journal for Equity in Health. 2012; 11(1):57.

26. Condon JR, Armstrong BK, Barnes A, Cunningham J. Cancer in indigenous Australians: A review. Cancer Causes & Control. 2003; 14(2):109-21.

27. Condon JR, Cunningham J, Barnes T, Armstrong BK, Selva-Nayagam S. Cancer diagnosis and treatment in the Northern Territory: assessing health service performance for indigenous Australians. Internal Medicine Journal. 2006; 36(8):498-505.

28. Sheppard AJM, Chiarelli AMP, Marrett LDP, Mirea LM, Nishri EDM, Trudeau MEMD. Detection of later stage breast cancer in First Nations Women in Ontario, Canada. Canadian Journal of Public Health. 2010; 101(1):101-5.

29. Bailes AA, Kuerer HM, Lari SA, Jones LA, Brewster AM. Impact of race and ethnicity on features and outcome of ductal carcinoma in situ of the breast. Cancer. 2013; 119(1):150-157.

30. Rose DP, Royak-Schaler R. Tumor biology and prognosis in black breast cancer patients: a review. Cancer Detection and Prevention. 2001; 25(1):16-31.

CHAPTER 5 COMPARISON OF RADIOPHARMACEUTICALS IN THE DETECTION OF DUCTAL CARCINOMA IN SITU WITH POSITRON EMISSION TOMOGRAPHY

5.1 Introduction

A diagnostic method not discussed in Chapter 2 is positron emission tomography (PET). PET works by giving the patient an intravenous injection of a radiopharmaceutical labelled with a positron-emitting radionuclide that targets specific tissue characteristics and scanning the patient using a PET scanner (camera). The camera is able to detect the high energy gamma emissions from the radiopharmaceutical caused by annihilation of the positrons in the tissues and generate a three-dimensional image of the region scanned. Areas which take up the radiopharmaceutical will show as a 'hot spot' on the image that can be measured to determine the tumour to background (TTB) ratio. Approximately 90% of clinical studies use ^{18}F-fluorodeoxyglucose (FDG), a positron-emitting analog of glucose, because a higher metabolism of glucose is noted in tumour cells.[1] The reported sensitivity of FDG PET in breast cancer (including in situ cancers) varies in the literature, from 25% to 96% and is higher for positron emission tomography – computer tomography (PET-CT).[2-4] Most studies report a poor sensitivity of PET for *in situ* and small size tumours.[2-4] Given this poor sensitivity, it is important to test FDG against another radiopharmaceutical to determine which is the best to use with ductal carcinoma in situ (DCIS). A number of radiopharmaceuticals that target other tissue characteristics have been studied in breast cancer and PET, again showing poor sensitivity and accuracy for in-situ and small size tumours.[1, 5] One radiopharmaceutical that is available in Perth, Western Australia (WA) and has not been reported in the literature for DCIS, is ^{18}F-fluoromethylcholine (FCH). Choline is a constituent of phosphatidylcholine. This is a major component of the phospholipid cell membrane (the fatty covering of cells). Malignant tumours have an increased intracellular choline pool and increased production and turn-over of cell membranes.[1]

The objectives of this study were to (1) determine if both FD) PET and FCH PET can detect newly diagnosed DCIS; (2) identify the TTB ratio for each radiopharmaceutical in DCIS; and (3) determine the best radiopharmaceutical to use with the PET probe.

5.2 Abbreviations

Below is a list of abbreviations used in this chapter:

BAC	Breast Assessment Centre
BMI	body mass index
CI	confidence interval
DCIS	ductal carcinoma in situ
FCH	^{18}F-fluoromethylcholine
FDG	^{18}F-fluorodeoxyglucose
MBq	megabecquerel
mm	millimetre
mmol/l	millimoles per litre
mSv	millisievert
PET	positron emission tomography
PET-CT	positron emission tomography – computer tomography
ROI	region of interest
RPH	Royal Perth Hospital
SD	standard deviation
SUV	standardised uptake value
TTB	tumour to background
WA	Western Australia
WLE	wide local excision

5.3 Methods

Patients with newly diagnosed DCIS at Royal Perth Hospital (RPH), Perth Western Australia, who met the inclusion criteria, were invited to participate in the study.

5.3.1 Eligibility criteria

The eligibility criteria for the subjects were:

Inclusion Criteria:

1. Patient with newly diagnosed DCIS of the breast that is ≥10mm on mammogram (as previous research showed PET has a poor sensitivity on tumours <10mm[2-4]),
2. Planned to undergo surgical excision of DCIS,
3. Female, between 50 and 69 years of age. A high incidence rate was reported for this age group in Chapter 4. Exclusion of women under 50 years and over 69 years excludes the at risk age group and reduces the risk of co-morbidities seen in the older population, and
4. Able to provide informed consent.

Exclusion Criteria:

1. Planned neoadjuvant therapy for DCIS;
2. Concurrent invasive carcinoma of the ipsilateral breast;
3. Previously diagnosed DCIS of the ipsilateral or contralateral breast, or primary malignancy of the breast;
4. Previous history of another primary malignancy;
5. Uncontrolled diabetes mellitus;
6. Pregnant at the time of PET scan;
7. Other indications not allowable by PET, such as pacemaker or weight in excess of 135kgs.

5.3.2 Sample size

These eligibility criteria were necessary for participants to undergo a PET scan and to reduce the risk of confounders. It was anticipated that this eligibility criteria, coupled with the radiation risk and time limitation to undergo two PET scans prior to surgery, would greatly impact on the number of patients eligible for and willing to consent for this study. Therefore, the sample size for this pilot study was ten participants.

5.3.3 Study procedure

Following ethical approval from Curtin University (Appendix B) and Royal Perth Hospital (Appendix C) and approval from the Radiological Council of Western Australia (Appendix D), the investigator attended the Breast Assessment Centre (BAC)

at RPH twice a week to assess all cases for eligibility in the study. When a patient was identified as meeting the eligibility criteria, the study information was attached to the front of the medical record with instructions to the attending surgeon to discuss the study with the patient when they attended for their appointment (Appendix E). At this time, if the patient expressed an interest in the study the information sheet and consent form was provided for them to take home to read and discuss with family and friends and the Surgeon would notify the investigator. Two business days after their appointment, the patient was contacted by telephone by the investigator to enquire if they had read the information and if they had any questions. If the patient agreed to participate in the study the investigator made an appointment to meet with the patient and then booked the two PET scans, at the Department of Nuclear Medicine, Sir Charles Gairdner Hospital, Perth Western Australia. At the appointment, informed consent was obtained and appointment details for the two PET scans was provided. The investigator also ensured the patient had already undergone mammography, ultrasound and biopsy prior to the PET scans. Where these had not been performed, the investigator liaised with the surgeon to organise these prior to the first PET scan. Figure 5.1 is a flowchart of the above process.

At the conclusion of each PET scan, regions of interest (ROI) were drawn and the activity and standard deviation was obtained for the DCIS, in the contralateral breast and in the mediastinal blood pool. From this the tumour to background (TTB) ratio was calculated. This is the measure of the radiopharmaceutical activity in the DCIS compared to that in the contralateral breast. The standardised uptake value (SUV) was not used as a measure of comparison as SUVs in FCH PET had not previously been validated at the time of the study. A PET clinician reported the PET scan findings, but results were not released to the surgeon prior to surgery, unless there were exceptional circumstances.

The reason for blinding the surgeon to the PET results was because PET in the diagnosis of DCIS had yet to be validated. Exceptional circumstances included:

- PET identified a tumour in the ipsilateral breast or regional lymph nodes, which could potentially alter the planned course of management.
- PET identified an incidental finding, such as a second primary tumour elsewhere in the body. If found to be benign and patient were to receive surgery for DCIS within the next month following the PET scan, the patient would remain in the study.

Should invasive breast cancer be found in the contralateral breast, the findings would be reported to the surgeon immediately, but the patient would not be withdrawn from the study.

The surgeon then removed the DCIS as planned. The pathologist documented the dimensions of the DCIS and other routine data was gathered (for example: grade, clearance of the margins, necrosis).

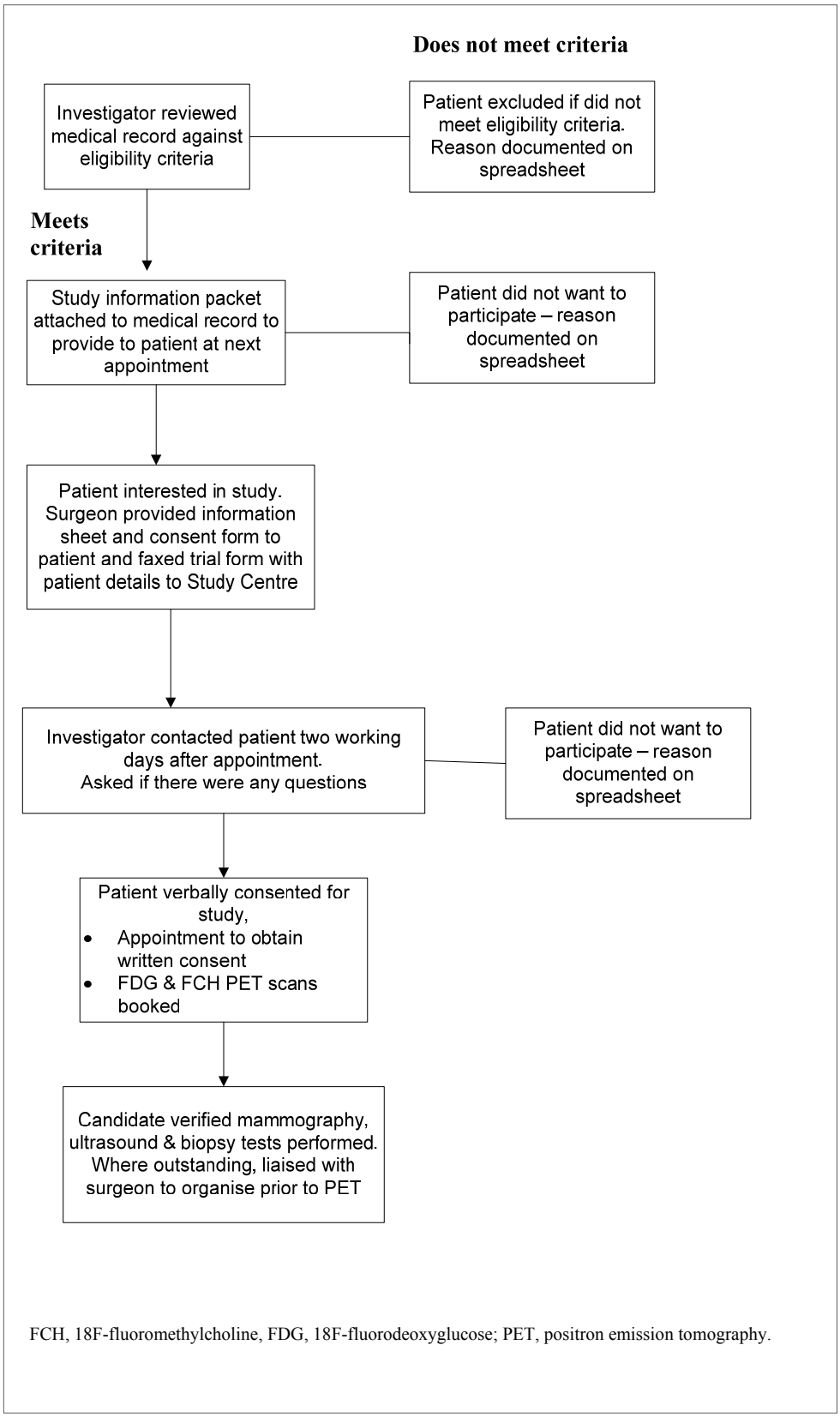
Following surgery, a multidisciplinary study meeting (separate to the multidisciplinary breast cancer meeting) was held to review the data. There was no data sharing between PET and the other disciplines prior to this meeting outside of exceptional circumstances. For each patient, data was presented in the following order:

1. Radiology specifies mammogram and ultrasound findings, including location and dimensions of DCIS.
2. Surgeon specifies type of surgery and location of surgery.
3. Pathologist specifies dimensions of DCIS, the margins and if there was presence of any residual disease.
4. Surgeon specifies if re-excision was needed and type of surgery and location of surgery if re-excision was required.
5. Pathologist specifies dimensions of DCIS, the margins and if there was presence of any residual disease.
6. PET specifies findings including location and tumour to background ratio for each tracer.

Presenting the data with the PET results at the end of the presentation assisted with blinding to the PET results. This provided a background to the patient's management

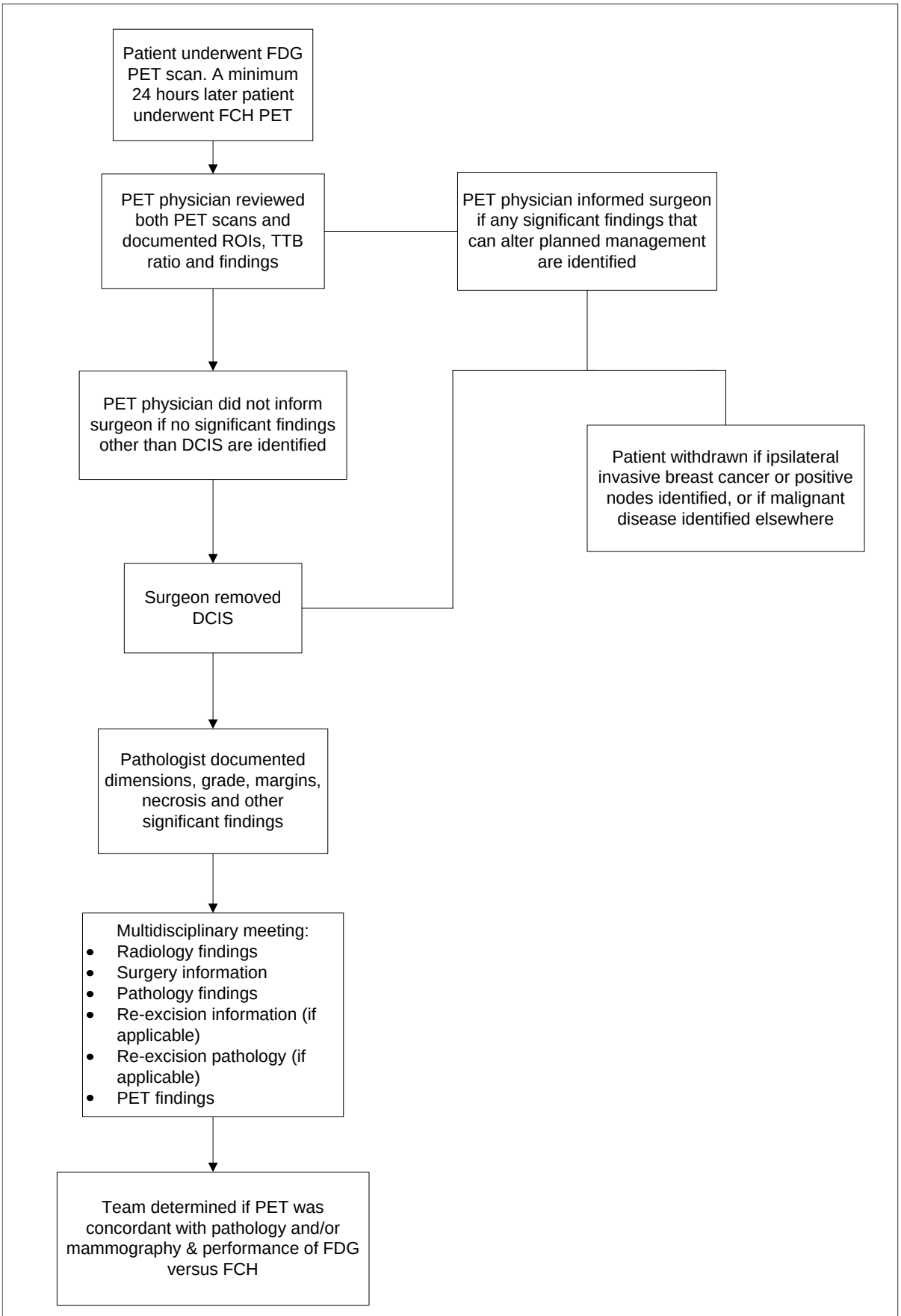
before revealing if the PET results were concordant with pathology and mammography. Five year follow-up information was obtained from medical records. Figure 5.2 is a flowchart of the study procedure.

Figure 5.1: Participant recruitment flowchart



FCH, 18F-fluoromethylcholine, FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography.

Figure 5.2: Study procedure flowchart



DCIS, ductal carcinoma in situ; FCH, 18F-fluoromethylcholine, FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography; ROIs, regions of interest, TTB, tumour to background

5.3.4 Radiation dose

Patients underwent both a FDG and a FCH PET scan. The effective dose of radiation for a whole body FDG PET scan in women is 5.7 millisievert (mSv). The effective dose of radiation for a whole body FCH PET scan in women is 7.3 mSv. This gives a 13 mSv effective dose of radiation. The amount of extra radiation exposure from these two PET scans is equal to about 8½ years of natural background radiation. This has a probability for the induction of cancer of 6.5×10^{-4} or one in 1500. The risk of this occurring is about one half of the risk of being killed on WA roads in the next 10 years. These figures were provided by the Radiological Council of Western Australia at the time of radiological approval.

5.3.5 PET imaging procedures

The imaging protocol for FDG PET was:

1. Patients fasted overnight or for 6 hours prior to the PET study. This is because foods containing glucose can affect the uptake of FDG. Patients were requested to drink liberal amounts of water to optimise hydration and promote urinary excretion of FDG.
2. An intravenous cannula was inserted into a peripheral vein.
3. Patient's height, weight and blood glucose levels were recorded and body mass index (BMI) calculated.
4. No generally accepted recommendations were available if the serum glucose level is elevated. Consequently, if the blood glucose level was greater than 10mmol/l (millimoles per litre), the investigator may have opted to continue with the scan, withdraw the patient from the study, administer insulin to normalize serum glucose and proceed as long as more than 4 hours can elapse between the last dose of short-acting insulin and FDG administration, or reschedule the study for a time when serum glucose was better controlled.
5. Approximately 370MBq (megabecquerel) FDG was administered intravenously. The injected dose of FDG was adjusted for patient BMI.
6. Patients remained in a relaxed position for a minimum of 45 minutes during the FDG uptake period. In selected cases, sedation may have been required to minimise muscle activity during the uptake period.
7. Patients who have not been catheterised were asked to void prior to commencement of the PET scan. In the case of patients who had been catheterised, the urinary catheter bag was drained prior to scanning.

8. At approximately 1 hour following FDG administration, PET emission and transmission data was acquired from the base of skull to below inguinal nodes.
9. ROIs for the DCIS site, contralateral breast and mediastinal blood pool were generated and activity and standard deviations (SD) in the ROI calculated, with a minimum of five recordings each. TTB ratios were then calculated.

The imaging protocol for FCH PET was:

1. Patients were not required to fast prior to the FCH PET study. This is because food consumption prior to an FCH injection will not affect FCH uptake. Patients were requested to drink liberal amounts of water to optimise hydration and promote urinary excretion of FCH.
2. An intravenous cannula was inserted into a peripheral vein.
3. Patient's height and weight were recorded and BMI calculated.
4. Patients were asked to void prior to commencement of the PET scan.
5. Approximately 200MBq of FCH was administered intravenously. The injected dose was adjusted for BMI.
6. Patients were imaged immediately after injection for 10-15 minutes using dynamic imaging of the breast only, and then PET emission and transmission data were acquired from the base of skull to below the inguinal nodes for the next 45 minutes.
7. ROIs for the DCIS site, contralateral breast and mediastinal blood pool were generated and activity and standard deviations (SD) in the ROI calculated, with a minimum of five recordings each. TTB ratios were then calculated.

5.3.6 PET image interpretation

The PET scans were read by two specialists credentialed for PET interpretation by the Joint Nuclear Medicine Credentialing and Accreditation Committee of the Royal Australasian College of Physicians and the Royal Australian and New Zealand College of Radiologists. They were not blinded to the results of the other scan data and had access to full clinical history, using attenuation corrected emission PET images. The ROIs and calculations were generated by the attending specialist and the investigator.

5.3.7 Data collection

Data collected included patient demographic data (age, age group), significant clinical history, pathological data (histological grade, necrosis, focality and extent of disease,

the margins, and presence of residual disease or invasion), surgical notes, imaging findings, management plan before surgery, postoperative clinical management and any adverse events. All data was entered onto a database at Curtin University.

5.4 Results

5.4.1 Patient recruitment.

Between September 2005 and December 2006,the medical records of 192 female patients attending the BAC at RPH were reviewed for consideration of inclusion in the study. All 192 patients were reported on mammography to have DCIS with no invasion. One patient was excluded as they were outside the age range suitable for the study, 29/192 (15.10%) were found to have an invasive component on biopsy and 68/192 (35.42%) were reported as having DCIS smaller than 10mm measured by mammography. Furthermore, 27/192 (14.06%) of patients had a past history of DCIS or invasive breast cancer and 59/192 (30.73%) had already undergone surgery or the planned surgery date would not allow time for the PET scans. Once the eligibility criteria were applied, only 8 patients (4.17%) were eligible and invited to participate in the study. Screening information is presented in Table 5.1.

Table 5.1: Screening information

Patients reviewed		192
Age of screening population	Range	31-73
	Mean	54.65 years
DCIS size on mammography of screening population	Range	2 – 90mm
	Mean	26.44mm
Reason for exclusion:		
Patients age <50 years or ≥ 70 years		1 (0.52%)
Patients with invasion detected by biopsy		29 (15.10%)
Patients with DCIS size on mammography ≤10mm		68 (35.42%)
Patients with past history of DCIS or invasion		27 (14.06%)
Patients already undergone surgery for DCIS or insufficient time before surgery for PET scans		59 (30.73%)
Patients remaining eligible for study		8 (4.17%)

DCIS, ductal carcinoma in situ; PET, positron emission tomography.

Of these eight eligible patients, four declined to participate in the study due to the radiation risks. Another patient declined due to family reasons and another did not

provide a reason for declining. Two patients agreed to participate in the study. The study team ceased recruitment at 16 months due to the difficulties in recruitment, and the study was examined as a case study with these two patients.

5.4.2 Patient 1

Patient 1, aged 63 years, was referred to the RPH BAC by her general practitioner following a mammogram identifying a localised cluster of calcification in the right breast. This patient was asymptomatic with no breast discharge, lump or pain. The patient reported no past history of breast or ovarian cancer and no known family history. Patient 1 had undergone a core biopsy approximately ten years prior for a benign lesion of the breast, site not recorded. Other clinical history included arthritis, recent right shoulder pain, uterine prolapsed and a stapedectomy many years prior. The patient commenced menarche at 13-14 years of age and had a past history of six pregnancies, with five resulting in a live birth, all breast fed, with the first pregnancy at eighteen years of age. There was no prior use of the contraceptive pill or hormone replacement therapy and the patient underwent menopause in her late 40s.

5.4.2.1 Patient 1: mammography and biopsy

Clinically, both breasts and axillae were normal. Mammographically, the lesion measured as 25mm in the lower outer quadrant of the right breast. A stereotactic core biopsy of the mammographic abnormality showed high grade DCIS. Immediately following the core biopsy, the patient was seen in the RPH BAC and provided with the information about the study.

5.4.2.2 Patient 1: positron emission tomography imaging

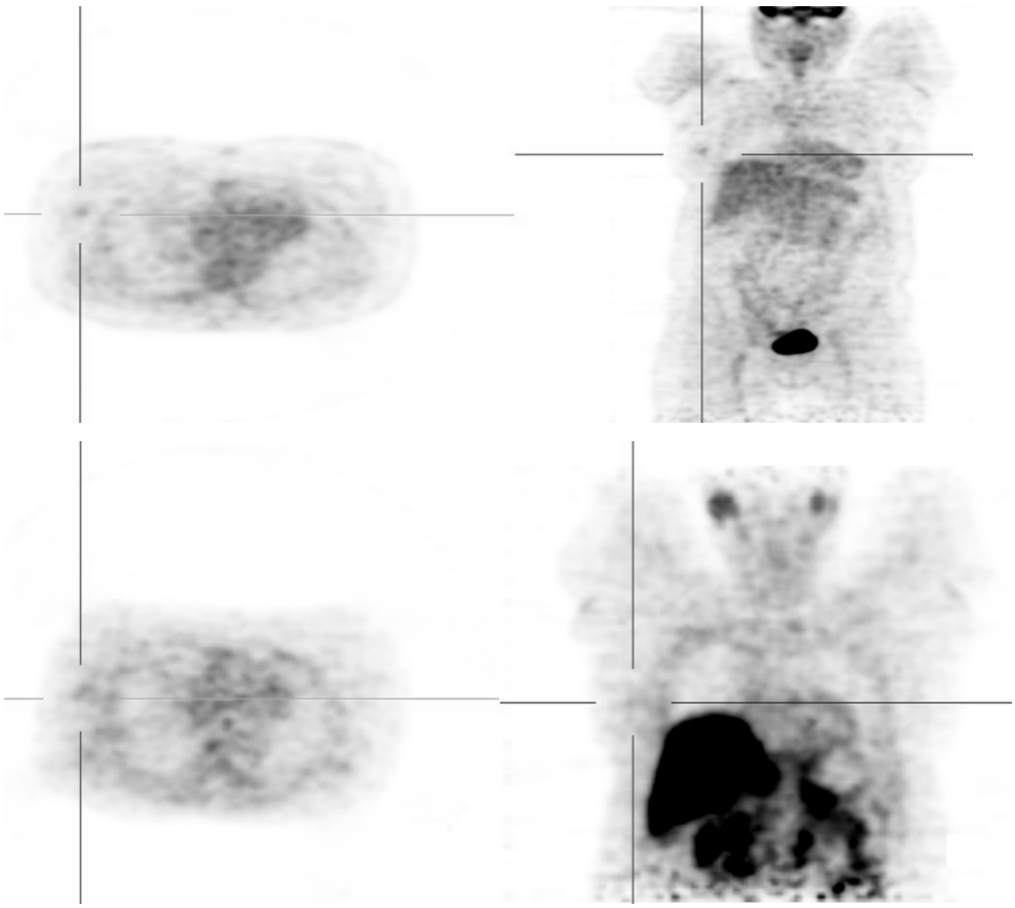
The patient was booked to undergo the FDG PET scan two weeks after the core biopsy. This was to allow sufficient time for any inflammatory response in the biopsy site to subside and was also booked before the FCH PET scan as the effect of FCH on a FDG PET scan was unknown and not reported in the literature at the time. The FCH PET scan was booked 24 hours after the FDG PET to allow time for decay and elimination of the FDG.

The patient was not a diabetic and had a BMI of 29.9. Her blood sugar level was measured as 6.0 mmol/l. The patient was injected with 386MBq of FDG and rested supine for 43 minutes in a dimly lit stall. The DCIS was visualised on the PET image.

No other incidental findings were reported. The tumour activity ranged from 1095 (standard deviation ±332) to 1139 (±462) in the tumour, 705 (±233) to 794 (±128) in the contralateral breast and 3038 (±312) to 3179 (±339), giving a TTB ratio of 1.494 (±0.084; 95% CI 0.740-2.248).

The following day, Patient 1 returned for the FCH PET scan. The patient reported no adverse effects from the PET scan the previous day. The patient was injected with 207MBq of FCH and imaged immediately. Whilst the DCIS could be visualised on the PET image, it was not as 'hot' as with the FDG scan. No other incidental findings were reported by either PET clinician. The tumour activity ranged from 424 to 2590 in the tumour, 203 to 1150 in the contralateral breast and 968 to 2610 , giving a TTB ratio of 1.486 (±0.695; 95% CI 0.241-3.212). The FDG PET and FCH PET images for Patient 1 are shown in Figure 5.3

Figure 5.3: Patient 1 FDG PET (top) and FCH PET (bottom) images for DCIS



DCIS, ductal carcinoma in situ; FCH, 18F-fluoromethylcholine, FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography.

5.4.2.3 Patient 1: surgery and histology

Patient 1 underwent a wide local excision (WLE) six days post FCH PET scan. A modified Koplan's hookwire was inserted in the lateral aspect of the right breast on the lateral medial compression on the morning of surgery. During the WLE a mass weighing 121g and measuring 85mm superior to inferior, 90mm medial to lateral and 20mm deep to superficial was excised. The hookwire was *in situ*. A shaving from the superior margin was also excised, measuring 75x50x15mm. The cavity surface appeared focally haemorrhagic. Of the excised tissue the deep margin was inked black and the remainder of the specimen inked blue. 19 serial slices from medial to lateral were taken. No definite lesion was identified and pins were put in place in slices 9 and 12.

Histology reported calcifications were present in the DCIS and benign breast changes with pseudoangiomatous hyperplasia recorded in the shaving. No invasive component was found. Cell type was classified as comedo/solid with comedo necrosis present. It was unifocal with a high nuclear grade. Microscopic dimensions of the tumour measured 15mm. The margin was 6mm from the superficial margin and greater than 10mm from all other margins. Normal parenchyma was seen between the DCIS and margins. Tubal score was 3 and Nottingham category B. Table 5.2 provides a summary of the above and in comparison to Patient 2.

5.4.2.4 Patient 1: post-surgery and follow-up

The case was reviewed at a multidisciplinary breast cancer meeting where it was determined that no further excisions would be undertaken and that surgery was complete. As the peripheral margins were clear, mastectomy was not recommended. The meeting recommended radiotherapy to the breast and chest wall only, and not the axillary nodes. Chemotherapy was not recommended. A follow-up mammography was recommended in one year's time.

Six weeks post WLE the scar still showed some puckering and swelling, with no erythema. There was good arm movement. The patient received postoperative radiotherapy to the right breast using tangents. Towards the end of radiotherapy a breast abscess formed and was treated with oral antibiotics (flucoxcallin).

Six months post WLE Patient 1 was reviewed in the BAC. No changes in the breast were noted, including no masses palpable in either breast or axilla. The patient reported a number of viral infections. Bilateral parenchyma was noted. A mammogram was booked for six months time. The patient requested an appointment with the BAC nine months post WLE, reporting chest wall pain. On examination, tenderness was reported in the costochondral junction and the patient was recommended non-steriodial treatment. Clinically, no masses were noted.

The bilateral mammogram was brought forward to ten months post WLE. The scan showed postsurgical scarring only. Architectural distortion and skin thickening inferiorly in the right breast was consistent with surgery. No contralateral stellate was noted. Bilateral calcifications appear mammographically benign, with no residual calcifications and no new suspicious microcalcifications. No axillary lymphadenopathy was noted.

The next mammogram was undertaken two years following the above mammogram. Less than 25% of parenchymal density was demonstrated in the breasts in unchanged distribution. No new masses, stronal distortion or pleomorphic microcalcifications were seen. A repeat mammogram performed 15 months later reported the same, with a small amount of residual parenchyma noted bilaterally, occupying now 25% of the breast volume. The last reported mammogram taken six years and nine months post WLE showed the residual fibrograndular tissue now occupied 25-50% of the breast tissue. There were persistent nodular densities throughout both breasts which are stable when compared to previous scans. No new lesion, distortion or masses were detected and no axillary lymphadenopathy.

The only other clinically relevant event post PET for Patient 1 was that she was referred to King Edward Memorial Hospital 5½ year post WLE for vaginal prolapsed surgical care. Permission was obtained from the Breast Surgeon at the RPH BAC to prescribe vaginal oestrogen therapy (Vagifem). Permission was granted with the recommendation of using Ovestin as it was less likely to have systematic oestrogenic effects. A review at the RPH Breast Clinic six years and nine months post WLE shows no signs of recurrence clinically or on mammography and the patient was still waiting to undergo the vaginal prolapsed repair and had not started on Ovestin. A five year follow-up with

the GP confirmed no recurrence or new masses had been detected and the patient was clinically stable.

5.4.3 Patient 2

Patient 2, aged 56 years, was referred to the RPH BAC by Breast Screen WA following her third screening mammography identifying calcification in the lower outer quadrant of the left breast. The patient was asymptomatic with no previous history or family history of breast or ovarian cancer. The patient reported four pregnancies which resulted in three live births, with the first pregnancy at 23 years of age. She did not breastfeed and reported using the contraceptive pill in the past for approximately three years. The patient was postmenopausal (at 47 years of age) and had never taken hormone replacement therapy. Significant past clinical history included removal of a left renal calculi.

5.4.3.1 Patient 2: mammography and biopsy

Clinically, both breasts and axillae were normal. Mammographically, the lesion was measured as 30mm in the lower outer quadrant of the left breast. A stereotactic core biopsy identified high grade DCIS with no invasive component in the biopsied sample. Because of the 30mm size of the tumour, it was classified as borderline for breast conservation therapy and the patient was provided with information about both a WLE with radiotherapy or mastectomy, in order to consider her options. The patient elected to undergo a WLE with radiotherapy. At this same appointment at the RPH BAC the patient was provided with the information about the study.

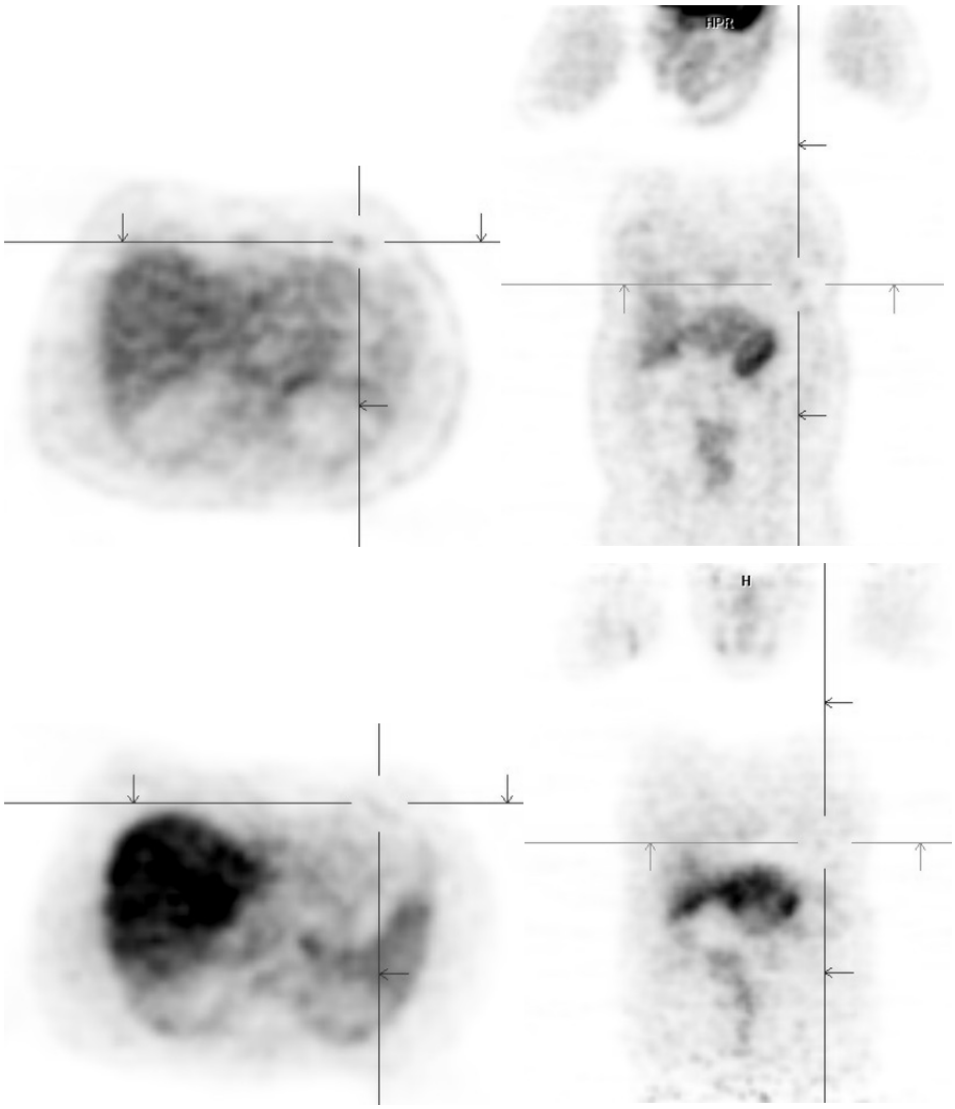
5.4.3.2 Patient 2: positron emission tomography imaging

The patient was booked to undergo the FDG PET scan four weeks after the core biopsy, with the FCH PET scan 24 hour later and the WLE two days following this. The patient was not a diabetic and had a BMI of 30.4. Her blood sugar level was measured as 5.3mmol/l. The patient was injected with 361MBq of FDG and rested supine for 42 minutes in a dimly lit stall. The DCIS could be visualised on the PET image and no other incidental findings were reported by either PET clinician. The tumour activity ranged from 1004 (±316) to 1182 (±473) in the tumour, 725 (±306) to 759 (±379) in the contralateral breast and 3439 (±802) to 3695 (±838), giving a TTB ratio of 1.471 (±0.122; 95% CI 0.375-2.567).

The following day, Patient 2 returned for the FCH PET scan. The patient reported no adverse effects from the PET scan the previous day. The patient was injected with 202MBq of FCH and imaged immediately. Whilst the DCIS could be visualised on the PET image, it was not as 'hot' as with the FDG PET scan. No other incidental findings were reported by either PET clinician. The tumour activity ranged from 517 (±208) to 589 (±209) in the tumour, 412 (±200) to 512 (±208) in the contralateral breast and 2107 (±173) to 2195 (±238), giving a TTB ratio of 1.203 (±0.074; 95% CI 0.539-1.866).

The FDG PET and FCH PET images for Patient 2 are shown in Figure 5.4.

Figure 5.4: Patient 2 FDG PET (top) and FCH PET (bottom) images for DCIS



DCIS, ductal carcinoma in situ; FCH, 18F-fluoromethylcholine, FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography.

5.4.3.3 Patient 2: surgery and histology

Patient 2 underwent a WLE two days post FCH PET scan. A modified Koplan's 9cm hookwire was inserted from the lateromedial approach of the left breast on the morning of the day case. During the WLE a mass weighing 21g and measuring 45mm superior to inferior, 55mm medial to lateral and 15mm deep to superficial was excised. The hookwire was *in situ*. Of the excised tissue the deep margin was inked black and the remainder of the specimen inked blue. 12 serial slices from medial to lateral at 5mm intervals were taken. No definite lesion was identified and pins were put in place in slices 4 and 8.

Histology reported secretory calcifications were present in the DCIS and some benign breast changes (microcysts, apocrine metaplasia). No invasive component was found. Cell type was classified as comedo/solid, cribriform, with comedo necrosis present. It was unifocal with an intermediate nuclear grade. Microscopic dimensions of the tumour measured 35x7x5mm. The margin was 1mm from the deep margin, 1mm from the inferior margin and 6mm from the superficial margin. All other margins were greater than 10mm. Normal parenchyma was seen between the DCIS and margins. Tubal score was 4 and Nottingham category A.

5.4.3.4 Patient 2: post-surgery & follow-up

The case was reviewed at a multidisciplinary breast cancer meeting where it was determined that no further excisions would be undertaken and surgery was complete. Mastectomy was not recommended. The meeting recommended radiotherapy to the breast and chest wall only and not the axillary nodes, and chemotherapy was not recommended. A follow-up mammography was recommended in one year's time.

Six weeks post WLE the patient received postoperative radiotherapy to the left breast. One week later the patient developed renal calculi. The patient completed radiotherapy after three months with no adverse effects other than a mild skin reaction. The patient was reviewed in the BAC six months post WLE. Although there was still some breast sensitivity, clinically there were no signs of recurrence in the scar and the remaining breast tissue was normal. The patient was referred to be followed by the radiation oncology department with bilateral mammogram booked for six months' time.

The patient was reviewed in Radiation Oncology ten months post WLE. The patient reported mild intermittent pain in the left breast but otherwise well. A clinical exam did not identify any masses in either breast and no axillary lymphadenopathy. There was some mild altered sensation in the left breast over the radiation therapy area and some mild discolouration. The mammogram report was not available for review but noted by the oncologist that no new suspicious microcalcifications were seen. Follow up appointment was made for six months' time.

The patient was again reviewed 16 months post WLE in Radiation Oncology with no change to the previous clinical findings. The patient was prescribed antibiotics for possible mastitis. No further mammogram data was available for this patient. A five year follow-up with the Radiation Oncologist and general practitioner confirmed no recurrence or new masses had been detected and the patient was clinically stable.

Table 5.2: Age, clinical, mammography, pathology and PET findings

Characteristics		Patient 1	Patient 2
Age		63.6	56.3
Significant past history		Benign breast lesion, site unspecified	Nil
Breast		Lower outer quadrant of right	Lower outer quadrant of left
Surgery type		WLE	WLE
Margin identification		Inking	Inking
Histological type		Comedo/solid, pseudoangiomatous change	Comedo/solid, cribriform, with comedo necrosis present
Grade/Focality		High/ Unifocal	Intermediate/ Unifocal
Size mammography		25mm	30mm
Size excised specimen	Superior to inferior	85mm	45mm
	Medial to lateral	90mm	55mm
	Deep to superficial	20mm	15mm
Weight		121g	21g
Microscopic dimensions of tumour		15mm	35mm x 7mm x 5mm
Volume		~3375mm^3	1225mm^3
Invasive components		No	No
Tubular score		3	4
Nottingham category		B	A
Margins – distance from DCIS to margin	Superficial	6mm	6mm
	Medial	>10mm	>10mm
	Deep	>10mm	1mm
	Lateral	>10mm	>10mm
	Inferior	>10mm	1mm
	Superior	>10mm	>10mm
Shaving		Superior margin 75x50x15mm. Benign changes	Not applicable
TTB ratio FDG (± standard deviation)		1.49 (±0.08)	1.47 (±0.12)
TTB ratio FCH (± standard deviation)		1.49 (±0.70)	1.20 (±0.07)

DCIS, ductal carcinoma in situ; mm, millimetre; FCH, 18F-fluoromethylcholine; FDG, 18F-fluorodeoxyglucose; g, gram; TTB, tumour to background; WLE, wide local excision

5.5 Discussion

The poor sensitivity of FDG PET in detecting DCIS has been well reported in the literature. Avril and colleagues reported a 50% sensitivity and accuracy for detecting DCIS larger than 20mm (3/6 cases) and 0% in tumours under 20mm in size (0/6 cases), with an overall 25% sensitivity (41.7% when sensitive image reading was used).[3] The same sensitivity was also reported by Heinisch, but the study only included two cases of DCIS.[6] This low sensitivity is presumed to be due to the low spatial resolution of PET and because DCIS has a decreased glycolytic activity and vascularity.[6] Tumour size, histological type and grade, hormone receptor status and other immunohistochemical factors can all impact on the uptake of FDG in breast cancer.[1] This conclusion was

supported by a study that reported a statistically significant difference ($p<0.05$) in sensitivity of PET between invasive ductal carcinoma (IDC) and DCIS (98% versus 60%), with higher uptake in IDC cases ($p=0.07$).[7] However there was better uptake of FDG in ductal carcinoma than lobular or other histological types of breast cancer.[1]

Abbey[8] performed FDG PET imaging on mice with a similar cancerous growth to DCIS. They were able to follow the development of disease in one mouse over a considerable period of time using PET. Although only a case study providing limited findings, it demonstrated that FDG PET was able to visualise the extent of DCIS and monitor its changes over time.

While there have been a small number of studies examining FCH in prostate and hepatocellular carcinoma, any published accounts of the use of FCH PET in diagnosis of breast cancer in women could not be found, which is supported by Peñuelas and colleagues.[1] There was a reported case of an incidental finding in a male during the examination of prostate cancer using FCH PET.[9] Uptake was good and pathology confirmed invasive ductal breast cancer. FCH PET was reported in a female with a past history of invasive breast cancer who had undergone a mastectomy three years prior. [10] The FCH PET was able to accurately identify metastatic disease with SUVs ranging from 5.0 to 9.5.

In this study, the DCIS for both patients was detected by both FDG and FCH PET. Both patients had tumours greater than 10mm (patient 1=15mm, patient 2=35mm) thus overcoming one of the limitations reported for PET in DCIS. The nuclear grade was intermediate and high, respectively, for each patient, and histological type was comedo/solid, which has also been reported as having a better outcome for PET.[1]

The TTB ratio for FDG PET was higher in both patients compared to the TTB ratio for FCH PET in both patients. This indicates that there was a better uptake of FDG by DCIS. A previous study reported the mean SUV in DCIS for a FDG PET is lower than in IDC, with a mean SUV of 3.1 (±2.1).[11] A separate study reported a wider range of SUV in DCIS for a FDG PET, with a mean SUV of 2.3 (SD 7.2) in 5 cases.[7]

FDG is the recommended radiopharmaceutical for DCIS imaging and hand-held PET technology given FDG PET performed better than FCH PET and is clinically available

more widely than FCH. A smaller FDG dose may be used when using hand-held PET technology directly on the disease area due to the high uptake of FDG by DCIS.

The limitation of this study is the low recruitment of participants. In retrospect, using a matched case sampling method, requiring participants to only undergo one PET scan, not two, and recruiting from a number of hospitals, may have increased the sample size of the study.

5.6 Conclusion

Both FDG and FCH PET were able to identify newly diagnosed DCIS. The higher uptake and clinical availability of FDG makes this the preferred radiopharmaceutical for DCIS imaging and hand-held PET technology. Given the radiation implications of PET and limited availability in some rural and remote locations in Australia, mammography is still the recommended imaging modality for breast screening. Further research is required to evaluate the role of PET and in particular PET-CT and the hand-held PET probe technology, in DCIS staging and monitoring for DCIS larger than 10mm and high grade cases.

5.7 References

1. Peñuelas I, Domínguez-Prado I, García-Velloso MJ, Martí-Climent JM, Rodríguez-Fraile M, Caicedo C, et al. PET tracers for clinical imaging of breast cancer. Journal of Oncology. 2012; 2012:710561.
2. Hayashi M, Murakami K, Oyama T, Domeki Y, Hagiwara S, Katsumata D, et al. PET/CT supports breast cancer diagnosis and treatment. Breast Cancer. 2008; 15(3):224-230.
3. Avril N, Rosé CA, Schelling M, Dose J, Kuhn W, Bense S, et al. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations. Journal of Clinical Oncology. 2000; 18(20):3495-3502.
4. Hodgson NC, Gulenchyn KY. Is there a role for positron emission tomography in breast cancer staging? Journal of Clinical Oncology. 2008; 26(5):712-720.
5. Treglia G, Giovannini E, Di Franco D, Calcagni ML, Rufini V, Picchio M, et al. The role of positron emission tomography using carbon-11 and fluorine-18 choline in tumors other than prostate cancer: a systematic review. Annals of Nuclear Medicine. 2012; 26(6):451-461.
6. Heinisch M, Gallowitsch HJ, Mikosch P, Kresnik E, Kumnig G, Gomez I, et al. Comparison of FDG-PET and dynamic contrast-enhanced MRI in the evaluation of suggestive breast lesions. Breast. 2003; 12(1):17-22.
7. Ikenaga N, Otomo N, Toyofuku A, Ueda Y, Toyoda K, Hayashi T, et al. Standardized uptake values for breast carcinomas assessed by fluorodeoxyglucose-positron emission tomography correlate with prognostic factors. The American Surgeon. 2007; 73(11):1151-7.
8. Abbey CK, Borowsky AD, McGoldrick ET, Gregg JP,Maglione JE, Cardiff RD, et al. In vivo positron-emission tomography imaging of progression and transformation in a mouse model of mammary neoplasia. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101(31):11438-11443.
9. Kwee SA, Coel MN. Detection of synchronous primary breast and prostate cancer by F-18 fluorocholine PET/CT. Clinical Nuclear Medicine. 2010; 35(2):128-129.
10. DeGrado TR, Baldwin SW, Wang S, Orr MD, Liao RP, Friedman HS, et al. Synthesis and evaluation of (18)F-labeled choline analogs as oncologic PET tracers. The Journal of Nuclear Medicine. 2001; 42(12):1805-14.
11. Ueda S, Tsuda H, Asakawa H, Shigekawa T, Fukatsu K, Kondo N, et al. Clinicopathological and prognostic relevance of uptake level using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (^{18}F-FDG PET/CT) in primary breast cancer. Japanese Journal of Clinical Oncology. 2008; 38(4):250-8.

CHAPTER 6 POSITRON EMISSION TOMOGRAPHY PROBE LABORATORY TESTING AND PHANTOM STUDY

6.1 Introduction

An intraoperative margin assessment (IMA) method that was not identified by the Chapter 3 systematic review is the positron emission tomography (PET) probe. There has been little research examining the use of this technology in breast cancer. Existing studies have focused on either animal models or use of the probe in surgery for other cancers. Unlike gamma rays that can travel several centimetres into tissue, positrons only travel millimetres allowing a handheld dual PET probe to identify microscopic diseased tissue with greater accuracy during surgery following injection of ^{18}F-fluorodeoxyglucose (FDG).[1,2] The PET probe works as a combined gamma and beta probe. The central scintillator detects both positron (beta) and gamma rays whilst the surrounding scintillator detects only gamma rays, allowing the unit to subtract one count from the other to generate only the positron count.[1,2] The main limitation for PET probes is the uptake of FDG by the heart, liver, bladder and brain can potentially return a false positive result if the site of interest is less than 10mm from one of these organs. Whilst the heart is close to the breast tissue, unless the tumour is deep it should not return a false positive count rate.

Raylman and colleagues[3] examined the use of a PET probe in rats implanted with mammary tumours. They found uptake of FDG in this model to only present in the bladder, liver and brain. The study reported good uptake of FDG by mammary tumour tissue and recommended the use of a smaller probe when applied to smaller tumours. The probe was able to differentiate between normal and tumour tissue and results between the probe and pathology correlated well, with a good sensitivity (percentage not reported). The findings are supported by another animal study, using a mouse model.[4] They found the PET probe was able to detect positron rays at a close range to the site of interest and concluded the PET probe may have a higher sensitivity compared to the gamma probe. Both studies recommended further research using the PET probe in breast surgery, including the timing from FDG injection and using the probe intraoperatively.

The ability of the PET probe to detect small tumours was supported by Essner and colleagues, however their studies did not include breast cancer cases.[1,5] Two other

studies applied the probe in breast surgery cases, but it was only applied to the lymph nodes.[6,7] Molina and colleagues[8] used the PET probe on three patients with a past history of breast cancer. All patients were intravenously injected with 370-444 megabecquerel (MBq) (10-12mCi) of FDG 3-4 hours prior to the procedure. The probe was able to accurately identify the recurrent breast lesions in all three cases, but the study only used the probe for lesion localisation and not for margin assessment, with large doses of FDG injected.

The only study to examine primary breast tumours was undertaken by Piert and colleagues.[9] The study included one case of invasive ductal breast cancer. The patient was intravenously injected with 41.1MBq of FDG and the probe was used 105 minutes after injection. The site of interest was identified by the PET probe, however the probe was only used for tumour localisation and not for margin assessment. The tumour to background ratio was 5.6 and the standardised uptake value (SUV) mean was 2.8. The study concluded the performance of the probe could vary due to: the uptake and metabolism of the injected radiopharmaceutical; the technical performance of the probe; the time between injection and using the probe; and the size of the probe tip. They also concluded that the radiation burden to theatre staff is less than that associated with high-energy gamma probes.

A literature search did not identify any studies where the PET probe was used to assess surgical margins in breast cancer cases (in situ or invasive). The potential application of the PET probe in this context was considered important for future research in three other articles not mentioned above.[10-12] Utilisation of a PET probe may allow more accurate delineation of normal from abnormal tissue and may accurately assess surgical margins, particularly in DCIS breast conserving therapy (BCT). Further research is required on the suitability of FDG for DCIS, timing between injection and using the probe and suitable injection quantities.

A PET probe laboratory test was conducted to determine how the PET probe worked under various conditions. The methods used by Daghighian[2], Piert[9] and Yamamoto[13] was replicated for benchmarking. A phantom PET study was then conducted to test the probe against various FDG doses and SUVs. The objectives for this study were to (1) identify the sensitivity and linearity, specific activity, spatial resolution, source detector distance and depth response of the PET probe in a laboratory setting, and (2) determine

the ideal level of activity correlating the probe response with PET standardised uptake value (SUV).

6.2 Abbreviations

Below is a list of abbreviations and symbols used in this chapter:

@	at
&	and
BCT	breast conserving therapy
CPS	counts per second
F-18	fluorine-18
FDG	^{18}F-fluorodeoxyglucose
FWHM	full width at half maximum
g	grams
I-131	iodine-131
IMA	intraoperative margin assessment
IMI	IntraMedical Imaging
kBq	kilobecquerel
keV	kiloelectronvolt
LSO	lutetium oxyorthosilicate
MBq	megabecquerel
MeV	megaelectron volt
ml	millilitres
mm	millimetre
NA	Not applicable
PET	positron emission tomography
SUV	standardised uptake value
TTB	tumour to background
μl	microliter
μm	micrometre

6.3 Methods

6.3.1 Equipment

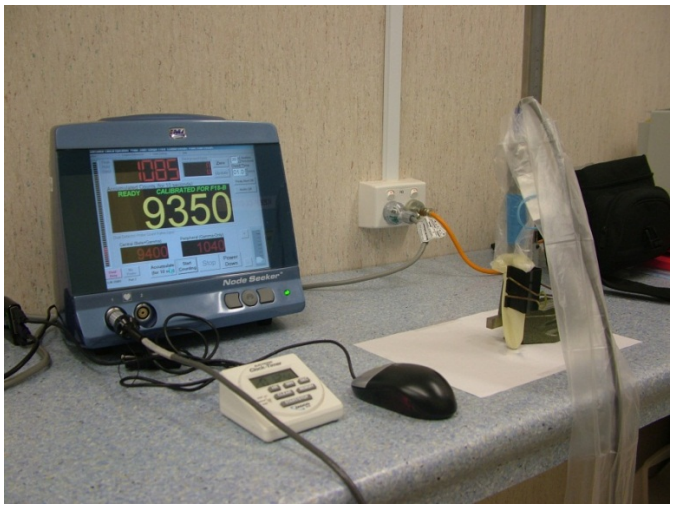
The PET probe to be tested is the IntraMedical Imaging (IMI) (Los Angeles) NodeSeeker PET probe, designed to detect the positrons emitted by the decay of F18. Figure 6.1 shows the PET probe.

Figure 6.1: Intramedical Imaging NodeSeeker PET probe

Source: http://www.gammaprobe.com/products/betaprobe/ (13/04/2008)

The probe consists of two detectors. The central detector is sensitive to positrons while remaining insensitive to the high energy gamma photons. This detector is a cerium-doped lutetium oxyorthosilicate (LSO) plastic scintillator, with an 8mm diameter and 7mm deep.[15] A second peripheral detector surrounds the central detector, and acts as a reference detector. This peripheral detector is shielded from positrons by 1mm stainless steel, which stops most beta particles with energy below 1.5 MeV.[2] Both detectors are scintillators connected to photomultiplier tubes by fibre optics. The control unit for the probe collects information from both detectors, and performs a weighted subtraction to obtain the positron count rate. The need for weighted subtraction is due to the differing efficiencies of the two detectors.[2] The NodeSeeker Control Unit is shown in Figure 6.2.

Figure 6.2: Laboratory testing setup for PET probe and control unit



A room dedicated to laboratory testing the PET probe and all equipment was provided by the Department of Medical Technology and Physics at Sir Charles Gairdner Hospital, Perth Western Australia. Figure 6.2 shows the PET probe within the surgical probe cover and control unit.

6.3.2 Sensitivity and linearity

The sensitivity and linearity test determines the sensitivity of the probe at set levels of FDG and if the probe counts per second (CPS) is linear to dose. To determine the sensitivity and linearity of the PET probe, the CPS were recorded over a 24 hour period. A 1 micro-litre drop of 459kBq (kilobecquerel) of FDG was placed on a piece of filter paper 5mm in diameter. CPS was taken 1mm and 10mm vertical distance from the source and with and without a 0.1mm thick latex probe cover. This test was performed twice with results averaged.

6.3.3 Specific activity

The specific activity test determines how the probe responds to sources with the same activity but different surface areas. This was achieved by placing a 1 micro-litre drop of 242kBq of FDG on 10 pieces of filter paper ranging from 3mm to 30mm in diameter. The probe was positioned 3mm above each source. The CPS was obtained with the probe cover on and recorded three times per source, with results averaged.

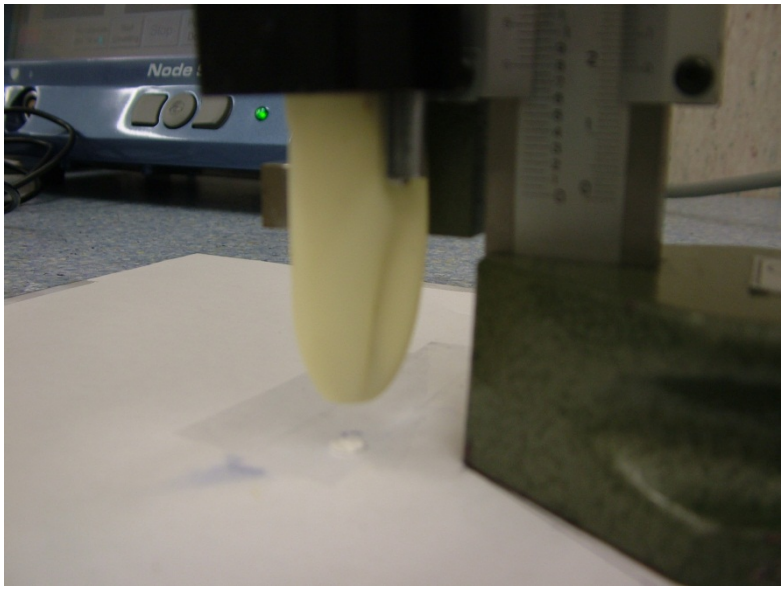
6.3.4 Spatial resolution

Spatial resolution tests how the probe will respond as it moves laterally away from the source. The approximate spatial resolution of the PET probe was determined by positioning the probe 1mm above a piece of filter paper 5mm in diameter on which a 1 micro-litre drop of 200kBq of FDG was placed. The source was then moved in 1mm steps to both sides of the probe for a maximum of 5mm in distance. The CPS was recorded with and without the probe cover and each test was performed three times, with results averaged. The full width at half maximum (FWHM) is calculated by determining the CPS when the probe is 1mm from the source and then moving away from the source until the CPS is half that at 1mm. Therefore the FWHM calculates the capacity of the probe at half of its maximum value.

6.3.5 Source detector distance

The source-detector distance determines how the probe will respond as it moves horizontally away from the source. As this laboratory test is specifically for clinical information, all testing was performed with the probe cover on. The probe was positioned 1mm above a piece of filter paper 5mm in diameter on which a 1 micro-litre drop of 185 kBq of FDG was placed. The probe was then moved in 1mm steps upwards from the source for a maximum of 10mm in distance and CPS recorded three times for each 1mm per test. The test was replicated three times and the results averaged to determine the FWHM. Figure 6.3 shows the probe setup for this test.

Figure 6.3: Probe setup for source detector distance test



6.3.6 Depth response

Although the aim is to use this probe on surgical margins, how the probe responds to sources when there is a layer of tissue between the probe and the tumour site needed to be determined. The depth test identifies how far beneath a tissue margin a tumour can be for the probe to accurately detect it. 5mm discs of filter paper containing a 1 micro-litre drop of 250kBq of FDG were placed into individual agar moulds from the surface (0mm) to 10mm in depth, varying by 0.5mm intervals. This resulted in 21 different agar moulds. A 1mm polycarbonate sheet was laid over each mould. The CPS were taken with the probe cover on holding the probe 1mm above the surface of each mould, recorded three times per source and the results averaged to determine the FWHM. There was no background activity in the agar moulds.

6.3.7 Laboratory test comparison

These laboratory tests have been undertaken by a number of different authors on the same and different PET probes. This study will compare the results of these experiments to the results from the studies reported by Daghighian[2], Piert[9] and Yamamoto[13]. The comparison of methods used is shown in Table 6.1.

Table 6.1: Published laboratory test methods for PET probe

Test	Method			
	This study (F-18 FDG)	Daghighian[2] (I-131 & F-18)	Piert[9] (F-18 FDG)	Yamamoto[13] (F18)
Manufacturer	Intramedical Imaging	Intramedical Imaging	Silicon Instruments	Kobe City College of Technology
Detector diameter	8mm	8mm	16mm	20mm
Sensitivity and linearity	• 1µl drop 459kBq. • Filter paper 5mm in diameter. • 1mm x 20mm aluminium covering source. • Probe 1mm & 10mm above. • 24 hours. • With & without 0.1mm thick latex probe cover.	• Small drop. • Tissue paper 5mm in diameter fixed between 25μm thick tape. • Probe 0mm above. • Time not specified. • With 0.1mm thick latex probe cover.	• 1µl drop 409kBq. • Filter paper 5mm in diameter. • 1mm x 20mm aluminium covering source. • Probe 1mm above. • 26.3 hours. • With & without probe cover.	Method not described
Specific activity	• 1µl drop of 242kBq. • 10 pieces filter paper ranging from 3mm to 30mm in diameter. • Probe 3mm above each. • With probe cover.	Not performed	Different method used based on weight	Not performed
Spatial resolution	• 1µl drop of 200kBq. • Filter paper 5mm in diameter. • Probe 1mm above. • Source moved 1mm steps to both sides to max. 5mm. • With & without probe cover.	Not described	• 1µl drop of 185kBq. • Source not specified. • Probe 1mm above. • Source moved 1mm steps to both sides. • With & without probe cover.	• 1µl drop of 100kBq. • Filter paper 1mm in diameter. • Probe 5mm, 10mm & 15mm above. • Source moved 1mm steps to both sides. • Without probe cover.
Source detector distance	• 1µl drop of 185 kBq. • Filter paper 5mm in diameter. • Probe 1mm above. • Probe moved 1mm steps upwards to max. 10mm. • With probe cover.	Not performed	Not performed	Not performed
Depth response	• 1µl drop of 250kBq. • 21 x filter paper 5mm in diameter. • Individual agar moulds (no background activity) from 0mm to 10mm in depth (by 0.5mm). • 1mm polycarbonate sheet • Probe 1mm above. • With probe cover	Not performed	Not performed	• Activity and dimension source not specified. • Plastic films different thickness inserted between source and probe • With & without 0.2mm thick probe cover

@, at; &, and; cps, counts per second; F-18, fluorine-18; F-18 FDG, 18F-fluorodeoxyglucose; FWHM, full width at half maximum; I-131, iodine-131; kBq, kilobecquerel; mm, millimetre; µl, microliter; μm, micrometre.

6.3.8 Level of activity

This test was to determine whether the PET probe could detect a 'tumour' which could not be visualised by the PET scanner. Five moulds of agar to represent the background tissue were made consisting of 100ml of agar and 3ml of 640kBq of FDG set in a 250ml semi-spheric Pyrex bowl. The mould weighed approximately 86g when set. Separately, five moulds of agar to represent the tumour were made, consisting of 7ml of agar, 3ml of varying levels of FDG activity (see Table 6.1) and a drop of blue food colouring, set in a 12ml semi-spheric plastic container. Only 4g of this mould when set was used to represent the tumour. The smaller moulds were made first followed immediately by the larger moulds, to allow the smaller moulds to set first and be inserted into the larger mould before it set. The moulds were then let to set for 110 minutes to represent one half-life of FDG prior to PET imaging.

After 110 minutes the moulds were transported to the Western Australia PET Service through the special elevator to transport radiopharmaceuticals (dumb waiter). Each mould was scanned individually on polystyrene trays and blueys to minimise possible contamination. The predicted activity at time of scanning is shown in Table 6.2.

Table 6.2: FDG activity for moulds at time of dispensing and scanning

Mould Number	FDG activity at 'dispensing' (kBq)	FDG activity at scanning (kBq)	Predicted TTB Ratio
Background	640	320	NA
1	1280	640	2:1
2	2560	1280	4:1
3	3840	1920	6:1
4	5120	2560	8:1
5	6400	3200	10:1

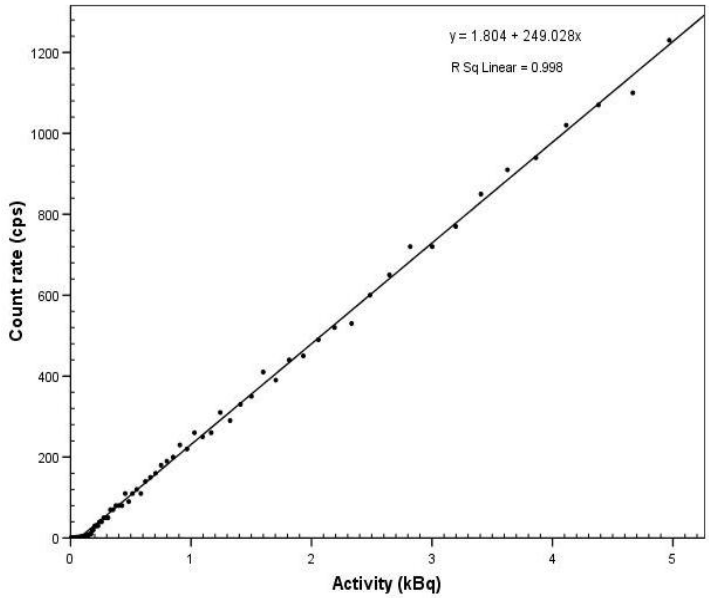
FDG, 18F-fluorodeoxyglucose; kBq, kilobecquerel; NA, not applicable; TTB = tumour to background.

6.4 Results

6.4.1 Sensitivity and linearity

The PET probe performed well in sensitivity and linearity testing, with a 21% decrease in sensitivity with the probe cover on when measured 1mm from the source. The sensitivity of the PET probe for F-18 detection was measured as 250 CPS per kBq at a distance of 1mm from a point source without a cover, as shown in Figure 6.4.

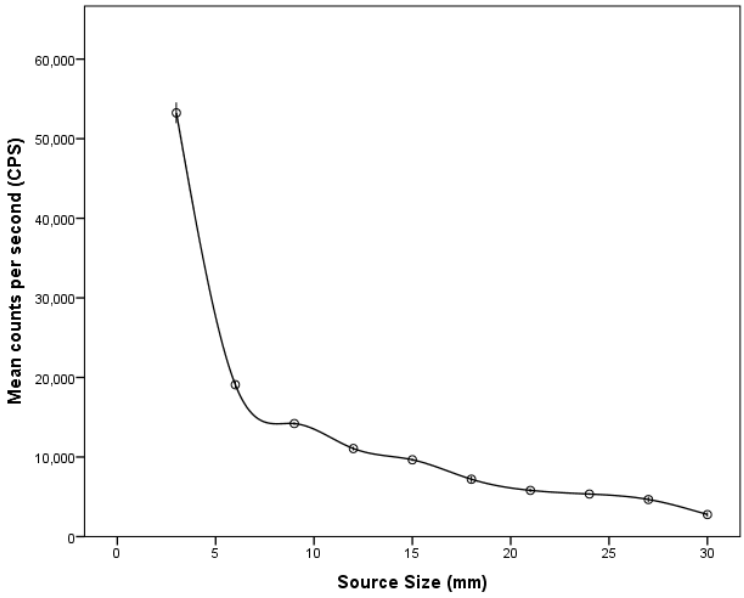
Figure 6.4: Sensitivity of PET probe



6.4.2 Specific activity

The results were in accordance to theoretical calculations, indicating that high specific activity improves detection. This is demonstrated in Figure 6.5.

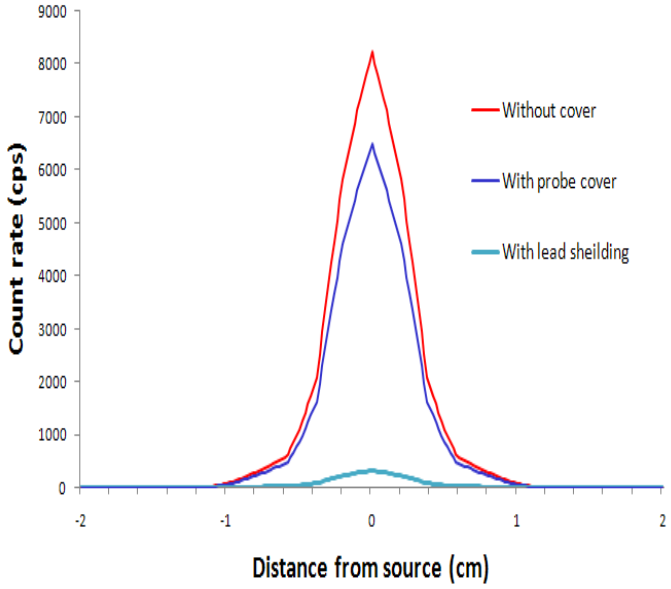
Figure 6.5: Specific activity of PET probe



6.4.3 Spatial resolution

The FWHM was 6mm at 1mm distance from point source. At a 10mm distance from source the resolution decreased slightly to a FWHM of 8mm. This is shown in Figure 6.6.

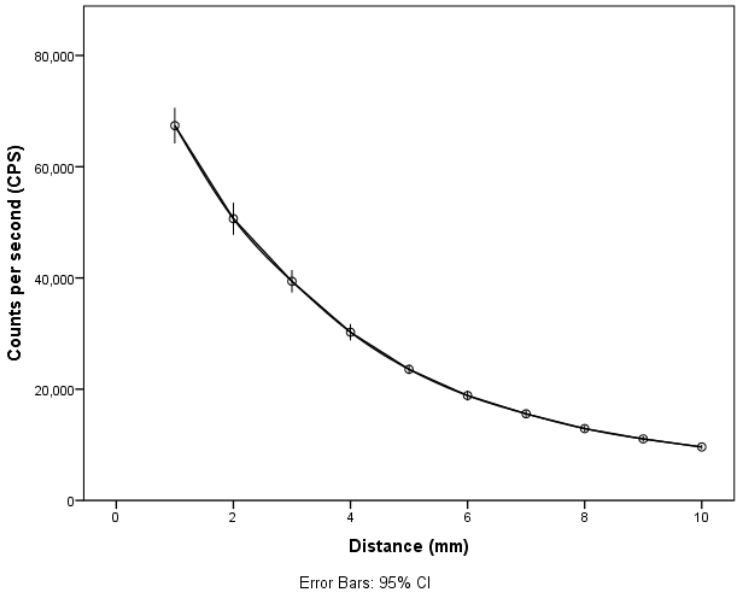
Figure 6.6: Spatial resolution of PET probe



6.4.4 Source detector distance

It was found that the beta count fell approximately half the FWHM of its 1mm value, at about 4mm in distance. This suggests how close the probe must be to the source in order to detect a lesion with a SUV of 2. This is shown in Figure 6.7.

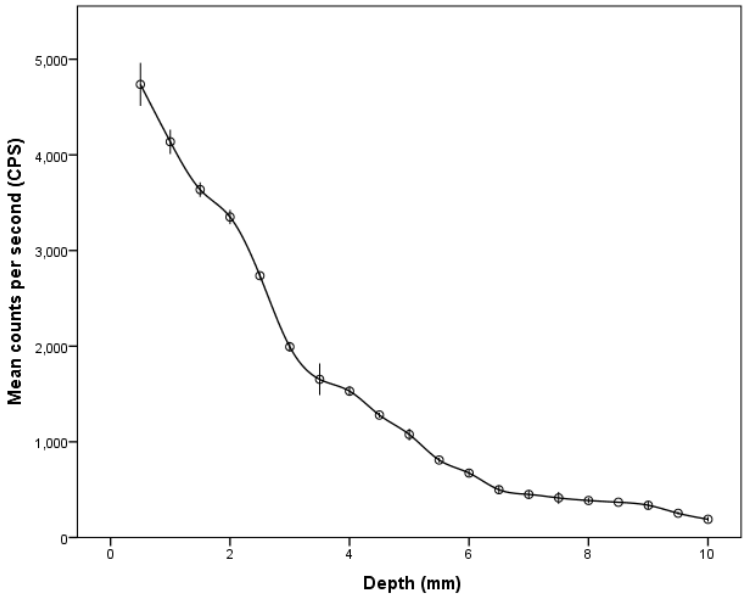
Figure 6.7: Source detector distance of PET probe



6.4.5 Depth response

Results show the beta count falls about half the FWHM of its 1mm value, at approximately 3mm in depth. This indicates how deep under a margin a source can be for the probe to detect a lesion with an SUV of 2. The range of values is shown in Figure 6.8.

Figure 6.8: Depth response of PET probe



6.4.6 Laboratory test comparison

The PET probe performed well when compared to other PET probe tests undertaken by Daghighian[2], Piert[9] and Yamamoto[13]. Table 6.3 shows the comparison of results to these experiments.

Table 6.3: Results published laboratory test methods for PET probe

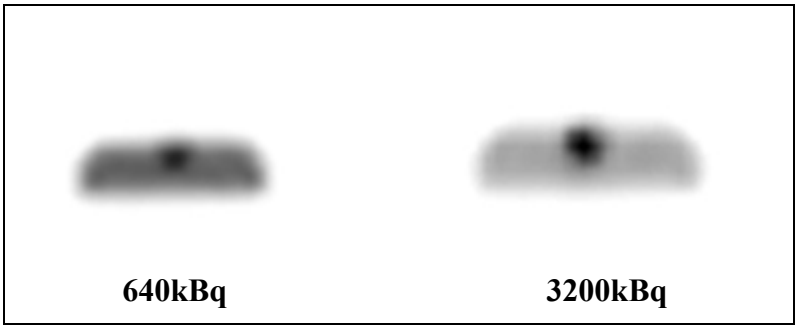
Test (at 1mm from source)	Results			
	This study (FDG)	Daghighian[2] (F-18)	Piert[9] (FDG)	Yamamoto[13] (F-18)
Sensitivity and linearity (1mm without cover)	250 cps/kBq	108 cps/kBq	250 cps/kBq	2.6 cps/kBq (@5mm)
Specific activity (FWHM)	5mm	Not applicable	Results reported tumour to background ratio	Not applicable
Spatial resolution (FWHM)	6mm	10mm	5mm	11mm (@5mm)
Source detector distance (FWHM)	4mm	Not applicable	Not applicable	Not applicable
Depth response (FWHM)	3mm	Not applicable	Not applicable	Not reported

@, at; cps, counts per second; F-18, fluorine-18; F-18 FDG, 18F-fluorodeoxyglucose; FWHM, full width at half maximum; kBq, kilobecquerel; mm, millimetre.

6.4.7 Level of activity

Figure 6.9 shows that the PET probe and PET scanner was able to detect each phantom tumour. At 640kBq and a SUV of 2.2 the CPS were on average 5320, held for 30 seconds. At 3200kBq and a SUV of 10.2 the CPS were on average 10850, held for 30 seconds. The experiment was therefore unable to identify a level where the probe could detect the phantom tumour and the PET scan could not. From SUV calculations we might expect that the 640kBq tumour was at the limit of detection by the PET scan. The PET probe has plenty of dynamic range and further investigation is required to test this hypothesis.

Figure 6.9: Levels of activity PET images



6.5 Discussion

PET imaging was first introduced in Australia in the 1990s. Since 2000 there has been interim approval to use FDG for 21 indications.[15] With more than 15,000 publications demonstrating the use of PET and various radiopharmaceuticals, PET has become part of routine clinical management for a number of indications.[16] However PET does have its limitations, such as false positives where there is the presence of inflammation or infection, uptake in normal tissue, such as the heart, liver, kidney and bladder, and poor sensitivity for tumours under 10mm in size. The development of a handheld device which can be used in surgery to localise tumours or nodes created a number of opportunities for radiopharmaceuticals in surgery. Isotopes such as technetium-99m or indium-111 have been used for a number of years for radioguidance and nodal assessment. However these probes are designed to detect low-energy particles and not high-energy photons. With such radiopharmaceuticals there may be waiting periods following injection before surgery can be performed and poor TTB ratios that can impact on sensitivity.

The administration of FDG allows (requires) surgery to be performed the same day and produces high-energy photons which allow for a better TTB uptake. However the use of FDG requires the use of a probe designed to detect 511keV (kiloelectronvolt). To date several gamma probes have been developed to detect high-energy gammas, but few positron probes to detect beta rays. Such probes will allow not only tumour localisation and nodal assessment, but also allow tumour margin assessment to identify if there is residual disease remaining in the incision site.

The PET probe tested performed well when compared against other reported experiments by Daghighian[2], Piert[9] and Yamamoto[13]. All four studies examined the sensitivity (with or without linearity) of the probe. Whilst the activity of the source was not described by Daghighian[2] or Yamamoto[13], the counts per second per kBq was notably smaller than that reported in this study and Piert[9]. Whilst this could imply the sensitivity of this probe is higher than Daghighian[2] and Yamamoto[13], the probe used in this study was manufactured by the same company as Daghighian[2] and only the type and level of the activity and size of the source could explain the difference. This study and Piert[9] noted a decrease in sensitivity with the probe cover, with a 21% decrease in reported in study and 33% in the Piert[9] study. As noted by Piert[9], gas sterilisation is not

possible and therefore an increased dose is required for intraoperative use to overcome this decrease in sensitivity.

The spatial resolution FWHM reported by Yamamoto[13] (11mm) is nearly twice of that reported by this study (6mm) and Piert[9] (5mm). This means the probe designed by Yamamoto[13] is able to detect a source from a larger lateral distance due to their wider detector diameter. Whilst this means the Yamamoto[13] probe has a wider field for tumour or node localisation, multiple or small tumours/nodes and margin assessment may be difficult to localise.

Piert[9] recommended that future research should include a depth test that identifies the probes' performance when there is 'tissue' of varying thickness between the probe and the tumour. This study found the FWHM was approximately 3mm when the probe was held 1mm above the tumour. This means the probe should be able to detect a lesion with a SUV of 2 up to 3mm beneath the margin, with CPS over 100. This is a significant finding when using the probe to assess surgical margins for residual disease. Yamamoto[13] did not quantify their findings but reported a similar sharp decrease in counts with increased thickness. They also reported a 40 - 50% decrease in sensitivity with the addition of a probe cover.

Piert[9] developed a phantom using small amounts of gel with varying levels of density (15, 25, 75, 250 or 1,000mg). These were inserted into a plastic container filled with gel. The tumour to background ratio was 10. The probe then measured the counts per second for each 'tumour', advancing by 1mm up to 10mm from the source, and CPS for the background activity. They reported the counting ratio between the 'tumour' and background, reporting a decrease as the size of the 'tumour' reduced. The tumour to background ratio for the 1g 'tumour was 1.4:1 and for the 250g tumour 1.3:1. While employing a different method, these results are similar to our specific activity test which found a sharp decrease to a FHWM of 5mm, but the CPS were still over 100 for the 30mm 'tumour'.

Both this study and Piert[9] examined how the PET probe performed against different levels of activity compared to a PET scan. Whilst the PET scan was able to detect all of our samples, we believe the smallest sample was the limit of detection for the PET scan, which returned 5320 CPS with the PET probe. Piert[9] and Raylman[17] suggested such a

limit does exist and small lesions not detected by a PET scan can be identified by an intraoperative PET probe.

Essner[1] compared the spatial resolution of the gamma probe against the PET probe in laboratory tests. They reported the gamma probe was most sensitive at a FWHM 1.7 but sensitivity to detect high-energy positrons was minimal. The PET probe, which was the same probe used in our laboratory tests, had a FWHM of less than 1cm but it was not affected by background radiation and was capable of detecting tumours as small as 2mm. They concluded that 50 CPS as the minimum counts to positively differentiate between tumour and background, with only a 2:1 ratio required.

These laboratory tests and phantom study enabled the investigator to determine that an injected dose of approximately 150MBq would be adequate to detect a source less than 10mm in diameter with the PET probe, cover on. The radiopharmaceutical should be injected 30-45 minutes prior to use and can be used up to two hours after injection. Counts above 50 counts per second should be used as the minimum limit to determine a positive reading.

6.6 Conclusion

The NodeSeeker PET probe performed well in laboratory tests. This probe is able to accurately identify tumours smaller than 10mm in diameter with a good sensitivity and detect tumours beneath a small margin of tissue. These positive findings support the potential use of the PET probe for intraoperative margin assessment. The probe performed well when used with FDG but the administrative dose needs to be increased for larger sized tumours. The findings from these laboratory tests inform clinical use. A much smaller dose compared to clinical imaging doses should be applied to accurately localise tumours/nodes and assess margins.

6.7 References

1. Essner R, Daghighian F, Giuliano AE. Advances in FDG PET probes in surgical oncology. Cancer Journal. 2002; 8(2):100-8.
2. Daghighian F, Mazziotta JC, Hoffman EJ, Shenderov P, Eshaghian B, Siegel S, et al. Intraoperative beta probe: a device for detecting tissue labeled with positron or electron emitting isotopes during surgery. Medical Physics. 1994; 21(1):153-7.
3. Raylman RR, Fisher SJ, Brown RS, Ethier SP, Wahl RL. Fluorine-18-fluorodeoxyglucose-guided breast cancer surgery with a positron-sensitive probe: validation in preclinical studies. Journal of Nuclear Medicine. 1995; 36(10):1869-1874.
4. Strong VE, Galanis CJ, Riedl CC, Longo VA, Daghighian F, Humm JL, et al. Portable PET probes are a novel tool for intraoperative localization of tumor deposits. Annals of Surgical Innovation and Research. 2009; 3:2-2.
5. Essner R, Hsueh EC, Haigh PI, Glass EC, Huynh Y, Daghighian F. Application of an [18F]Fluorodeoxyglucose-sensitive probe for the intraoperative detection of malignancy. Journal of Surgical Research. 2001; 96(1):120-126.
6. Gulec SA, Hoenie E, Hostetter R, Schwartzentruber D. PET probe-guided surgery: applications and clinical protocol. World Journal of Surgical Oncology. 2007; 5:65.
7. Gulec SA, Daghighian F, Essner R. PET-Probe: evaluation of technical performance and clinical utility of a handheld high-energy gamma probe in oncologic surgery. Annals of Surgical Oncology. 2006. July 24 (e-pub http://www.ncbi.nlm.nih.gov/pubmed/16865592).
8. Molina MA, Goodwin WJ, Moffat FL, Serafini AN, Sfakianakis GN, Avisar E. Intra-operative use of PET probe for localization of FDG avid lesions. Cancer Imaging. 2009; 9:59-62.
9. Piert M, Burian M, Meisetschläger G, Stein H, Ziegler S, Nährig J, et al. Positron detection for the intraoperative localisation of cancer deposits. European Journal of Nuclear Medicine and Molecular Imaging. 2007; 34(10):1534-1544.
10. Wahl RL. Current status of PET in breast cancer imaging, staging, and therapy. Seminars in Roentgenology. 2001; 36(3):250-60.
11. Pleijhuis RG, Graafland M, de Vries J, Bart J, de Jong JS, van Dam GM. Obtaining adequate surgical margins in breast-conserving therapy for patients with early-stage breast cancer: current modalities and future directions. Annals of Surgical Oncology. 2009; 16(10):2717-30.
12. Ravi A, Reilly RM, Holloway CM, Caldwell CB. Feasibility evaluation of radioimmunoguided surgery of breast cancer. International Journal of Molecular Imaging. 2012; 2012:545034.
13. Yamamoto S, Matsumoto K, Sakamoto S, Tarutani K, Minato K, Senda M. An intra-operative positron probe with background rejection capability for FDG-guided surgery. Annals of Nuclear Medicine. 2005; 19(1):23-8.
14. Hoffman EJ, Tornai MP, Janecek M, Patt BE, Iwanczyk JS. Intraoperative probes and imaging probes. European Journal of Nuclear Medicine. 1999; 26(8):913-35.

15. Davies PK. The Australian government's review of positron emission tomography: an open door. Medical Journal of Australia. 2004; 180(12):633.

16. Lenzo NP. The Australian government's review of positron emission tomography: evidence-based policy decision-making in action. Medical Journal of Australia. 2004; 181(9):516-7; author reply 517-8.

17. Raylman RR, Kison PV, Wahl RL. Capabilities of two- and three-dimensional FDG-PET for detecting small lesions and lymph nodes in the upper torso: a dynamic phantom study. European Journal of Nuclear Medicine. 1999; 26(1):39-45.

CHAPTER 7 INTRAOPERATIVE POSITRON EMISSION TOMOGRAPHY (PET) PROBE FOR MARGIN ASSESSMENT OF DUCTAL CARCINOMA IN SITU

7.1 Introduction

Chapter 4 reported that the rate of re-excision in Western Australia to obtain adequate surgical margins for ductal carcinoma in situ (DCIS) is 18%. This equates to nearly 1 in 5 women requiring a second operation for re-excision. This has implications on the patients' quality of life with the required additional time for surgery and recovery, the potential additional personal cost and the increased risk of infection or an adverse event. It also impacts on the health service with additional theatre time, staffing, resources and costs. Even when adequate margins were obtained there is a 17% breast cancer event rate in this population. With approximately 96% of breast cancer events occurring at or near the original DCIS site. It could be postulated that not all of the DCIS had been removed.[1, 2]

In Chapter 5 ^{18}F-fluorodeoxyglucose (FDG) was identified to be the most appropriate radiopharmaceutical to use with the positron emission tomography (PET) probe for DCIS surgery and Chapter 6 determined the protocol for use of the probe in surgery. The objectives for this study were to: (1) determine if the use of a PET probe can accurately assess the surgical margins intraoperatively in women undergoing breast conserving therapy (BCT) for DCIS; (2) determine if there is an association between PET probe findings and histological factors such as DCIS size, nuclear grade or necrosis; (3) compare the results of this study with those identified in the systematic literature review; and (4) determine the level of radiation exposure for the surgeon excising and handling the excised tissue.

7.2 Abbreviations

Below is a list of abbreviations used in this chapter:

BCT	breast conserving therapy
CPS	counts per second
DCIS	ductal carcinoma in situ
ER	oestrogen receptor
FDG	^{18}F-fluorodeoxyglucose

FN	false negative
FP	false positive
FUP	follow-up
HER2	human epidermal growth factor receptor 2
ID	identification number
MBq	megabecquerel
mm	millimetre
mSv	millisievert
NS	not specified
PET	positron emission tomography
PR	progesterone receptor
RAPID	Radiopharmaceutical Production and Development Centre
SD	standard deviation
SPSS	Statistical Package for the Social Sciences

7.3 Methods

All patients with newly diagnosed DCIS and booked to undergo BCT at the Mount Hospital, Perth Western Australia, who met the inclusion criteria, were invited to participate in the study.

7.3.1 Eligibility criteria

The eligibility criteria for the study were:

Inclusion Criteria

1. Newly diagnosed DCIS,
2. Planned to undergo wide local excision of DCIS, and
3. Able to provide informed consent.

Exclusion Criteria

1. Planned mastectomy or neoadjuvant therapy for DCIS;
2. Invasive component detected by biopsy;
3. Previous history of invasive breast disease;
4. Uncontrolled diabetes mellitus;
5. Pregnant at the time of surgery.

7.3.2 Sample size

The study was undertaken at a private hospital in Perth, Western Australia, which treated approximately 25 cases of DCIS per year by two surgeons. The study planned to recruit patients for three years and the sample size was calculated at a 50% recruitment rate. As a validation study, a sample size of 35 was determined sufficient to detect the accuracy of the probe in a small setting.

7.3.3 Study procedure

This study was approved by the Human Research Ethics Committees for Curtin University (Appendix B) and the Mount Hospital (Appendix F) and received approval from the Radiological Council of Western Australia (Appendix D). Two surgeons recruited patients for the study. Following identification of DCIS by mammography and diagnosis by biopsy, patients of each surgeon were invited to participate in the study. The surgeon provided the information sheet and consent form to the patient to take home and read. The surgeon would send to the study centre a form with the patient's demographic details (Appendix G). Two business days after the patient's appointment, the Investigator would contact the patient by telephone to enquire if she had read the information and if she had any questions. If the patient agreed to participate the Investigator would contact the RAPID (Radiopharmaceutical Production and Development Centre) team in the Department of Medical Technology and Physics at Sir Charles Gairdner Hospital, who provided the FDG, with information about the date and time of surgery and dose of FDG required. This same information was then sent to the nuclear medicine physician and the breast cancer nursing team at the Mount Hospital.

The FDG was transported from Sir Charles Gairdner Hospital to the Nuclear Medicine Department at the Mount Hospital by specialist courier on the morning of surgery. The Investigator would visit the patient in the morning to answer any other questions and to obtain her written consent (Appendix H). After all other pre-operative procedures have taken place, and approximately forty-five minutes prior to theatre, nuclear medicine physician would inject intravenously either 100 or 150 megabecquerels (MBq) of FDG, through a cannula placed in the arm contralateral to the breast undergoing surgery. The dose administered was alternated between each patient recruited (for example patient one received 100MBq, patient two received 150MBq and so on). A previous study by

Piert[3] indicated the lower dose was sufficient yet the laboratory tests and phantom study indicated a higher dose was required, hence the two dose levels were tested.

Following the injection a nurse from the breast cancer team would place a notice on the patient's room door to inform staff not to disturb the patient or enter the room unless necessary. The patient was then required to lie on her bed until it was time to transport to surgery, preferable in a dimly lit room. Approximately fifteen minutes prior to theatre an orderly would collect the patient, who was required to void before being transported on a gurney to theatre. The patient was then placed in the pre-operative room where the theatre nurse and the Investigator would ensure she had voided and answer any final questions. The patient would then be transported into theatre approximately 35-40 minutes post-injection and the DCIS removed surgically approximately 45-50 minutes post-injection.

Once the DCIS had been removed, the surgeon applied the PET probe with its cover on within the surgical cavity, slowly moving it across the surgical margins. The Investigator would monitor the control unit for the counts per second (CPS). If there was a count above zero, the Investigator would ask the surgeon to hold the probe in place to determine if the count could be replicated and held for 5 seconds. Any held CPS greater than 50 was classified as a positive result but all counts were documented. Although the control unit was electronically capturing and storing the data the Investigator also obtained the exact location (superior, inferior, medial, lateral and deep – superficial was not measured in the cavity) of the probe verbally from the surgeon and documented on a data collection form (Appendix I), the location, maximum and range of CPS captured. The control unit was turned away from the surgeon to blind them of the count rate and the audible tone was turned off. Once all the surfaces on the surgical cavity had been explored, the excised tissue was orientated and pinned to a Styrofoam tray for the Investigator to perform the same procedure on the excised tissue, including any shavings. The Investigator documented any findings on the data capture form, including CPS and margin (including superficial on the excised tissue and shavings). Lastly the Investigator applied the gamma probe over the excised tissue and documented the mean and range of the CPS. As this was a validation study no additional shavings were taken based on the probe result. However, if the surgeon took further shavings based on clinical findings, the PET probe was also applied to the shavings and they were recorded separately but analysed as 'excised tissue'.

The excised sample was then taken to pathology. The pathologist documented the dimensions of the DCIS and reported other routine data (for example, grade, the margins, and necrosis). Clearance was determined as ≥10mm between the surgical margin and the tumour.

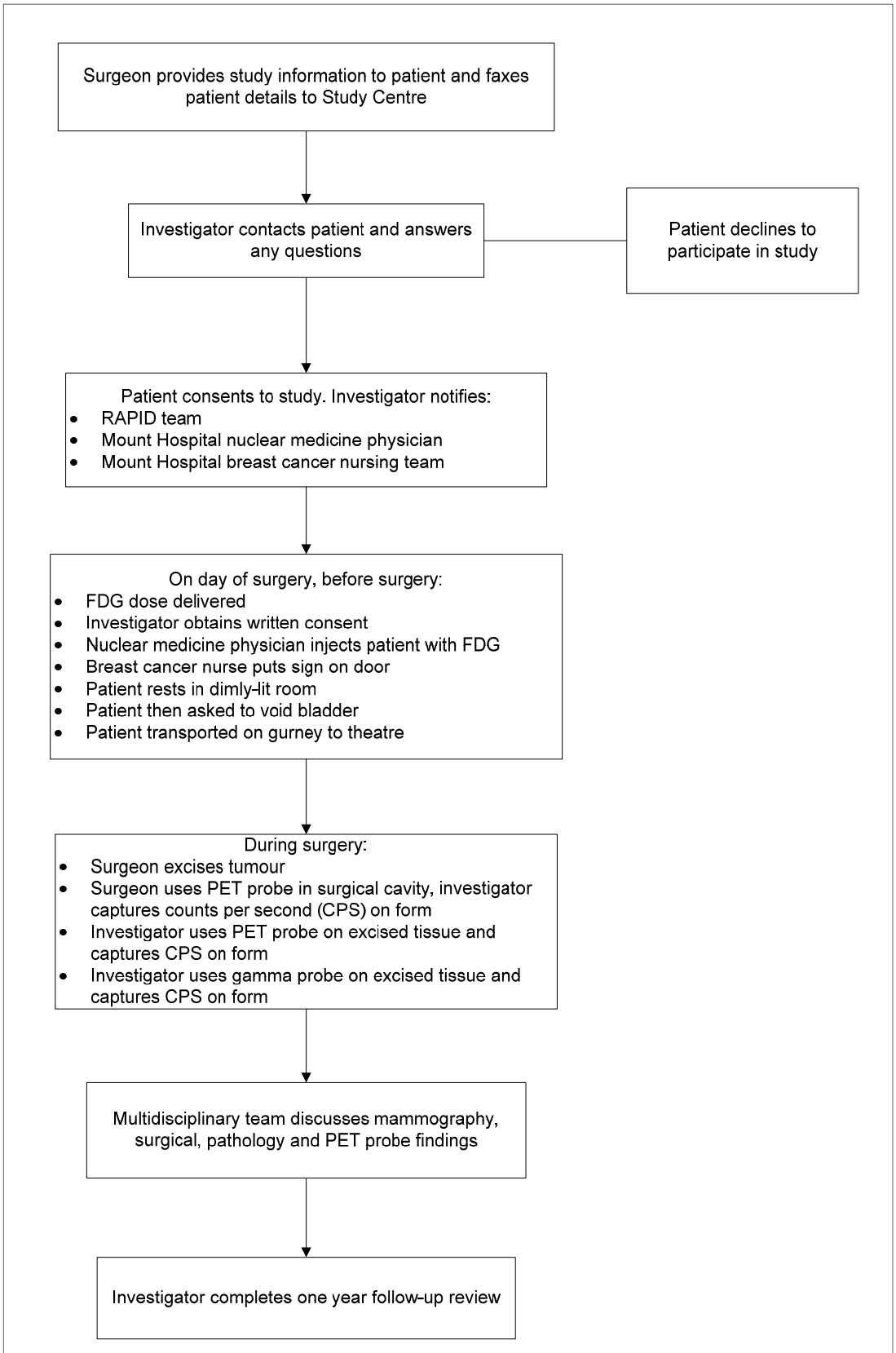
All investigators met within four weeks after final surgery (taking second operations into account) to review the data. No data sharing was arranged between the Investigator and the Mount Hospital prior to this meeting. For each patient, data was presented in the following order:

1. Surgeon specified mammogram and/or ultrasound findings
2. Surgeon specified type of surgery, location of surgery and any problems during surgery.
3. Pathologist specified dimensions of tumour, the margins and presence of any residual disease, specifically invasion.
4. Investigator specified probe findings.
5. Surgeon specified whether a second operation was needed and type of surgery and location of surgery if required.

The Investigator then collected from the hospital and the surgeon's medical records information regarding past medical history, diabetes status, adverse events following surgery, mammography, other imaging findings, other pathology information such as grade, hormonal and human epidermal growth factor 2 (HER2) status, and postoperative therapy (radiotherapy, chemotherapy and tamoxifen). These records were again reviewed 12 months following the initial surgical date, specifically mammography findings, for instances of breast cancer events (defined as recurrence or invasion more than four months following initial surgery). Where the patient had not returned to the surgeon the general practitioner was contacted for this information.

The patient recruitment and study procedures are summarised in Figure 7.1.

Figure 7.1: Participant recruitment flowchart



CPS, counts per second; FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography

7.3.4 Radiation dose and dosimetry

In this study, patients received a pre-surgical FDG injection. The effective dose of radiation for an injected dose of 150MBq of FDG in women is approximately a 4.5 mSv maximum effective dose of radiation. This equals to about eighteen months of natural background radiation.

Piert and colleagues reported a radiation dosimetry burden on clinical staff during surgery following injection of 41.4 to 47.0MBq of FDG.[3] Radiation exposure in surgeons was reported as 0.0025 to 0.0086 mSv/h (per hour), and exposure to the anaesthetist was 0.0008 mSv/h. In the phantom studies completed in Chapter 6, following a stimulated injection of 75MBq, the radiation exposure was 0.003mSv/h following a one hour uptake period.

A number of monitoring and precautionary procedures were put in place during the study. The surgeon, the nuclear medicine physician and the Investigator wore a radiation monitoring badge. Recordings were analysed monthly and procedures could be altered (or the study discontinued) for any abnormal readings, which did not occur. All staff handling the excised tissue or any other biological waste (including urine) was encouraged to wear two sets of gloves. Protocols were developed for urine disposal, distance from patient and room location requirements and provided to all staff in contact with the patient. All pregnant staff, other than the Investigator, was advised not to work closely with the patient until three hours after injection. The Investigator was required to wear a surgical iron gown whilst pregnant and breastfeeding.

7.3.5 Data classification

Each margin has been classified as:

- True positive: where the probe identified FDG avid tissue (the control unit detected an average CPS of ≥50) and histology reported less than 10mm between the margin and the DCIS.
- False Positive: where the probe identified FDG avid tissue (the control unit detected an average CPS of ≥50) but histology reported at least 10mm between the margin and the DCIS. These patients were required to undergo a mammography one year post-surgery to identify any recurrence at the suspected margin. If there was no future recurrence at the margin suspected, the margin

remained a false positive, but if recurrent disease or invasion was identified it became a true positive.

- False Negative: where the probe did not identify any FDG avid tissue (the control unit detected an average CPS of <50) but histology reported less than 10mm between the margin and the DCIS. This was reassessed based on re-excision histology results (where undertaken). If no residual disease was reported by pathology on re-excision, the margin was then classified as true negative. If residual disease was found on re-excision, the margin remained a false negative.
- True Negative: Both the probe did not identify any FDG avid tissue (the control unit detected an average CPS of <50) and histology reported at least 10mm between the margin and the DCIS.

7.3.6 Data collection

As mentioned in section 7.3.3 a data collection sheet was developed to capture intraoperative information. Data were entered onto a database at Curtin University, both electronically from the control unit and manually from data collection sheets. Information entered included age, clinical history and family history for breast diseases, pathology data (histological grade, necrosis, focality and extent of disease, the margins, and presence of residual disease or invasion), surgical notes, imaging findings, management plan before surgery, re-excision data, any adverse events and CPS for the excised tissue and excision cavities. Follow-up data were also entered onto the same database.

7.3.7 Data analysis

Accuracy statistics (including sensitivity and specificity) was calculated for the PET probe results compared to histology, with sub-analysis using injected FDG dose, histological grade and necrosis. T-test and multiple linear regressions were performed to detect the statistical differences when compared to pathological results. Hypothesised risk factors such as nuclear grade, tumour size and necrosis were taken into account. Pearson's correlations were used to assess the association between the probe findings and histological grade. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 21.

7.4 Results

Between December 2008 and January 2012, 44 patients were recruited to participate in the study. Five patients were removed from the study for the following reasons: a pre-surgical review of the biopsy report showed invasion, the FDG dose was not delivered to the Mount Hospital in time for surgery, the fuse on the control unit blew during surgery, and on two occasions surgery was cancelled and rescheduled for a time when the Investigator was unable to attend.

For the 39 patients included, a total of 49 procedures were performed; 39 wide local incisions and ten second operations (re-excision) (BCT or mastectomy). Only the margins during the first operation were examined, with 195 margins examined within the cavity and 234 margins examined on the excised tissue. The mean age of participants was 60.14 years (standard deviation [SD] ±6.37). There were 23 (59.0%) cases of high grade DCIS, and the mean tumour size was 16.14mm (±8.96). The mean follow-up time was 3.58 years (±0.85). There were eight (20.5%) cases of subsequent breast cancer events occurring between 0.44 to 2.83 years. Table 7.1 summarises the patient characteristics of the sample.

There were 50/234 (21.37%) close or involved margins, defined as less than 10mm between the DCIS and the surgical margin. Table 7.2 summarises the number of margins close or involved by margin.

The average dose injected was 110.65MBq (±38.76) of FDG. By the time the PET probe was applied in the surgical cavity, accounting for decay, the average dose was 72.40MBq (±30.37), and applied on the excised tissue was 70.11MBq (±29.45). The average time between injection and the start of surgery was 1 hour and 11 minutes, with the average time to apply the probe in the surgical cavity 1 hour and 22 minutes and on the excised tissue 1 hour and 25 minutes. The additional surgical time to use the probe in the surgical cavity was on average 4 minutes and 5 seconds. Table 7.3 provides the summary information for dose and time since injection.

Table 7.1: Patient characteristics

Age	Range	47.30 – 68.96 years
	Mean±SD	60.14 years±6.37
Breast		
Left		22 (56.41%)
Right		17 (43.59%)
No. procedures		
WLE		39
Re-excision		10 (25.64%)
Positive re-excision		6 (60%)
Histology		
Grade	Low	3 (7.7%)
	Intermediate	13 (33.3%)
	High	23 (59.0%)
Size (diameter)	Range	4 – 40mm
	Mean±SD	16.14mm±8.96
Necrosis present		19 (48.72%)
ER positive		12 (30.8%)
PR positive		8 (20.5%)
HER2 positive		4 (10.3%)
Margins		
In cavity		195
Excised		234
Involved or close margins (pathology)		
Number		50/234 (21.37%)
Range		0.1 – 8.8mm
Mean±SD		3.40mm±2.18
Positive margins by PET probe		
In cavity		47/195 (24.10%)
Excised tissue		58/234 (24.79%)
Gamma recordings	Range	21 – 381 CPS
	Mean±SD	117.69±83.23CPS
Follow-up	Range	1.43 - 4.51 years
	Mean±SD	3.58 years±0.85
Breast cancer events		
Number		10 (25.64%)
Number BCE at site pathology>10mm, PET CPS>0		8
Time to BCE	Range	0.44 – 2.83 years
	Mean±SD	1.37 years±0.82

BCE, breast cancer event; CPS, counts per second; ER, oestrogen receptor; HER2, human epidermal growth factor 2; mm, millimetre; No., number; PET, positron emission tomography; PR, progesterone receptor; SD, standard deviation; WLE, wide local excision.

Table 7.2: Summary of close or involved margin width by margin

Measurements	Superior	Inferior	Medial	Lateral	Superficial	Deep
Number	5	5	9	8	13	10
Range (mm)	2.2 – 3.5	0.5 – 8.0	0.1 – 8.8	1.5 – 7.8	0.7 – 5.0	0.2 – 5.0
Mean (mm) ±SD	3.02±0.49	3.70±2.82	3.43±3.18	5.07±2.39	2.62±1.60	3.08±1.53

mm, millimetre; SD, standard deviation.

Table 7.3: Dose and time since injection summary

	Range	Mean±SD
Injected dose (MBq)	41.4 – 158.8	110.65±38.76
Dose at time of using PET probe in cavity (MBq)	26.6 – 117.5	72.40±30.37
Dose at time of using PET probe on excised tissue (MBq)	26.3 – 113.8	70.11±29.45
Dose at time of using gamma probe on excised tissue (MBq)	25.8 – 111.7	68.26±28.72
Time between injection and start surgery (h:mm:ss)	0:20:00 – 2:30:00	1:11:09±0:04:45
Time between injection and PET probe in cavity(h:mm:ss)	0:30:00 – 2:44:00	1:22:32±0:04:55
Time between injection and probe on excised tissue (h:mm:ss)	0:35:00 – 2:46:00	1:25:56±0:04:49
Additional surgical time (minutes)	2 – 7	4.05±1.26

h:mm:ss, hour:minutes:seconds; MBq, megabecquerel; SD, standard deviation.

There was a high negative association between CPS and margin width within the cavity ($r=-0.785$, $p<0.001$) and on the excised tissue ($r=-0.778$, $p<0.001$). When controlled for dose the association remained significant for in cavity ($r=-0.781$, $p<0.001$) and the excised tissue ($r=-0.781$, $p<0.001$). Table 7.4 shows the correlation between CPS and margin width when adding the conditions of dose at injection, grade, tumour size and necrosis, for both in cavity and the excised tissue. There was a significant negative association between CPS and margin width when the conditions were added.

Table 7.4: Correlation between count per second and margin width, in cavity and excised tissue, with conditions

Conditions	In cavity *	Excised tissue*
Dose	-0.781	-0.781
Grade	-0.786	-0.776
Size	-0.781	-0.779
Necrosis	-0.785	-0.776
Dose + Grade	-0.782	-0.779
Dose + Size	-0.778	-0.781
Dose + Necrosis	-0.779	-0.778
Grade + Size	-0.781	-0.777
Grade + Necrosis	-0.781	-0.776
Size + Necrosis	-0.779	-0.776
Dose + Grade + Size	-0.779	-0.780
Dose + Grade + Necrosis	-0.782	-0.778
Dose + Size + Necrosis	-0.775	-0.778
Grade + Size + Necrosis	-0.782	-0.776
Dose + Grade + Size + Necrosis	-0.778	-0.778

* all values $p \leq 0.001$

Table 7.5 indicates that the accuracy of the PET probe in the cavity compared to a margin width less than 10mm was 89.7% ($p<0.001$) as opposed to 94.5% ($p<0.001$) on the excised tissue. As the literature has reported variable margin width, Table 7.5 provides the accuracy, sensitivity and specificity for 1mm, 2mm, 5mm and 10mm margin widths. At the 10mm margin width any counts recorded on the control unit above zero had a good sensitivity and specificity, with in the cavity sensitivity 83.8% and specificity 89.9%, and on the excised tissue sensitivity 92.0% and specificity 93.5%.

Table 7.5: Accuracy statistics PET probe

	Margin width ≤ (mm)	n	Summary statistics (%)			
			Accuracy*	95% CI	Sensitivity	Specificity
In cavity	10	195	89.7	82.3 – 97.1	83.8	89.9
	5	195	89.4	81.3 – 97.5	85.7	86.2
	2	195	92.5	81.6 - 100	90.9	79.9
	1	195	98.2	95.6 – 100	100	77.9
Excised tissue	10	234	94.5	89.9 – 99.1	92.0	93.5
	5	234	92.0	86.3 – 97.7	90.2	89.1
	2	234	96.5	95.6 – 99.3	93.3	90.1
	1	234	97.2	82.9 – 100	97.5	87.4

* all values $p \leq 0.001$

%, percentage; CI, confidence interval; mm, millimetre; n, number.

The accuracy of the PET probe on an individual margin basis demonstrated the best results in the lateral and deep margins (Tables 7.6 and 7.7), however with only 39 cases the conclusion is only tentative.

Table 7.6: Accuracy statistics by margin for in cavity

Margin	Accuracy (%)*	95% CI
Superior	92.9	77.4 - 100
Inferior	86.1	59.0 - 100
Medial	86.3	67.2 - 100
Lateral	100	100 - 100
Deep	97.2	92.7 - 100

* all values p≤0.001

%, percent; CI, confidence interval; n, number.

Table 7.7: Accuracy statistics by margin for excised tissue

Margin	Accuracy (%)*	95% CI
Superior	96.4	90.9 – 100
Inferior	100	100 – 100
Medial	93.5	81.1 – 100
Lateral	100	100 – 100
Superficial	93.3	83.0 – 100
Deep	100	100 - 100

* all values p≤0.001

%, percent; CI, confidence interval; n, number.

The accuracy of the PET probe was not improved in cases with a positive oestrogen receptor (p=0.341), progesterone receptor (p=0.522) or HER2 (p=0.264) status. The time between injection and applying the probe on the excised tissue did not impact on the accuracy of the probe but the dose did (Table 7.8). Controlling for doses ≥80MBq increased accuracy by 2.5% to 97%.

Table 7.8: Accuracy of PET probe on the excised tissue controlling for time since injection and injected dose.

Variable	Accuracy*	95% CI	Sensitivity	Specificity
No control	94.5	89.9 – 99.1	92.0	93.5
Time ≤150 minutes	94.5	89.9 – 99.1	92.0	93.5
Dose ≥80MBq	97.0	93.7 – 100	97.4	90.6

* all values p≤0.001

CI, confidence interval; MBq, megabecquerels

A multiple regression analysis found both CPS in the cavity (β=0.006, p<0.001) and the excised tissue (β=0.006, p<0.001) significantly correlated with the margin width when controlling for dose, grade, size and necrosis (Tables 7.9 and 7.10).

Table 7.9: Multiple linear regression in cavity results (margin width ≥10mm)

Variable	Coefficient (β)	95% CI	p-value
CPS	0.006	0.005 – 0.006	<0.001
Dose	-0.001	-0.002 – 0.000	0.285
Grade	0.038	-0.033 – 0.109	0.295
Size	0.002	-0.003 – 0.006	0.404
Necrosis	-0.043	-0.135 – 0.049	0.354

CI, confidence interval; CPS, counts per second; mm, millimetre.

Table 7.10: Multiple linear regression on the excised tissue results (margin width ≥10mm)

Variable	Coefficient (β)	95% CI	p-value
CPS	0.006	0.005 – 0.007	<0.001
Dose	-0.001	-0.002 – 0.000	0.022
Grade	-0.010	-0.070 – 0.050	0.738
Size	0.000	-0.004 – 0.004	0.956
Necrosis	-0.003	-0.081 – 0.076	0.946

CI, confidence interval; CPS, counts per second; mm, millimetre.

Multiple regression analyses were next performed for margin widths ≥1, 2, 5 and 10mm (Table 7.11). CPS in the cavity and the excised tissue for all widths significantly correlated with the margin width. Size also significant at ≥1mm in the cavity (p=0.001), dose significant at ≥10mm (p=0.022) and ≥5mm (p=0.022). Necrosis was significant at ≥1mm (p=0.047) and grade significant at ≥2mm (p=0.057).

Table 7.11: Multiple linear regression for varied margin widths

	Margin width ≥ (mm)	Variable p-value CPS	Dose	Grade	Size	Necrosis
In cavity	10	<0.001	0.285	0.295	0.404	0.354
	5	<0.001	0.197	0.768	0.315	0.414
	2	<0.001	0.348	0.103	0.301	0.322
	1	<0.001	0.116	0.811	0.001	0.560
Excised tissue	10	<0.001	0.022	0.738	0.956	0.946
	5	<0.001	0.022	0.738	0.956	0.946
	2	<0.001	0.096	0.057	0.751	0.624
	1	<0.001	0.122	0.943	0.082	0.047

CPS, counts per second; mm, millimetre.

An analysis of the thirteen cases classified as false positive or negative is presented in Table 7.12. In the case where there was a false negative the injected dose was only 55.99MBq. In four cases where the in cavity results were false positive but the excised tissue result agreed with pathology, all occurred in the left breast and the injected dose

was 113-154MBq. The other eight cases were false positive but a breast cancer event subsequently occurred four months or longer following final surgery.

Table 7.12: False positive and negative cases

ID	Age	Breast	Dose	Grade	Size[(a)]	Necrosis	ER	PR	HER2	FUP	Status	Comment
1	54.77	Left	105.31	3	20	+	-	-	-	2.93	Excised FP (superior)	Recurrence 23/52
2	47.30	Left	158.80	2	9	-	+	+	NS	3.59	In cavity & excised FP (superior)	Recurrence 67/52
3	67.19	Left	153.57	2	15	-	-	-	-	3.95	In cavity & excised FP (lateral)	Recurrence 63/52
4	53.12	Left	142.85	3	15	+	-	-	-	3.85	In cavity & excised FP (superficial)	Recurrence 147/52
5	67.78	Right	147.19	2	40	-	+	+	NS	3.60	In cavity & excised FP (superior)	Recurrence 147/52
6	48.62	Left	157.86	2	15	+	-	-	-	3.04	In cavity & excised FP (superficial)	Recurrence 42/52
7	63.61	Left	143.51	3	14	-	-	-	-	4.12	In cavity & excised FP (lateral)	Recurrence 47/52
8	66.62	Right	74.06	3	18	+	-	-	+	4.11	Excised FP (inferior & medial)	Invasion 203/52
9	65.14	Left	125.00	3	14	+	-	-	NS	4.51	In cavity FP	Paget's disease
10	54.73	Left	113.00	3	11	+	+	-	NS	4.31	In cavity FP	No subsequent BCE
11	64.83	Left	154.77	3	14	+	-	-	+	3.88	In cavity FP	No subsequent BCE
12	56.21	Left	127.22	3	7.2	+	-	-	-	4.28	In cavity FP	No subsequent BCE
13	56.93	Right	55.99	2	4	-	-	-	-	4.34	In cavity & excised FN	Injected dose 55.99MBq

(a) in millimetres

+, positive; -, negative; BCE, breast cancer event; ER, oestrogen receptor; FN, false negative; FP, false positive; FUP, follow-up; HER2, human epidermal growth factor 2; ID, identification number; MBq, megabecquerels; NS, not specified; PR, progesterone receptor.

The radiation dose to the surgeon was measured using a finger dosimeter worn in 29 of the cases, with the absorbed radiation dose ranging from 0.003 to 0.030 mSv and a mean 0.009mSv (±0.006). The average dose per hour was 0.021mSv/h and the average surgical time was 29 minutes. For cases with an injected dose ≥100MBq the average dose per hour was 0.025mSv/h. Based on 30 minutes per patient injected ≥100MBq and 50 patients per year, the surgeon's total absorbed radiation would be 0.625mSv, which is a fifth of the natural background radiation.

7.5 Discussion

Breast conserving therapy (BCT) is the preferred method of treatment for DCIS as it is a non-palpable, pre-invasive cancer, but the therapy is associated with a high risk of subsequent breast cancer events.[4] The ability to accurately identify positive margins with a high level of sensitivity whilst aiming for the best cosmetic outcome in DCIS surgery is essential.[5,6] Accurate intraoperative margin assessment can reduce the number of patients requiring a second operation.[7] This is important because second operations impact on the patient, including additional recovery time, time off work and possible need for additional care, decreased quality of life and psychological impacts, potential adverse events from complications, worse cosmetic outcomes and a delay in commencing radiotherapy. They also affect the health care system, including additional staff, theatre and resource requirements and cost.[8]

There is no universal standard margin measurement, with most surgeons aiming for between 2 to 10mm and second operation rates as high as 72%.[1,5,9,10] The site of DCIS, or the tumour bed, is frequently the site of subsequent breast cancer events and therefore complete excision of DCIS is required to reduce the risk of recurrence or invasion.[11] This presents a dilemma, whereby the surgeon needs to ensure adequate margins are obtained whilst achieving the best cosmetic outcome and reducing the need for a second operation.

Chapter 3 reported that pathological measures, such as frozen section, touch smear and imprint cytology, performed best among the intraoperative methods, but added considerable time to the length of the operation (often between 20-30 minutes). Ultrasound was the only other method identified through the systematic review of the literature with a good accuracy and short time duration to return results, yet it has

limitations where there is multifocal disease or calcifications. Whilst a number of other technologies (radiofrequency spectroscopy, optical coherence tomography, gamma camera/probe and mammography) were identified, their accuracy, sensitivity and specificity were much lower or the sample size was very small.

The PET probe in this study demonstrated a high level of accuracy, particularly on the excised tissue with 94.5% accuracy when compared to a margin width less than 10mm and 96.5% accuracy when compared to a margin width less than 2mm. Sensitivity and specificity was also good. The average additional surgical time was 4 minutes and 5 seconds. The probe did not perform differently with different hormonal receptor status, but there was a significant negative association between CPS and margin width when dose, tumour size and necrosis were controlled. Controlling for dose increased accuracy by 2.5% to 97%.

Table 7.13 compares the accuracy of the PET probe against the accuracy of intraoperative margin assessment methods reported in Chapter 3. A number of these studies examined the use of the IMA method with invasive breast cancer, without specifying the results for DCIS alone. This may have improved the statistical results for the method due to the pathology of invasive breast cancer. The PET probe performed well, with a high level of accuracy found with pathological assessment without the long additional surgical time. Whilst the accuracy of the PET probe was 3.1% lower than ultrasound at a ≥2mm margin width, the additional surgical time was not reported for ultrasound making it difficult to draw a conclusion. The PET probe performed better in accuracy than other types of probe technology, namely radiofrequency spectroscopy and the gamma probe, both in the cavity and on the excised tissue.

Table 7.13: Comparison of accuracy of various intraoperative margin assessment methods

IMA method	Author	Optimal margins (mm)	In cavity or on excised tissue	Accuracy (%)	Average additional time
PET probe	Investigator	≥10 ≥5 ≥2 ≥1	Excised	94.5 92.0 96.5 97.2	4 minutes
Ultrasound	Ramos[12]	≥2	Both	99.6	Not reported
Frozen section	Jorns[7]	≥3	Excised	98.3	27 minutes
	Sabel[8]	≥2	Excised	94.0	30 minutes
	Weber[13]	≥1	Excised	83.8	Not reported
	Olson[14]	NR	Excised	98.0	Not reported
Radiofrequency spectroscopy probe	Thill[15]	≥5 ≥2	Cavity	73.0 86.0	Not reported Not reported
Imprint cytology	Martin[16]	>0	Excised	77.8	22 minutes
	Creager[17]	>0	Excised	85.0	20 minutes
Touch smear cytology	Sumiyoshi[18]	>0	Excised	93.8	Not reported
Optical coherence tomography	Nguyen[19]	≥2	Excised	90.0	Not reported
Gamma camera & probe	Paredes[20]	≥5	Both	60	5 minutes
Gross tissue inspection	Cabioglu[21]	≥2	Excised	87.4	Not reported

IMA, intraoperative margin assessment; mm, millimetre; NR, not reported; PET, positron emission tomography.

The sensitivity and specificity rates are equally important measures for evaluating an intraoperative margin assessment method. Table 7.14 compares the sensitivity and specificity of the PET probe against the other methods reported in Chapter 3. Any intraoperative margin assessment should be able to correctly identify a positive margin at a high level. Ultrasound, as reported by Doyle[22], and optical coherence tomography, as reported by Nguyen[19], appeared to possess a higher sensitivity than the PET probe. With a similar small sample size to this study, the OCT specificity was lower than the PET probe. Although ultrasound was 100% sensitive in Doyle's study, other studies reported sensitivity as low as 25%.

Specificity is equally important to enable surgeons to achieve full resection whilst aiming for the best cosmetic outcome for the patient, as recommended by the National Breast Cancer Centre.[5] It is therefore important to identify negative tissue so additional shavings are not unnecessarily taken. Pathological measure, frozen section and imprint cytology, reported a higher specificity than the PET probe, however the additional time in surgery for their application was much higher than the PET probe. Whilst one study for ultrasound only reported 25% sensitivity, the specificity was 95%.

Table 7.14: Comparison of sensitivity and specificity of various intraoperative margin assessment methods.

IMA method	Author	Optimal margins (mm)	In cavity or on excised tissue	Sensitivity (%)	Specificity (%)	Average additional time
PET probe	This study	≥10 ≥5 ≥2 ≥1	Excised	92.0 90.2 93.3 97.5	93.5 89.1 90.1 87.4	4 minutes
Ultrasound	Ramos[12] Olsha[23] Doyle[22]	≥2 ≥2 NR	Both Excised Both	80 25 100	86.6 95 74	NR
Frozen section	Jorns[7] Weber[13] Olson[14]	≥3 ≥1 NR	Excised Excised Excised	91.1 80 73.1	100 87.5 99.6	27 minutes NR NR
Imprint cytology	Martin[16] Creager[17]	>0 >0	Excised Excised	71.4 80	100 85	22 minutes 20 minutes
Touch smear cytology	Sumiyoshi[18]	>0	Excised	70	97.1	NR
Optical coherence tomography	Nguyen[19]	≥2	Excised	100	82	NR
Gross tissue inspection	Cabioglu[21]	≥2	Excised	91.7	77.8	NR
Microscopic margin assessment	Fleming[24]	≥5	Excised	73	88	NR
Radiofrequency spectroscopy probe	Karni[25]	≥1	Excised	71	68	7 minutes
Digital specimen mammography	Kaufman[26]	NR	Excised	36	71	NR
Standard specimen mammography	Kaufman[26] McCormick[27]	NR NR	Excised Excised	31 54.6	74 87.8	NR 15

IMA, intraoperative margin assessment; mm, millimetre; NR, not reported; PET, positron emission tomography.

Overall, the PET probe performed better in sensitivity and specificity than all of the other methods assessed in Chapter 3 except frozen section where PET has a higher sensitivity but frozen section was reported to have a higher specificity and accuracy.

The PET probe performed better when the dose was ≥80MBq. The data showed no statistically significant improvement in accuracy when the time between injection and using the probe intraoperatively was shorter. But accuracy, sensitivity and specificity were improved when the probe was used on the excised tissue as opposed to in the cavity. This may have been due to the time available to slowly examine the excised tissue whilst the surgeon continued with the surgery, however the in cavity results shows the method still has a high level of accuracy, sensitivity and specificity. It

appears that when time is a factor to act upon results from the probe on the excised tissue, accuracy would not be greatly compromised.

Piert[3] reported a lower radiation exposure burden than this study, however they used a smaller injected dose. In this study, for cases with an injected dose ≥100MBq, the average dose was 0.025mSv/h compared to Piert's 0.0025 to 0.0086 mSv/h where 41.4 to 47.0MBq of FDG was injected.

A major limitation of this study is the small sample size and results from the probe were not acted upon, not allowing the impact on second operation rates to be calculated. It is recommended that a large, multi-centre study be undertaken using the PET probe in DCIS surgery, where results are acted upon in the study. The injected dose for patients should be ≥80MBq, the probe be used both in the cavity and the excised tissue (but only the excised tissue where time is a factor) and it is recommended surgery be performed within 2 hours of injection. The probe should also be tested on a range of breast carcinomas. It is also recommended an economic feasibility study be undertaken to determine the cost-benefits of the PET probe.

7.6 Conclusion

In order to achieve adequate margins during breast conserving therapy for DCIS, an intraoperative margin assessment method that can be utilised during surgery to return immediate results with a high accuracy and sensitivity whilst not significantly extending the time of surgery is ideal. The literature has demonstrated that pathological methods, such as frozen section or imprint or touch smear cytology, have a high level of accuracy, sensitivity and specificity, yet they can add an additional 20 to 30 minutes to the surgical time. Ultrasound has demonstrated in some studies to perform well, whilst not incurring too much time to the operation, yet other studies have shown a poor sensitivity for ultrasound and it has limitations where multifocal disease or calcifications are present.

This is the first reported study using a PET probe in DCIS breast conserving therapy. The study findings from 234 surgical margins indicate 94.5% accuracy at ≥10mm and 97.2% accuracy at ≥1mm when used on the excised tissue. The sensitivity and specificity of the probe on the excised tissue was also high, being 92.0% and 93.5% at a

margin width of ≥10mm and 97.5% and 87.4% at ≥1mm, respectively. Ideally the probe should be used within two hours of an injected dose of ≥80MBq and can be used in the cavity or on the excised tissue, but is easier to apply to the excised tissue. It is recommended that this technology be tested in a large multi-centre study to obtain a larger sample size and further test the probe's capacities.

7.7 References

1. Pinder SE. Ductal carcinoma in situ (DCIS): pathological features, differential diagnosis, prognostic factors and specimen evaluation. Modern Pathology. 2010; 23 Suppl 2:S8-13.
2. Silverstein MJ, Figueira Fo A, Novais-Dias E, Salvador-Silva HA, Barros A. The dilemma of appropriate therapy for DCIS. The Van Nuys Breast Centre expereince. 8th International Congress on Senology (Breast Diseases); 1995; Rio de Janeiro, Brazil: Elsevier; 8-12 May 1994. p. 165 - 169.
3. Piert M, Burian M, Meisetschläger G, Stein H, Ziegler S, Nährig J, et al. Positron detection for the intraoperative localisation of cancer deposits. European Journal of Nuclear Medicine and Molecular Imaging. 2007; 34(10):1534-1544.
4. Dener C, Inan A, Sen M, Demirci S. Interoperative frozen section for margin assessment in breast conserving energy. Scandinavian Journal of Surgery. 2009; 98(1):34-40.
5. National Breast Cancer Centre. The clinical management of ductal carcinoma in situ, lobular carcinoma in situ and atypical hyperplasia of the breast, 2003. Camperdown, NSW: National Breast Cancer Centre.
6. Kim SHH, Cornacchi SD, Heller B, Farrokhyar F, Babra M, Lovrics PJ. An evaluation of intraoperative digital specimen mammography versus conventional specimen radiography for the excision of nonpalpable breast lesions. American Journal of Surgery. 2013; 205(6):703-10.
7. Jorns JM, Visscher D, Sabel M, Breslin T, Healy P, Daignaut S, et al. Intraoperative frozen section analysis of margins in breast conserving surgery significantly decreases reoperative rates: one-year experience at an ambulatory surgical center. American Journal of Clinical Pathology. 2012; 138(5):657-669.
8. Sabel MS, Jorns JM, Wu A, Myers J, Newman LA, Breslin TM. Development of an intraoperative pathology consultation service at a free-standing ambulatory surgical center: clinical and economic impact for patients undergoing breast cancer surgery. The American Journal of Surgery. 2012; 204(1):66-77.
9. Silverstein MJ, Buchanan C. Ductal carcinoma in situ: USC/Van Nuys Prognostic Index and the impact of margin status. The Breast. 2003; 12(6):457-471.
10. Dillon MF, Mc Dermott EW, O'Doherty A, Quinn CM, Hill AD, O'Higgins N. Factors affecting successful breast conservation for ductal carcinoma in situ. Annals of Surgical Oncology. 2007; 14(5):1618-28.
11. Duarte GM, Cabello C, Torresan RZ, Alvarenga M, Telles GHQ, Bianchessi ST, et al. Radioguided Intraoperative Margins Evaluation (RIME): preliminary results of a new technique to aid breast cancer resection. European Journal of Surgical Oncology. 2007; 33(10):1150-1157.
12. Ramos M, Diaz JC, Ramos T, Ruano R, Aparicio M, Sancho M, et al. Ultrasound-guided excision combined with intraoperative assessment of gross macroscopic margins decreases the rate of reoperations for non-palpable invasive breast cancer. Breast. 2013; 22(4):520-524.

13. Weber W, Engelberger S, Viehl C, Zanetti-dallenbach R, Kuster S, Dirnhofer S, et al. Accuracy of frozen section analysis versus specimen radiography during breast-conserving surgery for nonpalpable lesions. World Journal of Surgery. 2008; 32(12):2599-2606.

14. Olson TP, Harter J, Muñoz A, Mahvi DM, Breslin T. Frozen section analysis for intraoperative margin assessment during breast-conserving surgery results in low rates of re-excision and local recurrence. Annals of Surgical Oncology. 2007; 14(10):2953-2960.

15. Thill M, Roder K, Diedrich K, Dittmer C. Intraoperative assessment of surgical margins during breast conserving surgery of ductal carcinoma in situ by use of radiofrequency spectroscopy. Breast. 2011; 20(6):579-80.

16. Martin DT, Sandoval S, Ta CN, Ruidiaz ME, Cortes-Mateos MJ, Messmer D, et al. Quantitative automated image analysis system with automated debris filtering for the detection of breast carcinoma cells. Acta Cytologica. 2011; 55(3):271-80.

17. Creager AJ, Shaw JA, Young PR, Geisinger KR. Intraoperative evaluation of lumpectomy margins by imprint cytology with histologic correlation: a community hospital experience. Archives of Pathology & Laboratory Medicine. 2002; 126(7):846-8.

18. Sumiyoshi K, Nohara T, Iwamoto M, Tanaka S, Kimura K, Takahashi Y, et al. Usefulness of intraoperative touch smear cytology in breast-conserving surgery. Experimental and Therapeutic Medicine. 2010; 1(4):641-645.

19. Nguyen FT, Zysk AM, Chaney EJ, Adie SG, Kotynek JG, Oliphant UJ, et al. Optical coherence tomography: the intraoperative assessment of lymph nodes in breast cancer. IEEE Engineering in Medicine and Biology. 2010; 29(2):63-70.

20. Paredes P, Vidal-Sicart S, Zanón G, Roé N, Rubí S, Lafuente S, et al. Radioguided occult lesion localisation in breast cancer using an intraoperative portable gamma camera: first results. European Journal of Nuclear Medicine and Molecular Imaging. 2008; 35(2):230-235.

21. Cabioglu N, Hunt KK, Sahin AA, Kuerer HM, Babiera GV, Singletary SE, et al. Role for intraoperative margin assessment in patients undergoing breast-conserving surgery. Annals of Surgical Oncology. 2007; 14(4):1458-71.

22. Doyle TE, Factor RE, Ellefson CL, Sorensen KM, Ambrose BJ, Goodrich JB, et al. High-frequency ultrasound for intraoperative margin assessments in breast conservation surgery: a feasibility study. BMC Cancer. 2011; 11:444.

23. Olsha O, Shemesh D, Carmon M, Sibirsky O, Abu Dalo R, Rivkin L, et al. Resection margins in ultrasound-guided breast-conserving surgery. Annals of Surgical Oncology. 2011; 18(2):447-452.

24. Fleming FJ, Hill AD, Mc Dermott EW, O'Doherty A, O'Higgins NJ, Quinn CM. Intraoperative margin assessment and re-excision rate in breast conserving surgery. European Journal of Surgical Oncology. 2004; 30(3):233-7.

25. Karni T, Pappo I, Sandbank J, Lavon O, Kent V, Spector R, et al. A device for real-time, intraoperative margin assessment in breast-conservation surgery. American Journal of Surgery. 2007; 194(4):467-73.

26. Kaufman CS, Jacobson L, Bachman BA, Kaufman LB, Mahon C, Gambrell L-J, et al. Intraoperative digital specimen mammography: rapid, accurate results expedite surgery. Annals of Surgical Oncology. 2007; 14(4):1478-1485.

27. McCormick JT, Keleher AJ, Tikhomirov VB, Budway RJ, Caushaj PF. Analysis of the use of specimen mammography in breast conservation therapy. American Journal of Surgery. 2004; 188(4):433-436.

CHAPTER 8 CONCLUSION AND RECOMMENDATIONS

8.1 Conclusion

Ductal carcinoma in situ (DCIS) is a heterogeneous disease characterised as a proliferation of neoplastic cells confined to the mammary duct system of the breast.[1] Research has shown when left untreated, approximately a third of low grade, noncomedo DCIS cases will within 15 years develop into invasive breast cancer.[2] Given these findings the risk of progression for high grade DCIS is much higher. A study identified that 96% of recurrences following complete resection of DCIS were at or near the initial surgical site, and concluded that there was inadequate resection of the primary DCIS.[3] Inadequate margin width can result in a patient requiring a second operation. This rate can vary from 5-72%, with most studies reporting a 20-25% second operation rate.[4] Therefore, the review of DCIS in Chapter 2 concluded that accurately assessing margins intraoperative would reduce the number of second operations required to obtain adequate margins and potentially reduce the subsequent breast cancer event rate.

Intraoperative pathological methods have a high level of accuracy in assessing the surgical margin in breast cancer. However, these methods significantly increase operation time, reported between 20-30 minutes on average. In addition, touch smear and imprint cytology methods only assess the direct surgical margin and do not identify where there may be residual disease deeper than the surface. Ultrasound is often used to guide surgery but the literature showed a high accuracy when used to assess the surgical margins. The advantages of ultrasound is its utilisation in the operating theatre and that it produces results immediately, allowing the decision to take further shavings with minimal impact on operating times. Ultrasound does not generally perform well where there are calcifications or multifocal disease, thus limiting its applicability in DCIS surgery, and a low sensitivity has been reported in the literature.[5] Radiofrequency (RF) spectroscopy reports a statistically significant level of concordance with the standard assessment (pathology) but half of the studies examined used small sample sizes making it difficult to generalise results. Mammography technologies and optical coherence tomography (OCT) have shown promising results, but further research in both of these technologies is required. A review of the literature in Chapter 3 concluded intraoperative pathological methods, including frozen section or imprint/touch smear cytology, and ultrasound currently offer the best means for accurately assessing the surgical margins in DCIS surgery but they have significant limitations.

Chapter 4 reported the epidemiology of DCIS in Western Australia (WA). Between 1996 to 2005 there was 1356 cases of newly diagnosed DCIS in WA, with an *age-standardised incidence rate* (ASR) of 15.4 cases per 100,000 females in 2005. There was 18.07% of cases that required a second operation and 17.3% of cases reporting a subsequent breast cancer event (recurrence or invasion) by the 31 December 2010. An 8-fold increased risk for women under 40 years, relative to those over 40 years, to have a subsequent BCE was determined. And there was a 5-fold increased risk where the DCIS was grade 3, relative to grade 1-2 DCIS. There was an increased risk of a subsequent BCE ($p<0.001$), and specifically invasion ($p<0.001$), where a second operation was not performed. Given the second operation rate reported in WA is lower than that reported in the literature, and the significant rate of subsequent BCEs, Chapter 4 concludes that under the WA protocol, sufficient margins may not be taken during the primary surgery and residual DCIS is remaining in the breast.

Based on the background review of existing technology and the WA epidemiology, there clearly is the need for an intraoperative method that can accurately assess the margins during surgery for DCIS, returning results immediately and therefore decreasing the need for a second operation and potentially reducing subsequent breast cancer event rates. Therefore, a validation study was conducted to (1) identify a suitable radiopharmaceutical tracer for DCIS, and (2) determine the accuracy of a positron emission tomography (PET) probe to evaluate the margin status during BCT for DCIS.

In Chapter 5 two case studies using PET to diagnose DCIS were performed to determine the appropriate radiopharmaceutical to use with the PET probe in DCIS surgery. In both patients the ^{18}F-fluorodeoxyglucose (FDG) reported a better tumour to background ratio over ^{18}F-fluoromethylcholine (FCH) and therefore appeared to be the preferred radiopharmaceutical to use with the PET probe. In addition FDG is clinically available more widely than FCH.

Laboratory testing of the PET probe in Chapter 6 concluded that it was able to accurately identify tumours smaller than 10mm in diameter with a good sensitivity and detect tumours beneath a small margin of tissue. The experiments assisted in establishing the performance of the probe. The recommended dose for surgery (100-150MBq), uptake time (~45 minutes with a 120 minutes post injection window) and

count limits (>50 counts per second) were determined through these experiments, which had not previously been reported in the literature.

The PET probe was used in surgery for 39 patients with primary DCIS. The study findings reported in Chapter 7 from the examination of 234 surgical margins showed an accuracy of 94.5% at a ≥10mm clearance of margins and 97.2% accuracy at a ≥1mm clearance of margins when used on the excised tissue. The sensitivity and specificity of the probe on the excised tissue was also excellent, 92.0% and 93.5% respectively at a clearance margin width of ≥10mm and 97.5% and 87.4% at ≥1mm, respectively. The PET probe performed better in accuracy than other types of probe technology, namely RF spectroscopy, OCT and the gamma probe, both in the cavity and on the excised tissue. Intraoperative pathological methods and ultrasound reported a higher accuracy, but have a number of limitations which was not the case for the PET probe. Overall, the PET probe performed better in sensitivity and specificity than all other IMA methods, except frozen section where PET has a higher sensitivity and returned results immediately whereas frozen section reported a higher specificity and accuracy but took approximately 20 – 30 minutes to return a result.

Overall, the PET probe performed better when the dose was 80MBq or higher and when the time between injection and using the probe was under one hour. Although the probe performed better on the excised tissue, the in cavity results shows the method still has a high level of accuracy, sensitivity and specificity.

In conclusion the PET probe has a high level of accuracy in determining the margin status in DCIS surgery when FDG is injected. Application of the probe added an average four minutes to surgical time and returned results immediately through the control unit. As results were not acted upon, it is difficult to state with certainty the impact this method would have on second operation rates and potentially on subsequent breast cancer events. However, if action were taken, the number of second operations and subsequent breast cancer events could be greatly reduced in the future. Therefore this method has the potential to alter breast conserving surgery for DCIS.

8.2 Recommendations

Subsequent to this research, the following recommendations are made:

1. Undertake a 10 year follow-up for the 39 patients from this study to determine the subsequent BCE rate for comparison against the PET probe result, especially in false positive cases. This will allow identification of cases where there is a subsequent BCE and examine if there is an association to the PET probe results.

2. Conduct further research with a larger sample size and acting on PET probe result in surgery to determine true effect on second operation rates and subsequent breast cancer event rates. It is recommended a multicentre study be conducted to achieve a larger sample size, with a longer recruitment period, to obtain a minimum sample size of 200 patients. Comparisons can be then made to evaluate variation in results with different operators.

3. Conduct a randomised control trial against intraoperative frozen section, with subjects matched by age, cell type and grade as determined by biopsy. As OCT is currently being trialled in Western Australia,[6] there is also the potential to trial this technology with the PET probe. This will allow a comparison of properties such as accuracy, sensitivity and specificity, additional surgical time, second operation rate and BCE rates between methods.

4. With recommendations two and three above, include other in situ and invasive breast cases to determine the accuracy of the PET probe across breast cancer surgical cases. This would potentially widen the application of this technology.

5. Perform an economic evaluation of the above recommendations to identify the cost-benefit of using PET probe technology in breast surgery. This would provide greater information as to the suitability of this technology in routine clinical use.

8.3 References

1. Australian Institute of Health and Welfare, National Breast and Ovarian Cancer Centre. Risk of invasive breast cancer in women diagnosed with ductal carcinoma in situ in Australia between 1995 and 2005, 2010. Canberra, ACT: Australian Institute of Health and Welfare.
2. Sanders ME, Schuyler PA, Dupont WD, Page DL. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. Cancer. 2005; 103(12):2481-2484.
3. Silverstein MJ, Figueira Fo A, Novais-Dias E, Salvador-Silva HA, Barros A. The dilemma of appropriate therapy for DCIS. The Van Nuys Breast Centre expereince. 8th International Congress on Senology (Breast Diseases); 1995; Rio de Janeiro, Brazil: Elsevier; 8-12 May 1994. p. 165 - 169.
4. National Breast Cancer Centre. The clinical management of ductal carcinoma in situ, lobular carcinoma in situ and atypical hyperplasia of the breast, 2003. Camperdown, NSW: National Breast Cancer Centre.
5. Olsha O, Shemesh D, Carmon M, Sibirsky O, Abu Dalo R, Rivkin L, et al. Resection margins in ultrasound-guided breast-conserving surgery. Annals of Surgical Oncology. 2011; 18(2):447-452.
6. McLaughlin RA, Quirk BC, Curatolo A, Kirk RW, Scolaro L, Lorenser D, et al. Imaging of breast cancer with optical coherence tomography needle probes: feasibility and initial results. IEEE Journal of Selected Topics in Quantum Electronics. 2012; 18(3):1184-1191.

9. REFERENCES

Abbey CK, Borowsky AD, McGoldrick ET, Gregg JP,Maglione JE, Cardiff RD, et al. In vivo positron-emission tomography imaging of progression and transformation in a mouse model of mammary neoplasia. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101(31):11438-11443.

Allweis TM, Kaufman Z, Lelcuk S, Pappo I, Karni T, Schneebaum S, et al. A prospective, randomized, controlled, multicenter study of a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. American Journal of Surgery. 2008; 196(4):483-489.

American Cancer Society. Types of biopsy procedures. 2012 [cited 21 December]. Available from: http://www.cancer.org/treatment/understandingyourdiagnosis/examsandtestdescriptions/forwomenfacingabreastbiopsy/breast-biopsy-biopsy-types.

Ariad SS, Milk NN, Bolotin AA, Gopas JJ, Sion-Vardy NN, Benharoch DD. Measles virus antigens in breast cancer. Anticancer research. 2011; 31(3):913-920.

Asjoe FT, Altintas S, Huizing MT, Colpaert C, Marck EV, Vermorken JB, et al. The value of the Van Nuys Prognostic Index in ductal carcinoma in situ of the breast: a retrospective analysis. Breast Journal. 2007; 13(4):359-67.

Australian and New Zealand Breast Cancer Trials Group. Protocol ANZ 9002: DCIS. In: 2003 Annual Scientific Report. Newcastle; 2003. p. 125 - 131.

Australian Bureau of Statistics. Population distribution. Aboriginal and Torres Strait Islander Australians Issue Cat. No. 4705.0, 2002. Canberra: Australian Bureau of Statistics;

Australian Institute of Health and Welfare & Australasian Association of Cancer Registries. Cancer in Australia: an overview, 2012 Issue Cat. no. CAN 70, 2012. Canberra: AIHW.

Australian Institute of Health and Welfare & Cancer Australia. Breast cancer in Australia: an overview Issue Cat. no. CAN 67, 2012. Canberra: AIHW.

Australian Institute of Health and Welfare & National Breast and Ovarian Cancer Centre. Breast cancer in Australia: an overview, 2009 Issue Cat. no. CAN 46, 2009. Canberra: AIHW.

Australian Institute of Health and Welfare, National Breast and Ovarian Cancer Centre. Risk of invasive breast cancer in women diagnosed with ductal carcinoma in situ in Australia between 1995 and 2005, 2010. Canberra, ACT: Australian Institute of Health and Welfare.

Australian Institute of Health and Welfare. BreastScreen Australia monitoring report 2009–2010 Issue Cat. no. CAN 68, 2012. Canberra: AIHW.

Avril N, Rosé CA, Schelling M, Dose J, Kuhn W, Bense S, et al. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations. Journal of Clinical Oncology. 2000; 18(20):3495-3502.

Bailes AA, Kuerer HM, Lari SA, Jones LA, Brewster AM. Impact of race and ethnicity on features and outcome of ductal carcinoma in situ of the breast. Cancer. 2013; 119(1):150-157.

Berg WA, Gutierrez L, NessAiver MS, Carter WB, Bhargavan M, Lewis RS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology. 2004; 233(3):830-849.

Bernardes CM, Whop LJ, Garvey G, Valery PC. Health service utilization by indigenous cancer patients in Queensland: a descriptive study. International Journal for Equity in Health. 2012; 11(1):57.

Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. Journal of Clinical Oncology. 2001; 19(8):2263-71.

Boppart, S.A, Luo, W, Marks, DL, Singletary, KW. Optical coherence tomography: feasibility for basic research and image-guided surgery of breast cancer. Breast Cancer Research and Treatment, 2004. 84(2): p. 85-97.

Cabioglu N, Hunt KK, Sahin AA, Kuerer HM, Babiera GV, Singletary SE, et al. Role for intraoperative margin assessment in patients undergoing breast-conserving surgery. Annals of Surgical Oncology. 2007; 14(4):1458-71.

Cardenose G. Breast imaging companion, 1997. Philadelphia: Lippincott-Raven Publishers.

Cendan JC, Coco D, Copeland EM, 3rd. Accuracy of intraoperative frozen-section analysis of breast cancer lumpectomy-bed margins. Journal of the American College of Surgeons. 2005; 201(2):194-8.

Chagpar A, Yen T, Sahin A, Hunt KK, Whitman GJ, Ames FC, et al. Intraoperative margin assessment reduces reexcision rates in patients with ductal carcinoma in situ treated with breast-conserving surgery. American Journal of Surgery. 2003; 186(4):371-377.

Chakrabarti J, Evans AJ, James J, Ellis IO, Pinder SE, Macmillan RD. Accuracy of mammography in predicting histological extent of ductal carcinoma in situ (DCIS). European Journal of Surgical Oncology. 2006; 32(10):1089-92.

Cheng LL, Al-Kaisi NKN, Gordon NHN, Liu AYA, Gebrail FF, Shenk RRR. Relationship between the size and margin status of ductal carcinoma in situ of the breast and residual disease. Journal of the National Cancer Institute. 1997; 89(18):1356-1360.

Claus EBE, Stowe MM, Carter DD. Breast carcinoma in situ: risk factors and screening patterns. Journal of the National Cancer Institute. 2001; 93(23):1811-1817.

Condon JR, Armstrong BK, Barnes A, Cunningham J. Cancer in indigenous Australians: A review. Cancer Causes & Control. 2003; 14(2):109-21.

Condon JR, Cunningham J, Barnes T, Armstrong BK, Selva-Nayagam S. Cancer diagnosis and treatment in the Northern Territory: assessing health service performance for indigenous Australians. Internal Medicine Journal. 2006; 36(8):498-505.

Creager AJ, Shaw JA, Young PR, Geisinger KR. Intraoperative evaluation of lumpectomy margins by imprint cytology with histologic correlation: a community hospital experience. Archives of Pathology & Laboratory Medicine. 2002; 126(7):846-8.

Crew KD, Gammon MD, Steck SE, Hershman DL, Cremers S, Dworakowski E, et al. Association between plasma 25-hydroxyvitamin D and breast cancer risk. Cancer Prevention Research. 2009; 2(6):598-604.

Curatolo, A, McLaughlin, RA, Quirk, BC, Kirk, RW, Bourke, AG, et al., Ultrasound-guided optical coherence tomography needle probe for the assessment of breast cancer tumor margins. American Journal of Roentgenology, 2012. 199(4): p. W520-W522.

Daghighian F, Mazziotta JC, Hoffman EJ, Shenderov P, Eshaghian B, Siegel S, et al. Intraoperative beta probe: a device for detecting tissue labeled with positron or electron emitting isotopes during surgery. Medical Physics. 1994; 21(1):153-7.

Davies PK. The Australian government's review of positron emission tomography: an open door. Medical Journal of Australia. 2004; 180(12):633.

DeGrado TR, Baldwin SW, Wang S, Orr MD, Liao RP, Friedman HS, et al. Synthesis and evaluation of (18)F-labeled choline analogs as oncologic PET tracers. The Journal of Nuclear Medicine. 2001; 42(12):1805-14.

Dener C, Inan A, Sen M, Demirci S. Interoperative frozen section for margin assessment in breast conserving energy. Scandinavian Journal of Surgery. 2009; 98(1):34-40.

Dervan P. Understanding breast cancer. North Carolina: McFarland & Company, Inc. Publishers; 2001.

D'Halluin F, Tas P, Rouquette S, Bendavid C, Foucher F, Meshba H, et al. Intra-operative touch preparation cytology following lumpectomy for breast cancer: a series of 400 procedures. Breast. 2009; 18(4):248-53.

Dillon MF, Mc Dermott EW, O'Doherty A, Quinn CM, Hill AD, O'Higgins N. Factors affecting successful breast conservation for ductal carcinoma in situ. Annals of Surgical Oncology. 2007; 14(5):1618-28.

Douglas-Jones AG, Logan J, Morgan JM, Johnson R, Williams R. Effect of margins of excision on recurrence after local excision of ductal carcinoma in situ of the breast. Journal of Clinical Pathology. 2002; 55(8):581-6.

Doyle TE, Factor RE, Ellefson CL, Sorensen KM, Ambrose BJ, Goodrich JB, et al. High-frequency ultrasound for intraoperative margin assessments in breast conservation surgery: a feasibility study. BMC Cancer. 2011; 11:444.

Duarte GM, Cabello C, Torresan RZ, Alvarenga M, Telles GH, Bianchessi ST, et al. Radioguided Intraoperative Margins Evaluation (RIME): preliminary results of a new technique to aid breast cancer resection. European Journal of Surgical Oncology. 2007; 33(10):1150-7.

Ellsworth DL, Ellsworth RE, Liebman MN, Hooke JA, Shriver CD. Genomic instability in histologically normal breast tissues: implications for carcinogenesis. Lancet Oncology. 2004; 5(12):753-8.

Ernster VL, Ballard-Barbash R, Barlow WE, Zheng Y, Weaver DL, Cutter G, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. Journal of the National Cancer Institute. 2002; 94(20):1546-54.

Esbona K, Li Z, Wilke LG. Intraoperative imprint cytology and frozen section pathology for margin assessment in breast conservation surgery: a systematic review. Annals of Surgical Oncology. 2012; 19(10):3236-3245.

Essner R, Daghighian F, Giuliano AE. Advances in FDG PET probes in surgical oncology. Cancer Journal. 2002; 8(2):100-8.

Essner R, Hsueh EC, Haigh PI, Glass EC, Huynh Y, Daghighian F. Application of an [18F]Fluorodeoxyglucose-sensitive probe for the intraoperative detection of malignancy. Journal of Surgical Research. 2001; 96(1):120-126.

Estévez LG, Álvarez I, Seguí MÁ, Muñoz M, Margelí M, Miró C, et al. Current perspectives of treatment of ductal carcinoma in situ. Cancer Treatment Reviews. 2010; 36(7):507-517.

Fisher ER, Costantino J, Fisher B, Palekar AS, Redmond C, Mamounas E. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17. Intraductal carcinoma (ductal carcinoma in situ). The National Surgical Adjuvant Breast and Bowel Project Collaborating Investigators. Cancer. 1995; 75(6):1310-9.

Fleming FJ, Hill AD, Mc Dermott EW, O'Doherty A, O'Higgins NJ, Quinn CM. Intraoperative margin assessment and re-excision rate in breast conserving surgery. European Journal of Surgical Oncology. 2004; 30(3):233-7.

Gill JK, Maskarinec G, Pagano I, Kolonel LN. The association of mammographic density with ductal carcinoma in situ of the breast: the Multiethnic Cohort. Breast Cancer Research. 2006; 8(3):R30.

Gilleard O, Goodman A, Cooper M, Davies M, Dunn J. The significance of the Van Nuys prognostic index in the management of ductal carcinoma in situ. World Journal of Surgical Oncology. 2008; 6:61.

Gøtzsche PC. Re: Trends in the treatment of ductal carcinoma in situ of the breast. Journal of the National Cancer Institute. 2004; 96(16):1257.

Gulec SA, Daghighian F, Essner R. PET-Probe: evaluation of technical performance and clinical utility of a handheld high-energy gamma probe in oncologic surgery. Annals of Surgical Oncology. 2006. July 24 (e-pub http://www.ncbi.nlm.nih.gov/pubmed/16865592).

Gulec SA, Hoenie E, Hostetter R, Schwartzentruber D. PET probe-guided surgery: applications and clinical protocol. World Journal of Surgical Oncology. 2007; 5:65.

Hall JA, Knaus JV. An atlas of breast disease. Boca Raton: The Parthenon Publishing Group; 2003.

Harris G, Pinder S, Ellis I. Ductal carcinoma in situ: diagnosis and classification. Current Diagnostic Pathology. 2004; 10(3):204-210.

Hayashi M, Murakami K, Oyama T, Domeki Y, Hagiwara S, Katsumata D, et al. PET/CT supports breast cancer diagnosis and treatment. Breast Cancer. 2008; 15(3):224-230.

Heinisch M, Gallowitsch HJ, Mikosch P, Kresnik E, Kumnig G, Gomez I, et al. Comparison of FDG-PET and dynamic contrast-enhanced MRI in the evaluation of suggestive breast lesions. Breast. 2003; 12(1):17-22.

Hodgson NC, Gulenchyn KY. Is there a role for positron emission tomography in breast cancer staging? Journal of Clinical Oncology. 2008; 26(5):712-720.

Hoffman EJ, Tornai MP, Janecek M, Patt BE, Iwanczyk JS. Intraoperative probes and imaging probes. European Journal of Nuclear Medicine. 1999; 26(8):913-35.

Hughes LL, Wang M, Page DL, Gray R, Solin LJ, Davidson NE, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. Journal of Clinical Oncology. 2009; 27(32):5319-24.

Huston TL, Simmons RM. Locally recurrent breast cancer after conservation therapy. American Journal of Surgery. 2005; 189(2):229-35.

Hwang ES. The impact of surgery on ductal carcinoma in situ outcomes: The use of mastectomy. Journal of the National Cancer Institute Monographs. 2010; 2010(41):197-199.

Ikenaga N, Otomo N, Toyofuku A, Ueda Y, Toyoda K, Hayashi T, et al. Standardized uptake values for breast carcinomas assessed by fluorodeoxyglucose-positron emission tomography correlate with prognostic factors. The American Surgeon. 2007; 73(11):1151-7.

Innos K, Horn-Ross PL. Risk of second primary breast cancers among women with ductal carcinoma in situ of the breast. Breast Cancer Research and Treatment. 2008; 111(3):531-40.

James TA, Harlow S, Sheehey-Jones J, Hart M, Gaspari C, Stanley M, et al. Intraoperative ultrasound versus mammographic needle localization for ductal carcinoma in situ. Annals of Surgical Oncology. 2009; 16(5):1164-1169.

Jeong JW, Shin DC, Do SH, Blanco C, Klipfel NE, Holmes DR, et al. Differentiation of cancerous lesions in excised human breast specimens using multiband attenuation profiles from ultrasonic transmission tomography. Journal of Ultrasound in Medicine. 2008; 27(3):435-51.

Jorns JM, Visscher D, Sabel M, Breslin T, Healy P, Daignaut S, et al. Intraoperative frozen section analysis of margins in breast conserving surgery significantly decreases reoperative rates: one-year experience at an ambulatory surgical center. American Journal of Clinical Pathology. 2012; 138(5):657-669.

Kabat GC, Kim M, Shikany JM, Rodgers AK, Wactawski-Wende J, Lane D, et al. Alcohol consumption and risk of ductal carcinoma in situ of the breast in a cohort of postmenopausal women. Cancer Epidemiology Biomarkers & Prevention. 2010; 19(8):2066-2072.

Karni T, Pappo I, Sandbank J, Lavon O, Kent V, Spector R, et al. A device for real-time, intraoperative margin assessment in breast-conservation surgery. American Journal of Surgery. 2007; 194(4):467-73.

Kaufman CS, Jacobson L, Bachman BA, Kaufman LB, Mahon C, Gambrell L-J, et al. Intraoperative digital specimen mammography: rapid, accurate results expedite surgery. Annals of Surgical Oncology. 2007; 14(4):1478-1485.

Kerlikowske K, Barclay J, Grady D, Sickles EA, Ernster V. Comparison of risk factors for ductal carcinoma in situ and invasive breast cancer. Journal of the National Cancer Institute. 1997; 89(1):76-82.

Kerlikowske K, Molinaro A, Cha I, Ljung BM, Ernster VL, Stewart K, et al. Characteristics associated with recurrence among women with ductal carcinoma in situ treated by lumpectomy. Journal of the National Cancer Institute. 2003; 95(22):1692-702.

Ketcham A, Moffat F. Vexed surgeons, perplexed patients, and breast cancer which may not be be cancer. Cancer. 1990; 65:387 - 393.

Kim SHH, Cornacchi SD, Heller B, Farrokhyar F, Babra M, Lovrics PJ. An evaluation of intraoperative digital specimen mammography versus conventional specimen radiography for the excision of nonpalpable breast lesions. American Journal of Surgery. 2013; 205(6):703-710.

Klimberg VS, Harms S, Korourian S. Assessing margin status. Surgical Oncology. 1999; 8(2):77-84.

Kricker A, Armstrong B. Surgery and outcomes of ductal carcinoma in situ of the breast: a population-based study in Australia. European Journal of Cancer. 2004; 40(16):2396-2402.

Kricker A, Goumas C, Armstrong B. Ductal carcinoma in situ of the breast, a population-based study of epidemiology and pathology. British Journal of Cancer. 2004; 90(7):1382-1385.

Kumar S, Sacchini V. The surgical management of ductal carcinoma in situ. Breast Journal. 2010; 16 Suppl 1:S49-52.

Kwee SA, Coel MN. Detection of synchronous primary breast and prostate cancer by F-18 fluorocholine PET/CT. Clinical Nuclear Medicine. 2010; 35(2):128-129.

Lenzo NP. The Australian government's review of positron emission tomography: evidence-based policy decision-making in action. Medical Journal of Australia. 2004; 181(9):516-7; author reply 517-8.

Li CI, Malone KE, Saltzman BS, Daling JR. Risk of invasive breast carcinoma among women diagnosed with ductal carcinoma in situ and lobular carcinoma in situ, 1988-2001. Cancer. 2006; 106(10):2104-12.

Longnecker M, Bernstein L, Paganini-Hill A, Enger S, Ross R. Risk factors for in situ breast cancer. Cancer Epidemiology, Biomarkers & Prevention. 1996; 5:961 - 965.

Ma H, Henderson K, Sullivan-Halley J, Duan L, Marshall S, Ursin G, et al. Pregnancy-related factors and the risk of breast carcinoma in situ and invasive breast cancer among postmenopausal women in the California Teachers Study cohort. Breast Cancer Research. 2010; 12(3):R35.

Macdonald HR, Silverstein MJ, Lee LA, Ye W, Sanghavi P, Holmes DR, et al. Margin width as the sole determinant of local recurrence after breast conservation in patients with ductal carcinoma in situ of the breast. The American Journal of Surgery. 2006; 192(4):420-422.

MacDonald HR, Silverstein MJ, Mabry H, Moorthy B, Ye W, Epstein MS, et al. Local control in ductal carcinoma in situ treated by excision alone: incremental benefit of larger margins. The American Journal of Surgery. 2005; 190(4):521-525.

Man YG, Zhang Y, Shen T, Zeng X, Tauler J, Mulshine JL, et al. cDNA expression profiling reveals elevated gene expression in cell clusters overlying focally disrupted myoepithelial cell layers: implications for breast tumor invasion. Breast Cancer Research and Treatment. 2005; 89(2):199-208.

Martin DT, Sandoval S, Ta CN, Ruidiaz ME, Cortes-Mateos MJ, Messmer D, et al. Quantitative automated image analysis system with automated debris filtering for the detection of breast carcinoma cells. Acta Cytologica. 2011; 55(3):271-80.

Masood S. Is it time to retire the term of “In Situ Carcinoma” and use the term of “Borderline Breast Disease?”. The Breast Journal. 2010; 16(6):571-572.

McCormick JT, Keleher AJ, Tikhomirov VB, Budway RJ, Caushaj PF. Analysis of the use of specimen mammography in breast conservation therapy. American Journal of Surgery. 2004; 188(4):433-436.

McLaughlin RA, Quirk BC, Curatolo A, Kirk RW, Scolaro L, Lorenser D, et al. Imaging of breast cancer with optical coherence tomography needle probes: feasibility and initial results. IEEE Journal of Selected Topics in Quantum Electronics. 2012; 18(3):1184-1191.

Meijnen P, Gilhuijs KG, Rutgers EJ. The effect of margins on the clinical management of ductal carcinoma in situ of the breast. Journal of Surgical Oncology. 2008; 98(8):579-84.

Meijnen P, Peterse JL, Oldenburg HSA, Woerdeman LAE, Rutgers EJT. Changing patterns in diagnosis and treatment of ductal carcinoma in situ of the breast. European Journal of Surgical Oncology. 2005; 31(8):833-839.

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. International Journal of Surgery. 2010; 8(5):336-341.

Mokbel K, Cutuli B. Heterogeneity of ductal carcinoma in situ and its effects on management. The Lancet Oncology. 2006; 7(9):756-765.

Molina MA, Goodwin WJ, Moffat FL, Serafini AN, Sfakianakis GN, Avisar E. Intra-operative use of PET probe for localization of FDG avid lesions. Cancer Imaging. 2009; 9:59-62.

Moore MM, Whitney LA, Cerilli L, Imbrie JZ, Bunch M, Simpson VB, et al. Intraoperative ultrasound is associated with clear lumpectomy margins for palpable infiltrating ductal breast cancer. Annals of Surgery. 2001; 233(6):761-768.

Morrow M, O'Sullivan MJ. The dilemma of DCIS. The Breast. 2007; 16(Supplement 2):59-62.

National Breast and Ovarian Cancer Centre. Understanding ductal carcinoma in situ., 2010. Surry Hills, NSW: National Breast and Ovarian Cancer Centre.

National Breast Cancer Centre. Ductal carcinoma in situ, 2004. Camperdown: National Breast Cancer Centre.

National Breast Cancer Centre. The clinical management of ductal carcinoma in situ, lobular carcinoma in situ and atypical hyperplasia of the breast, 2003. Camperdown, NSW: National Breast Cancer Centre.

Neuschatz AC, DiPetrillo T, Safaii H, Lowther D, Landa M, Wazer DE. Margin width as a determinant of local control with and without radiation therapy for ductal carcinoma in situ (DCIS) of the breast. International Journal of Cancer. 2001; 96 Suppl:97-104.

Neuschatz AC, DiPetrillo T, Steinhoff M, Safaii H, Yunes M, Landa M, et al. The value of breast lumpectomy margin assessment as a predictor of residual tumor burden in ductal carcinoma in situ of the breast. Cancer. 2002; 94(7):1917-24.

Nguyen FT, Zysk AM, Chaney EJ, Kotynek, JG, Oliphant UJ, Bellafiore FJ, et al. Intraoperative evaluation of breast tumor margins with optical coherence tomography. Cancer Research, 2009. 69(22): p. 8790-8796.

Olsha O, Shemesh D, Carmon M, Sibirsky O, Abu Dalo R, Rivkin L, et al. Resection margins in ultrasound-guided breast-conserving surgery. Annals of Surgical Oncology. 2011; 18(2):447-452.

Olson TP, Harter J, Muñoz A, Mahvi DM, Breslin T. Frozen section analysis for intraoperative margin assessment during breast-conserving surgery results in low rates of re-excision and local recurrence. Annals of Surgical Oncology. 2007; 14(10):2953-2960.

Page D, Dupont W, Rogers L, Jensen R, Schuyler P. Continued local recurrence of carcinoma 15-25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated only by biopsy. Cancer. 1995; 76:1197 - 1200.

Paredes P, Vidal-Sicart S, Zanon G, Roe N, Rubi S, Lafuente S, et al. Radioguided occult lesion localisation in breast cancer using an intraoperative portable gamma camera: first results. European Journal of Nuclear Medicine and Molecular Imaging. 2008; 35(2):230-5.

Peñuelas I, Domínguez-Prado I, García-Velloso MJ, Martí-Climent JM, Rodríguez-Fraile M, Caicedo C, et al. PET tracers for clinical imaging of breast cancer. Journal of Oncology. 2012; 2012:710561.

Phillips M, Cataneo RN, Saunders C, Hope P, Schmitt P, Wai J. Volatile biomarkers in the breath of women with breast cancer. Journal of Breath Research. 2010; 4(2).

Piert M, Burian M, Meisetschläger G, Stein H, Ziegler S, Nährig J, et al. Positron detection for the intraoperative localisation of cancer deposits. European Journal of Nuclear Medicine and Molecular Imaging. 2007; 34(10):1534-1544.

Pinder S, Ellis I. The diagnosis and management of pre-invasive breast disease: Ductal carcinoma in situ (DCIS) and atypical ductal hyperplasia (ADH) - current definitions and classification. Breast Cancer Research. 2003; 5(5):254 - 257.

Pinder SE, Duggan C, Ellis IO, Cuzick J, Forbes JF, Bishop H, et al. A new pathological system for grading DCIS with improved prediction of local recurrence: results from the UKCCCR/ANZ DCIS trial. British Journal of Cancer. 2010; 103(1):94-100.

Pinder SE, Provenzano E. Pathology: ductal carcinoma in situ and lesions of uncertain malignant potential. In: Mitchell M, editor. Breast Cancer. Cambridge: Cambridge University Press; 2010. p. 127 - 145.

Pinder SE. Ductal carcinoma in situ (DCIS): pathological features, differential diagnosis, prognostic factors and specimen evaluation. Modern Pathology. 2010; 23 Suppl 2:S8-13.

Pleijhuis RG, Graafland M, de Vries J, Bart J, de Jong JS, van Dam GM. Obtaining adequate surgical margins in breast-conserving therapy for patients with early-stage breast cancer: current modalities and future directions. Annals of Surgical Oncology. 2009; 16(10):2717-30.

RadiologyInfo. Breast Ultrasound. 2012 [cited 21 December 2013]. Available from: http://www.radiologyinfo.org/en/info.cfm?pg=breastus.

RadiologyInfo. Mammography. 2012 [cited 21 December 2013]. Available from: http://www.radiologyinfo.org/en/info.cfm?pg=mammo.

RadiologyInfo. MRI of the Breast. 2012 [cited 21 December 2013]. Available from: http://www.radiologyinfo.org/en/info.cfm?pg=breastmr.

Rahusen FD, Bremers AJ, Fabry HF, J, van Amerongen AH, Boom RP, Meijers S, et al. Ultrasound-guided lumpectomy of nonpalpable breast cancer versus wire-guided resection: a randomized clinical trial. Annals of Surgical Oncology. 2002; 9(10):994-8.

Rakovitch E, Pignol JP, Chartier C, Hanna W, Kahn H, Wong J, et al. The management of ductal carcinoma in situ of the breast: a screened population-based analysis. Breast Cancer Research and Treatment. 2007; 101(3):335-47.

Ramos M, Diaz JC, Ramos T, Ruano R, Aparicio M, Sancho M, et al. Ultrasound-guided excision combined with intraoperative assessment of gross macroscopic margins decreases the rate of reoperations for non-palpable invasive breast cancer. Breast. 2013; 22(4):520-524.

Ravi A, Reilly RM, Holloway CM, Caldwell CB. Feasibility evaluation of radioimmunoguided surgery of breast cancer. International Journal of Molecular Imaging. 2012; 2012:545034.

Raylman RR, Fisher SJ, Brown RS, Ethier SP, Wahl RL. Fluorine-18-fluorodeoxyglucose-guided breast cancer surgery with a positron-sensitive probe: validation in preclinical studies. Journal of Nuclear Medicine. 1995; 36(10):1869-1874.

Raylman RR, Fisher SJ, Brown RS, Ethier SP, Wahl RL. Fluorine-18-fluorodeoxyglucose-guided breast cancer surgery with a positron-sensitive probe: validation in preclinical studies. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 1995; 36(10):1869-1874.

Raylman RR, Kison PV, Wahl RL. Capabilities of two- and three-dimensional FDG-PET for detecting small lesions and lymph nodes in the upper torso: a dynamic phantom study. European Journal of Nuclear Medicine. 1999; 26(1):39-45.

Reeves GK, Pirie K, Green J, Bull D, Beral V. Comparison of the effects of genetic and environmental risk factors on in situ and invasive ductal breast cancer. International Journal of Cancer. 2012; 131(4):930-937.

Rivera RJ, Holmes DR, Tafra L. Analysis of the impact of intraoperative margin assessment with adjunctive use of MarginProbe versus standard of care on tissue volume removed. International Journal of Surgical Oncology. 2012; 2012:868623.

Rosai J. Borderline epithelial lesions of the breast. American Journal of Surgical Pathology. 1991; 15(3):209-21.

Rose DP, Royak-Schaler R. Tumor biology and prognosis in black breast cancer patients: a review. Cancer Detection and Prevention. 2001; 25(1):16-31.

Rundle A, Tang D, Hibshoosh H, Estabrook A, Schnabel F, Cao W, et al. The relationship between genetic damage from polycyclic aromatic hydrocarbons in breast tissue and breast cancer. Carcinogenesis. 2000; 21(7):1281-9.

Sabel MS, Jorns JM, Wu A, Myers J, Newman LA, Breslin TM. Development of an intraoperative pathology consultation service at a free-standing ambulatory surgical center: clinical and economic impact for patients undergoing breast cancer surgery. The American Journal of Surgery. 2012; 204(1):66-77.

Sakorafas GH, Farley DR. Optimal management of ductal carcinoma in situ of the breast. Surgical Oncology. 2003; 12(4):221-40.

Sanders ME, Schuyler PA, Dupont WD, Page DL. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. Cancer. 2005; 103(12):2481-2484.

Schouten van der Velden AP, Peeters PH, Koot VC, Hennipman A. Local recurrences after conservative treatment of ductal carcinoma-in-situ of the breast without radiotherapy: the effect of age. Annals of Surgical Oncology. 2006; 13(7):990-8.

Schouten van der Velden AP, Van Dijck JAAM, Wobbes T. Variations in treatment of ductal carcinoma in situ of the breast: A population-based study in the East Netherlands. European Journal of Surgical Oncology. 2007; 33(4):424-429.

Shamliyan T, Wang SY, Virnig BA, Tuttle TM, Kane RL. Association between patient and tumor characteristics with clinical outcomes in women with ductal carcinoma in situ. Journal of the National Cancer Institute Monographs. 2010; 2010(41):121-9.

Sheppard AJM, Chiarelli AMP, Marrett LDP, Mirea LM, Nishri EDM, Trudeau MEMD. Detection of later stage breast cancer in First Nations Women in Ontario, Canada. Canadian Journal of Public Health. 2010; 101(1):101-5.

Shiraishi A, Kurosaki Y, Maehara T, Suzuki M, Kurosumi M. Extension of ductal carcinoma in situ: histopathological association with MR imaging and mammography. Magnetic Resonance in Medical Sciences. 2003; 2(4):159-63.

Shugg D, White VM, Kitchen PR, Pruden M, Collins JP, Hill DJ. Surgical management of ductal carcinoma in situ in Australia in 1995. Australian and New Zealand Journal of Surgery. 2002; 72(10):708-15.

Sigal-Zafrani B, Lewis JS, Clough KB, Vincent-Salomon A, Fourquet A, Meunier M, et al. Histological margin assessment for breast ductal carcinoma in situ: precision and implications. Modern Pathology. 2004; 17(1):81-8.

Silverstein M, Poller D, Waisman J, Colburn W, Barth A, Gierson E, et al. Prognostic classification of breast ductal carcinoma-in-situ. Lancet. 1995; 345:1154 - 1157.

Silverstein MJ, Figueira Fo A, Novais-Dias E, Salvador-Silva HA, Barros A. The dilemma of appropriate therapy for DCIS. The Van Nuys Breast Centre expereince. 8th International Congress on Senology (Breast Diseases); 1995; Rio de Janeiro, Brazil: Elsevier; 8-12 May 1994. p. 165 - 169.

Silverstein MJ, Buchanan C. Ductal carcinoma in situ: USC/Van Nuys Prognostic Index and the impact of margin status. The Breast. 2003; 12(6):457-471.

Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. New England Journal of Medicine. 1999; 340(19):1455-1461.

Singh V, Saunders C, Wylie L, Bourke A. New diagnostic techniques for breast cancer detection. Future Oncol. 2008; 4(4):501-13.

Smith BD, Gross CP, Smith GL, Galusha DH, Bekelman JE, Haffty BG. Effectiveness of radiation therapy for older women with early breast cancer. Journal of the National Cancer Institute. 2006; 98(10):681-90.

Stoll BA. Adiposity as a risk determinant for postmenopausal breast cancer. International Journal of Obesity and related Metabolic Disorders. 2000; 24(5):527-33.

STROBE Initiative. STROBE statement. 2013 [cited 31 May 2013]. Available from: http://www.strobe-statement.org/

Strong VE, Galanis CJ, Riedl CC, Longo VA, Daghighian F, Humm JL, et al. Portable PET probes are a novel tool for intraoperative localization of tumor deposits. Annals of Surgical Innovation and Research. 2009; 3:2-2.

Sumiyoshi K, Nohara T, Iwamoto M, Tanaka S, Kimura K, Takahashi Y, et al. Usefulness of intraoperative touch smear cytology in breast-conserving surgery. Experimental and Therapeutic Medicine. 2010; 1(4):641-645.

The JS, Schilling KJ, Hoffmeister JW, Friedmann E, McGinnis R, Holcomb RG. Detection of breast cancer with full-field digital mammography and computer-aided detection. 2009; American Journal of Roentgenology. 192(2):337-40.

Thill M, Roder K, Diedrich K, Dittmer C. Intraoperative assessment of surgical margins during breast conserving surgery of ductal carcinoma in situ by use of radiofrequency spectroscopy. Breast. 2011; 20(6):579-80.

Thill M. MarginProbe(®): intraoperative margin assessment during breast conserving surgery by using radiofrequency spectroscopy. Expert Review of Medical Devices. 2013; 10(3):301-315.

Treglia G, Giovannini E, Di Franco D, Calcagni ML, Rufini V, Picchio M, et al. The role of positron emission tomography using carbon-11 and fluorine-18 choline in tumors other than prostate cancer: a systematic review. Annals of Nuclear Medicine. 2012; 26(6):451-461.

Ueda S, Tsuda H, Asakawa H, Shigekawa T, Fukatsu K, Kondo N, et al. Clinicopathological and prognostic relevance of uptake level using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (^{18}F-FDG PET/CT) in primary breast cancer. Japanese Journal of Clinical Oncology. 2008; 38(4):250-8.

van de Vijver MJ. Biological variables and prognosis of DCIS. The Breast. 2005; 14(6):509-519.

Vapiwala N, Harris E, Hwang WT, Solin LJ. Long-term outcome for mammographically detected ductal carcinoma in situ managed with breast conservation treatment: prognostic significance of reexcision. Cancer Journal. 2006; 12(1):25-32.

Verkooijen HM, Fioretta G, De Wolf C, Vlastos G, Kurtz J, Borisch B, et al. Management of women with ductal carcinoma in situ of the breast: a population-based study. Annals of Oncology. 2002; 13(8):1236-45.

Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. Journal of the National Cancer Institute. 2010; 102(3):170-8.

WA Cancer Registry. Health data collections, 2004. Perth: Department of Health Western Australia.

Wahl RL. Current status of PET in breast cancer imaging, staging, and therapy. Seminars in Roentgenology. 2001; 36(3):250-60.

Warren JL, Weaver DL, Bocklage T, Key CR, Platz CE, Cronin KA, et al. The frequency of ipsilateral second tumors after breast-conserving surgery for DCIS: a population based analysis. Cancer. 2005; 104(9):1840-8.

Weber WP, Engelberger S, Viehl CT, Zanetti-Dallenbach R, Kuster S, Dirnhofer S, et al. Accuracy of frozen section analysis versus specimen radiography during

breast-conserving surgery for nonpalpable lesions. World Journal of Surgery. 2008; 32(12):2599-2606.

Weiss HA, Brinton LA, Brogan D, Coates RJ, Gammon MD, Malone KE, et al. Epidemiology of in situ and invasive breast cancer in women aged under 45. British Journal of Cancer. 1996; 73(10):1298–1305.

Weng EY, Juillard GJ, Parker RG, Chang HR, Gornbein JA. Outcomes and factors impacting local recurrence of ductal carcinoma in situ. Cancer. 2000; 88(7):1643-9.

White V, Pruden M, Kitchen P, Villanueva E, Erbas B. The impact of publication of Australian treatment recommendations for DCIS on clinical practice: A population-based, "before-after" study. European Journal of Surgical Oncology. 2010; 36(10):949-956.

Willsher P, Wylie L, Bettenay F, Anderson J, Saunders C, Metcalf C, et al. 4th Scientific Meeting of the Australasian Society for Breast Disease. How accurate is the mammogram in determining the extent of DCIS? , 2004 The Breast.

Wong AY, Salisbury E, Bilous M. Recent developments in stereotactic breast biopsy methodologies: an update for the surgical pathologist. Advances in Anatomical Pathology. 2000; 7(1):26-35.

Yamada T, Mori N, Watanabe M, Kimijima I, Okumoto T, Seiji K, et al. Radiologic-pathologic correlation of ductal carcinoma in situ. Radiographics. 2010; 30(5):1183-1198.

Yamamoto S, Matsumoto K, Sakamoto S, Tarutani K, Minato K, Senda M. An intra-operative positron probe with background rejection capability for FDG-guided surgery. Annals of Nuclear Medicine. 2005; 19(1):23-8.

Yang WT, Tse GMK. Sonographic, mammographic, and histopathologic correlation of symptomatic ductal carcinoma in situ. American Journal of Roentgenology. 2004; 182(1):101-110.

Zakhour H, Wells C. Diagnostic cytopathology of the breast. London: Harcourt Publishers Ltd.; 1999.

Zeleniuch-Jacquotte A, Gu Y, Shore RE, Koenig KL, Arslan AA, Kato I, et al. Postmenopausal levels of sex hormones and risk of breast carcinoma in situ: Results of a prospective study. International Journal of Cancer. 2005; 114(2):323-327.

Zelis JJ, Sickle-Santanello BJ, Liang WC, Nims TA. Do not contemplate invasive surgery for ductal carcinoma in situ. The American Journal of Surgery. 2002; 184(4):348-349.

APPENDIX A: QUALITY ASSESSMENT TOOL (CHAPTER 3).

Category	Parameters	/Score
Title/abstract/ background	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found *(c)* Explain the scientific background and rationale for the investigation being reported *(d)* State specific objectives, including any pre-specified hypotheses	1
Methods	*(a)* Present key elements of study design early in the paper *(b)* Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (*c*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria & the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants *(d)* Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable *(e)* For each variable of interest, give sources of data & details of methods of assessment. Describe comparability of assessment methods if there is more than one group *(f)* Describe any efforts to address potential sources of bias *(g)* Explain how the study size was arrived at	4
Statistical Analysis	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4
Results	*(a)* Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed *(b)* Give reasons for non-participation at each stage *(c)* Consider use of a flow diagram *(e)* Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders *(f)* Indicate number of participants with missing data for each variable of interest *(g) Cohort study*—Summarise follow-up time (eg, average and total amount) *Cohort study*—Report numbers of outcome events or summary measures over time *Case-control study*—Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study*—Report numbers of outcome events or summary measures *(h)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
Discussion	*(a)* Summarise key results with reference to study objectives *(b)* Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias *(c)* Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence *(d)* Discuss the generalisability (external validity) of the study results	3
Funding	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1
	Overall score	20

APPENDIX B: HUMAN RESEARCH ETHICS COMMITTEE CURTIN UNIVERSITY LETTER OF APPROVAL

memorandum

To	Professor Andy Lee Public Health
From	Dr Stephan Millett, Executive Officer, Human Research Ethics Committee
Subject	Protocol Approval **HR 58/2006**
Date	10 August 2006
Copy	Ms Kerryn Butler-Henderson, Public Health Graduate Studies Officer, Division of Health Sciences

Curtin University of Technology
Office of Research and Development
Human Research Ethics Committee
TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

Thank you for your application submitted to the Human Research Ethics Committee (HREC) for the project titled "*Positron Emission Tomography (PET) and Beta Probe in the Staging of Ductal Carcinoma In Situ of the Breast*". Your application has been reviewed by the HREC and is **approved**.

- You are authorised to commence your research as stated in your proposal.
- The approval number for your project is **HR 58/2006**. *Please quote this number in any future correspondence.*
- Approval of this project is for a period of twelve months **08-08-2006** to **08-08-2007**. To renew this approval a completed Form B (attached) must be submitted before the expiry date **08-08-2007**.
- If you are a Higher Degree by Research student, data collection must not begin before your Application for Candidacy is approved by your Divisional Graduate Studies Committee.

Applicants should note the following:

- It is the policy of the HREC to conduct random audits on a percentage of approved projects. These audits may be conducted at any time after the project starts. In cases where the HREC considers that there may be a risk of adverse events, or where participants may be especially vulnerable, the HREC may request the chief investigator to provide an outcomes report, including information on follow-up of participants.

The attached **FORM B** should to be completed and returned to the Secretary, HREC, C/- Office of Research & Development:

- When the project has finished, or
- If at any time during the twelve months changes/amendments occur, or
- If a serious or unexpected adverse event occurs, or
- 14 days prior to the expiry date if renewal is required.

An application for renewal may be made with a Form B three years running, after which a new application form (Form A), providing comprehensive details, must be submitted.

Regards,

Dr Stephan Millett
Executive Officer
Human Research Ethics Committee

Please Note: The following standard statement must be included in the information sheet to participants:
This study has been approved by the Curtin University Human Research Ethics Committee. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au.

APPENDIX C: HUMAN RESEARCH ETHICS COMMITTEE ROYAL PERTH HOSPITAL LETTER OF APPROVAL

Department of Health
Government of Western Australia
East Metropolitan Health Service

Royal Perth Hospital
ABN 13 993 250 709

ETHICS COMMITTEE

Clin Prof J A Millar PhD FRCP FRACP
Dept of Internal Medicine *Chairman*
Tel: 9224 2461 Fax: 9224 2346
Email alasdair.millar@health.wa.gov.au

Room 4112, Level 4, Kirkman House
Tel: 9224 2292

Ref: 2005/068
(This number must be quoted on all correspondence)

14 March 2005

See note, p3.

Dr N Lenzo
Nuclear Medicine
Royal Perth Hospital

Dear Nat

EC 2005/068 – Positron emission tomography (PET) and beta probe in the staging of ductal carcinoma in situ of the breast

Thank you for letter dated 8th March 2005 enclosing the revised Patient Information Sheet and Consent Form. The study is now **APPROVED.**

Please note that approval of the study is conditional on compliance with the requirements for the investigator to report adverse events accompanied by a statement as to whether or not the trial should continue. The Committee reserves the right to not receive reports whose complexity or level of detail requires the expenditure of unreasonable time and effort. In addition, the Committee has decided that, as the responsibility for the conduct of trials lies with the investigator, all correspondence should be signed by the investigator.

Where study fees are being provided by an Australian sponsor, you should now contact the Accounts Department and arrange to open a suitable account for the trial, for GST purposes.

Please note the changes that have come into effect regarding administrative process relating to receipt and acknowledgment of Ethics Committee hardcopy or electronic documents. The Committee shall not provide written confirmation of receipt of any document except changes requiring its full approval and will deem that evidence of submission of a document is evidence of receipt. The evidence of submission will be the covering letter from the sender filed in the office of the Chief Investigator.

Transfer from the Committee to local investigators of the current obligation to provide written acknowledgment will not be permitted. Please advise the study sponsor of this administrative change.

The following general conditions also apply to all approvals by this Committee, and the act of starting a trial or research project following the issue of ethics approval will be deemed to be an acceptance of them by all named study investigators:

1. Any income arising from the study, for example capitation fees, must be lodged in a hospital special purposes account. Studies may be aggregated into a single account but the Accounts Department must be able to identify the account that pertains to each study.

2. Performance of a clinical trial for a sponsor is a service for tax purposes and investigators are obliged to ensure that all GST obligations are met.

3. All trial drugs must be dispensed by the Pharmacy Department. A fee is generally levied for this service and investigators must regard this fee as an item requiring a budget allocation. Alternatively, if a sponsor agrees, separate direct funding of pharmacy services may be undertaken. There are provisions for this fee to be waived for locally-inspired unfunded studies not having an external sponsor.

4. Though state institutions are outside the jurisdiction of the Privacy Act and related legislation, the Committee will assume that the privacy provisions of that Act will be the minimum standards applying during the conduct of a trial at Royal Perth Hospital. Traditional standards of patient confidentiality will apply.

5. The Committee will not acknowledge trial communications as a matter of course, unless they relate to a matter requiring Committee approval. Evidence of dispatch of a letter will be deemed to be evidence of receipt. This rule may be waived at the Committee's discretion on provision of a *pro forma* receipt by the investigator for the Chairman's signature and return. However, trivial correspondence (as judged by the Committee) will not be acknowledged even if a *pro forma* receipt is provided. Where an investigator requests written approval or written record of a matter for special purposes (say at the request of a sponsor), the investigator should prepare the required letter for the chairman's signature rather than expect the Committee secretary to prepare it. This mechanism increases the probability that the trial details in the letter are correct.

6. The submission of an application for ethics approval will be deemed to indicate that the investigator and any sponsor recognises the Committee as a registered (with AHEC) Health Research Ethics Committee and that it complies in all respect with the National Statement on Ethical Conduct Research Involving Humans and all other national and international ethical requirements. The Committee will not enter into further correspondence on this point.

7. The Committee will provide the names and representative affiliation of members on request, but will not provide personal details or voting records.

8. A brief annual report on each project approved will be required at the end of each fiscal year, in default of which approval for the study will be suspended.

9. The Committee has the authority to audit the conduct of any trial without notice. Exercise of this authority will only be considered if there are grounds to believe that some irregularity has occurred or if a complaint is received from a third party.

10. Complaints relating to the conduct of a clinical trial should be directed to the Chairman and will be promptly investigated. Complaints about the Ethics Committee decisions or policies that cannot be resolved by discussion with the Chairman or about any actions of a particular member including the Chairman, should be directed to the Director of Clinical Services or the most senior member of the executive whose responsibility is for this hospital only. Complaints given verbally will be given significantly less weight that those submitted in writing.

11. The Committee receives voluminous paperwork relating to adverse event reporting. From time to time the Committee chairman may require these reports to be summarised and approval is granted subject to the agreement of the investigator that he or she will prepare such a summary on request.

Investigators of sponsored studies are advised to draw the above conditions to the attention of the sponsor.

Yours sincerely

J A Millar
Chairman, Royal Perth Hospital Ethics Committee

The Royal Perth Hospital Ethics Committee is constituted and operates in accordance with NHC & MRC Guidelines.

cc: The Chief Pharmacist, RPH

PS Can you change "Surgeon" to "surgeon" throughout the PIS?

Thanks

G

APPENDIX D: RADIOLOGICAL COUNCIL OF WESTERN AUSTRALIA LETTER OF APPROVAL

RADIOLOGICAL COUNCIL
Government of Western Australia

Address all correspondence to
The Secretary

Your ref
Our ref 050414ma1_442 RS Rsrch Appl RPH-1-2005
Enquiries Ms M Aerts (08) 9346 2260

The Director of Medical Services
Attn: Dr D Causer, Radiation Safety Officer, Dept of Medical Physics
Royal Perth Hospital
GPO Box X2213, PERTH WA 6001

Dear Sir

RADIATION SAFETY ACT

Research project using radiation RPH-1-2005: PET and Beta Probe in Ductal Carcinoma In Situ of the Breast

Thank you for your application for a research project using radiation entitled: *Positron Emission Tomography and Beta Probe in the Staging of Ductal Carcinoma In Situ of the Breast* (Responsible Investigator Drs N Lenzo) as submitted on 17 March 2005.

This has been considered and approved by the Radiological Council.

However would you please amend the protocols and patient information sheet to insert the word "fatal" before "cancer" in the phrase "probability for the induction of cancer."

Yours faithfully

pp Ms Hazel Upton
Secretary, Radiological Council
14 April 2005

Letters: Locked Bag 2006 P O Nedlands W A 6009
18 Verdun Street Nedlands W A 6009
Telephone (61 8) 9346 2260 **Facsimile** (61 8) 9381 1423

APPENDIX E: ROYAL PERTH HOSPITAL PATIENT INFORMATION SHEET AND INFORMED CONSENT (CHAPTER 5)

THIS PATIENT IS ELIGIBLE FOR THE DCIS & PET (PART A) TRIAL.

TRIAL INVESTIGATORS:
BREAST ASSESSMENT CENTRE:
Dr Christobel Saunders
Dr Lee Jackson
Dr Peter Willsher
PET SERVICE:
Dr Nat Lenzo
RESEARCH OFFICER:
Kerryn Butler-Henderson (043 899 3067)

Royal Perth Hospital

PATIENT INFORMATION SHEET
Version 1
DATE 1st February 2005

Positron Emission Tomography (PET) and Beta Probe in the Staging of Ductal Carcinoma In Situ of the Breast (Part A).

Principal Investigator: Dr Nat Lenzo

Introduction

You are being invited to take part in a research study for patients who are being investigated for ductal carcinoma in situ (DCIS) of the breast. In order for you to decide whether you should agree to be part of this study, you should understand enough about its risks and benefits to make an informed decision. This process is known as informed consent.

DCIS is an increase of abnormal cells within the mammary ducts of the breast. Normal breasts contain lobules where the milk is produced, and tubes called ducts that take the milk from the lobules to the nipple. DCIS are said to be "pre-cancerous" and develops inside the lobules and may spread along the ducts. We have been informed that your biopsy results indicate DCIS and you are planned to have surgery to remove and test the tissue.

Both research and clinical experience indicates that approximately 20% of patients will need to have a second operation (re-excision) when some of the DCIS remains in the breast after the first operation. We wish to see how well positron emission tomography (PET) imaging could stage your DCIS before surgery. There have been a small number of animal and human studies that show PET is very good at providing the important information to your surgeon as to where exactly your DCIS is located.

We would like you to have two PET studies before you have surgery. The reason for the two studies is because we wish to know which of two different PET isotopes, fluorodeoxyglucose (FDG) and fluorocholine (FCH) is better at staging your DCIS. This information is important because should one isotope be better at staging your DCIS then the other, and it provided more information than your mammogram or ultrasound, then this could reduce the number of times a patient needs to have a second operation. Participating in this trial will not delay your surgery.

What will happen in this study?
As part of this trial you will be asked to undergo a number of standard assessments. These include:

- Mammogram (which you have already had),
- Biopsy (which you have already had),
- Ultrasound (which you may or may not already had).

You will then be required to undergo an FDG-PET scan. A PET scan is similar to a CT scan. For the FDG PET scan, you will need to fast for 6 hours before your appointment time. You will then receive an injection of the FDG in your arm. After the injection you will rest for about an hour. You may be given a small amount of muscle relaxant prior to the FDG-PET scan. The muscle relaxant may impair your ability to drive and you should arrange to have someone come with you who can take you home. The scan itself takes about 45 minutes, during which time you will be lying comfortably under the camera.

In the following days, you will undergo a FCH PET scan. You do not need to fast for a FCH PET scan. Again, you will be given a small injection in your arm, but this time you will be scanned immediately. This scan will be for one hour, with no rest period before being imaged. Your PET results will not be shared with your surgeon until after your surgery. This is because the accuracy of PET to stage DCIS has yet to be validated and to provide this information to your surgeon to make a decision on would be irresponsible.

Alternatives
If you decide not to take part in this study, you will still receive the standard assessments.

Possible Risks
You will need to fast for 6 hours before having the FDG-PET scan. **If you have unstable diabetes or are unable to fast for other reasons you should not enter this study**.

Complications related to insertion of the intravenous catheter (IV line) used to give the PET tracer can occasionally occur. These mainly involve slight bruising but very infrequently, infections can occur. You will be given appropriate treatment at the Hospital if a reaction or complication occurs.

The study will involve the use of approximately 300MBq of FDG or 200 MBq of FCH, which gives an estimated dose of 13mSv effective dose of radiation. The amount of extra radiation exposure from the PET scan is equal to about six and a half years of natural background radiation. This has a probability for the induction of fatal cancer of one in 1500. The risk of this occurring is about one half of the risk of being killed on WA roads in the next 10 years. Other than the radiation exposure there are no documented side effects associated with the administration of the PET isotope.

Women who are pregnant or breast-feeding and women who may become pregnant, but who are not taking adequate contraceptive measures, must not participate in this trial. Participants are strongly advised to use effective contraception if appropriate during the course of the study. You should discuss methods of effective contraception with your doctor.

There may be additional risks that are unforeseeable at this time. You will be informed of any new and significant information that could affect your willingness to continue participation. In the case of an unforeseen side effect, prompt treatment will be initiated.

Possible Benefits
As your results will not be discussed with your surgeon until after your operation, you may not receive any benefits from participating in this trial. Because PET is an imaging tool that is used to diagnose a number of different cancers, you should be aware that there might be an incidental finding when you have your PET scan, which may have otherwise gone undetected. There is also the possibility that PET may detect invasion into the breast tissue, which would indicate breast cancer. Should either of these circumstances arise, you will be withdrawn from the trial and the PET findings will be released immediately to your surgeon.

The knowledge gained from patients participating in the study will assist us in determining the role of PET scans in the staging of DCIS. Should this technique be validated, then in the future the information will be shared with the surgeon, who can use it when planning your surgery. This has the potential of reducing the re-excision rate in women in the future who have a PET scan before surgery for DCIS.

Confidentiality and Disclosure of Information
Any information obtained in connection with this project that can identify you, including information from medical practitioners, other health professionals, hospitals, diagnostic imaging services or laboratories outside this hospital, will remain confidential. It will only be disclosed with your permission, except as required by law.

It is anticipated that results will be published in a relevant medical journal. In any publication, information will be provided in such a way that you cannot be identified.

All data collected will be kept in a safe and secure location. All hardcopy data will be kept in a locked cabinet in the WA PET/Cyclotron Service and electronic data will be password protected. Only authorised staff will have access to your information. All data will be kept for the minimum 15 years retention period.

Participation is Voluntary
Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the WA PET/Cyclotron Service.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw.

In the event that you suffer an adverse event or a medical accident during this study that arises from your participation in the study, Royal Perth Hospital will offer you all full and necessary treatment.

New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person/s supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

Further Information or Any Problems

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact:

Principal Investigator	Dr Nat Lenzo (PET Service)	Phone: 9346 2656
Co-Investigator	Dr Lee Jackson (Breast Surgeon)	Phone: 9224 2294
Research Coordinator	Kerryn Butler-Henderson (PET Service)	Phone: 9346 7483

If you want to discuss the study with someone who is not directly involved in it (about the information you have received, the conduct of the study, your rights as a participant, or a complaint you have), please contact Associated Professor A Millar, Chairman of the Royal Perth Hospital Ethics Committee (9224 2292).

CONSENT FORM

Positron Emission Tomography (PET) and Beta Probe in the Staging of Ductal Carcinoma In Situ of the Breast (Part A).

Principal Investigator: Dr Nat Lenzo

Subject Name:_____ Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.
3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.
4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I hereby give permission for medical practitioners, other health professionals, hospitals, diagnostic imaging services or laboratories outside this hospital to release information concerning my disease and treatment that is needed for this study to the WA PET/Cyclotron Service and I understand that such information will remain confidential.
6. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.
7. I do not wish to participate in the substudy *(delete should you consent to participate in the substudy)*.

If you are unclear about anything you have read in the Patient Information Sheet or this Consent Form, please speak to your doctor before signing.

Name of Patient	Signature of Patient	Date
Name of Witness to Patient Signature	Witness to Signature	Date
Name of Investigator	Signature of Investigator	Date

The Royal Perth Hospital Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact Associated Professor A Millar, Chairman of the Royal Perth Hospital Ethics Committee (9224 2292).

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

CONSENT FORM for women of child-bearing potential

……. *(Doctor's name)* has reviewed information on pregnancy prevention for women of childbearing potential in clinical trials with me. I understand that I should not become pregnant while I am participating in this study.

I understand that I should immediately telephone Kerryn Butler-Henderson *at WA PET/Cyclotron Service, telephone number 9346 7483 in case:*

- I am pregnant or think I might be pregnant.
- I have missed my period or it is late, or I have a change in my usual menstrual cycle (for example, heavier bleeding during my period or bleeding between periods).

I should also telephone if I have changed or plan to change my birth control method, or if I need to take any prescription drug or other medication not given to me or known by Kerryn Butler-Henderson.

Patient's name (in print)…….

Patient's signature…….

Date…….

Doctor's name (in print)……. .

Doctor's signature……

Date……

APPENDIX F: HUMAN RESEARCH ETHICS COMMITTEE MOUNT HOSPITAL LETTERS OF APPROVAL

22 September 2005

Dr Peter Willsher
Suite 41
146 Mounts Bay Road
PERTH WA 6000

Mount Hospital

Dear Dr Willsher

EC28.1 Positron emission tomography (PET) and beta probe in the staging of ductal carcinoma in situ of the breast

I write further to my letter dated 16 July 2005, providing final approval for the above study by Chairman's action.

I am pleased to advise that final approval of this study was confirmed by the full Committee at the Mount Hospital Ethics Committee meeting held on 23 August 2005. A copy of the composition of this meeting is enclosed for your information.

I also confirm approval by the full Committee of Protocol Version 2 dated 8 June 2005, including:

- Patient Information Sheet and Consent Form (Part A) Version 2, dated 8 June 2005 (including a separate consent form for women of child-bearing potential)
- Patient Information Sheet and Consent Form (Part B) Version 2, dated 8 June 2005 (including a separate consent form for women of child-bearing potential).

This approval is valid for the duration of the project or three years, whichever is earlier.

It is a condition of approval that a report be provided to the Committee at least annually and on completion of the study. Any adverse experiences associated with the study should be reported to this Committee as they occur.

The Mount Hospital Ethics Committee is constituted and functions in accordance with NHMRC National Statement on Ethical Conduct in Research Involving Humans (June 1999) and the NHMRC Statement on Human Experimentation and Supplementary Notes 5 and 7 as issued in October 1983 and November 1992, respectively.

Please quote **EC28.1** on all future correspondence in relation to this study.

I wish you every success for the conduct of the study.

Yours sincerely

Clinical A/Prof G.J. Dobb
Chairman, Mount Hospital Ethics Committee

150 Mounts Bay Road, Perth, WA 6000 **Telephone** 08 9481 1822 **Facsimile** 08 9321 2208

Mount Hospital
150 Mounts Bay Road
Perth WA 6000
Tel: (08) 9481 1822
Fax: (08) 9321 2208
www.healthscope.com.au
A Healthscope Hospital

21 October 2008

Dr Peter Willsher
Suite 41
146 Mounts Bay Road
PERTH WA 6000

Dear Dr Willsher

EC28.1 Positron emission tomography (PET) and beta probe in the staging of ductal carcinoma in situ of the breast

I am pleased to confirm that the following documents were approved by Mount Hospital Ethics Committee at its meeting held on 14 October 2008 (meeting composition enclosed):

- PET & Beta Probe in Staging of Ductal Carcinoma In Situ of the Breast: Protocol Version 3 dated 9 April 2008
- Patient Information Sheet & Consent Form Version 3 dated 9 April 2008

The Mount Hospital Ethics Committee is constituted and functions in accordance with the National Statement on Ethical Conduct in Human Research (March 2007).

Yours sincerely

Professor Ross Baker
Chairman
Mount Hospital Ethics Committee

Enclosure

Mount Hospital
150 Mounts Bay Road
Perth WA 6000
Ph: (08) 9481 1822
Fax: (08) 9321 2208
www.healthscope.com.au

A Healthscope Hospital

21 April 2010

Dr Peter Willsher
Suite 41
146 Mounts Bay Road
PERTH WA 6000

Dear Dr Willsher,

EC28.1 Positron emission tomography (PET) and beta probe in the staging of ductal carcinoma in situ of the breast

Thank you for your letter dated 15 March 2010 in relation to the above study.

I am pleased to confirm that the following documents were approved by Mount Hospital Ethics Committee at its meeting held on 20 April 2010 (meeting composition enclosed):

- PET & Beta Probe in Staging of Ductal Carcinoma In Situ of the Breast: Protocol Version 4 dated 8 March 2010
- Patient Information Sheet & Consent Form Version 4 dated 8 March 2010

The Mount Hospital Ethics Committee is constituted and functions in accordance with the National Statement on Ethical Conduct in Human Research (March 2007).

Yours sincerely

Professor Ross Baker
Chairman
Mount Hospital Ethics Committee

Enclosure

APPENDIX G: NOTIFICATION FORM (CHAPTER 7)

ATTENTION KERRYN BUTLER-HENDERSON
Please fax to: 9266 2958
Please notify that fax has been sent: 0408956082

DCIS TRIAL FORM A

Inclusion Criteria

To be eligible for inclusion, a patient must satisfy **ALL** of the following:

- ❑ Newly diagnosed DCIS,
- ❑ Planned to undergo wide local excision of DCIS, and
- ❑ Able to provide informed consent.

Exclusion Criteria

Patients will be excluded from the study if **ANY** of the following apply:

- Planned mastectomy or neoadjuvant therapy for DCIS;
- Invasive component detected by biopsy;
- Previous history of invasive breast disease;
- Uncontrolled diabetes mellitus;
- Pregnant at the time of surgery.

Patient name: _____
First Name Middle Name Last Name

Date of Birth: _____

Breast: Left Right

Please ensure patient has:
* Mammography
* Positive biopsy

Date of surgery: _____

Time of hookwire: _____ am / pm

Planned time of surgery: _____ am / pm

Surgeon: PW DI
Height: _____ cm
Weight: _____ kg

Patient must fast for 6 hours prior to injection

APPENDIX H: MOUNT HOSPITAL PATIENT INFORMATION SHEET AND CONSENT FORM (CHAPTER 7)

Mount Hospital

PATIENT INFORMATION SHEET
Version 3
DATE 8th March 2010

Positron Emission Tomography (PET) and Beta Probe in the Staging of Ductal Carcinoma In Situ of the Breast.

Principal Investigator: Dr Peter Willsher & Kerryn Butler-Henderson

Introduction
You are being invited to take part in a research study for patients who are being investigated for ductal carcinoma in situ (DCIS) of the breast. In order for you to decide whether you should agree to be part of this study, you should understand enough about its risks and benefits to make an informed decision. This process is known as informed consent.

DCIS is an increase of abnormal cells within the mammary ducts of the breast. Normal breasts contain lobules where the milk is produced, and tubes called ducts that take the milk from the lobules to the nipple. DCIS are said to be "pre-cancerous" and develops inside the lobules and may spread along the ducts. We have been informed that your biopsy results indicate DCIS and you are planned to have surgery to remove and test the tissue.

Both research and clinical experience indicates that approximately 20% of patients will need to have a second operation (re-excision) when some of the DCIS remains in the breast after the first operation. We are testing a new technology called the positron emission tomography (PET) probe. This probe can detect radioactivity attached to a substance called fluorodeoxyglucose (FDG) which is taken up by the DCIS cells. In the study the probe will be used to try and accurately assess the extent of the DCIS in the breast during surgery. The true microscopic extent of DCIS is difficult to assess with our currents tests (i.e. clinical examination, mammography and ultrasound) and microscopic (minute or tiny) disease is, of course, not visible to the naked eye. At the time of surgery we aim to remove all of the DCIS with a margin of surrounding normal breast tissue (the margin). The PET probe is being tested to see if it can accurately identify if all DCIS cells have been removed (i.e. the margins are clear of DCIS cells). In the future we are optimistic that this technique will improve the chances of getting clear margins at the first operation, meaning fewer women will need to have further surgery.

What will happen in this study?
As part of this trial you will be asked to undergo a number of standard assessments. These include:

- Mammogram (which you have already had),
- Biopsy (which you have already had),
- Possibly an ultrasound (which you may or may not have already had).

On the day of your surgery, an hour before your operation, you will be injected with a small amount of FDG through an intravenous line in your arm. We are testing to see if the PET probe can find DCIS cells which have taken up the FDG. During your surgery, the surgeon will use the PET probe inside the breast after your tissue has been removed to see if there is any residual activity (or cells still containing the FDG). The surgeon will also use the probe to test the surface of the tissue that has been removed to see if there is any activity. Recordings will be made of the amount and location of any FDG activity and this will then be correlated with the pathology results after the surgery. We will then be able to see if FDG activity corresponds to the presence of DCIS cells at the margins.

Your surgeon will perform the standard recommended surgery to the breast as you have discussed pre-operatively - no changes to the surgical plan will be made based on the presence of FDG activity.

Alternatives
If you decide not to take part in this study, you will still receive the standard assessments.

Possible Risks
Complications related to insertion of the intravenous catheter (IV line) used to give the FDG can occasionally occur. These mainly involve slight bruising but very infrequently, infections can occur. You will be given appropriate treatment at the Hospital if a reaction or complication occurs.

The study will involve the use of approximately 100 - 150 MBq of FDG pre-surgery, which gives an estimated dose of 2.847mSv effective dose of radiation. The amount of extra radiation exposure from this injection is equal to about eleven months of natural background radiation. This is about the same amount of radiation as that from a mammography and about half that from a chest CT. Other than the radiation exposure there are no documented side effects associated with the administration of the PET isotope.

Women who are pregnant or breast-feeding and women who may become pregnant, but who are not taking adequate contraceptive measures, must not participate in this trial. Participants are strongly advised to use effective contraception if appropriate during the course of the study. You should discuss methods of effective contraception with your doctor.

There may be additional risks that are unforeseeable at this time. You will be informed of any new and significant information that could affect your willingness to continue participation. In the case of an unforeseen side effect, prompt treatment will be initiated.

Possible Benefits
As your results will not be discussed with you or your Surgeon until after your operation, you may not receive any benefits from participating in this trial. The knowledge gained from patients participating in the study will assist us in determining the role of a PET probe in the treatment of DCIS. Should this technique be validated, then in the future the information will be shared with the Surgeon, who can use it during surgery. This has the potential of reducing the number of women who may need second operations in the future.

Confidentiality and Disclosure of Information
Any information obtained in connection with this project that can identify you, including information from medical practitioners, other health professionals, hospitals, diagnostic imaging services or laboratories outside this hospital, will remain confidential. It will only be disclosed with your permission, except as required by law.

It is anticipated that results will be published in a relevant medical journal. In any publication, information will be provided in such a way that you cannot be identified.

All data collected will be kept in a safe and secure location. All hardcopy data will be kept in a locked cabinet at Curtin University of Technology and electronic data will be password protected. Only authorised staff will have access to your information. All data will be kept for the minimum 15 years retention period.

Participation is Voluntary
Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Mount Hospital.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers. If you decide to withdraw from this project, please notify a member of the research team before you withdraw.

In the event that you suffer an adverse event or a medical accident during this study that arises from your participation in the study, Mount Hospital will offer you all full and necessary treatment.

New Information Arising During the Project
During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person/s supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

Further Information or Any Problems
If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact:

Principal Investigator	Dr Peter Willsher (Breast Surgeon)	Phone: 9481 4522
Co-Investigator	Kerryn Butler-Henderson (PET Probe)	Phone: 9266 7531
		040 895 6082

If you want to discuss the study with someone who is not directly involved in it (about the information you have received, the conduct of the study, your rights as a participant, or a complaint you have), please contact Dr Ross Baker, Chairman of the Ethics Committee, telephone (08) 9483 2841.

MOUNT HOSPITAL

CONSENT FORM

Positron Emission Tomography (PET) and Beta Probe in the Staging of Ductal Carcinoma In Situ of the Breast.

Principal Investigator: Dr Peter Willsher & Kerryn Butler-Henderson

Subject Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.
3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.
4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I hereby give permission for medical practitioners, other health professionals, hospitals, diagnostic imaging services or laboratories outside this hospital to release information concerning my disease and treatment that is needed for this study to Curtin University of Technology and I understand that such information will remain confidential.
6. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Patient Information Sheet or this Consent Form, please speak to your doctor before signing.

Name of Patient	Signature of Patient	Date

Name of Witness to Patient Signature	Witness to Signature	Date

Name of Investigator	Signature of Investigator	Date

The Mount Hospital Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact Dr Ross Baker, Chairman of the Ethics Committee, telephone (08) 9483 2841.

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

CONSENT FORM for women of child-bearing potential

……. *(Investigator's name)* has reviewed information on pregnancy prevention for women of childbearing potential in clinical trials with me. I understand that I should not become pregnant while I am participating in this study.

I understand that I should immediately telephone Kerryn Butler-Henderson at *Curtin University of Technology, telephone number 9266 7531 in case:*

* I am pregnant or think I might be pregnant.
* I have missed my period or it is late, or I have a change in my usual menstrual cycle (for example, heavier bleeding during my period or bleeding between periods).

I should also telephone if I have changed or plan to change my birth control method, or if I need to take any prescription drug or other medication not given to me or known by Kerryn Butler-Henderson.

Patient's name (in print)…….

Patient's signature…….

Date…….

Investigator's name (in print)……. .

Investigator's signature……

Date……

APPENDIX I: DATA COLLECTION FORM (CHAPTER 7)

PET PROBE STUDY

DEMOGRAPHIC DATA

Patient ID: _____ DOB: _____ Date of Surgery: _____

Weight: _____ Height: _____ BMI: _____

Surgeon: ☐ PW ☐ DH

Breast: ☐ Left ☐ Right Diabetes: ☐ Yes ☐ No

INJECTION DATA

Time of injection: _____ ☐ am ☐ pm

Comments: _____

_____

_____

_____

PRE-SURGERY DATA

Monitoring Device Reading Surgeon: _____ Investigator: _____

SURGERY

Time of surgery: _____ ☐ am ☐ pm

	Time	Superior	Inferior	Medial	Lateral	Superficial	Deep
In cavity CPS							
Excised CPS							
Shaving							

Gamma Excised Time: _____ CPS: _____

POST-SURGERY

Monitoring Device Reading Surgeon: _____ Investigator: _____

COMMENTS: _____