THE UNIVERSITY OF
SYDNEY

Precision Imaging Ultrasound Technology - Does It Improve Accuracy and Increase Confidence in Diagnosing Breast Tumours ?

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A thesis submitted in fulfilment of the requirements for the degree of

Master of Applied Science

Faculty of Health Sciences

The University of Sydney

September 2015

Declaration

I, Siu Fong Louisa Lau, hereby declare that the work contained within this thesis is my own, and no other person's work has been used without due acknowledgement.

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Abstract

Introduction

Image quality is important in medical imaging as it can facilitate lesion detection and characterisation, with shifts in contrast and resolution potentially enabling the practitioner to make a more effective diagnostic decision. Historically, speckle has been identified as a key factor in degraded ultrasound image quality, with different speckle reduction techniques being currently used in clinical diagnostic ultrasound. Precision Imaging (PI), an innovative speckle reduction algorithm, is used by Toshiba Medical Systems in some of their ultrasound machines. Until now there has been no published work that scientifically evaluates the usefulness of the PI algorithm for breast ultrasound examinations. Therefore the aim of the current research was to investigate if PI could be shown to improve the ability of clinicians to correctly classify the nature of a breast tumour.

Material and methods

Patients aged from 20 to 84 years were included in this research, screened by a busy urban breast clinic between October 2010 and June 2011. A commercial ultrasound scanner Toshiba AplioMX, Model SSA-780A, (Toshiba Medical Systems, Otawara-shi, Tochigi-ken, Japan) with compact linear transducers 15-7MHz (PLT-1204BT) and 12-5 MHz (PLT-805AT) was used for image acquisition. A single projection image that was considered to best represent the lesion was recorded without PI (L0), and then with the three available levels of PI, namely Precision 1 (L1), Precision 2 (L2) and Precision 3 (L3), with higher numbers signifying greater speckle reduction.

Fifty one breast lesions (20 malignant and 31 benign) were selected from over 200 collected lesions, with selection criteria based on the 1-5 classification system developed by National Breast Cancer Centre (NBCC) in collaboration with the Royal Australian and New Zealand College of Radiologists (RANZCR). These selected images were cropped to remove the technical details, which included patient information as well as PI level.

Images were evaluated by six radiologists and six sonographers dedicated to breast imaging, scoring each lesion using a 1-6 scale where: 1 - definitely benign; 2 - probably benign; 3 - possibly benign; 4 - possibly malignant; 5 - probably malignant; 6 - definitely malignant.

Q-Perform software (Ziltron, Limerick, Ireland) was used to collect and analyse data (true positives, false positives, true negatives, false negatives), and to calculate metrics for each reader. These metrics included: receiver operator characteristic (ROC) values, sensitivity (number of malignant lesions correctly identified over the total number of malignant lesions present in the test set) and specificity (number of benign lesions correctly identified over the total number of benign lesions present in the test set).

Results

The ROC values for each Precision level varied as followed : L0 from 0.71-0.87; L1 from 0.77-0.85; L2 from 0.67-0.88 and L3 from 0.74-0.88. Mean values were recorded as 0.79, 0.80, 0.81 and 0.81 for L0, L1, L2 and L3 respectively. A receiver operating characteristics analysis (ROC) used the Dorfman, Berbaum, Metz multi-reader multi-case approach (DBMMRMC 2.32 Build 3 software) to assess individual pairings of PI and no significant statistical difference was found.

A Wilcoxon signed-rank test was employed to identify any significant differences in sensitivity or specificity between any of the PI pairings and again no statistically significant differences were found.

Conclusion

Analysis of ROC, sensitivity, and specificity values did not demonstrate any significant improvement in diagnostic efficacy amongst expert observers when PI is employed. These results highlight the importance of comprehensive assessments of any new technology, whilst not relying on quality assessment as a surrogate of diagnostic efficacy.

Acknowledgement

I am very glad to have reached the submission phase. This has been a long learning process.

My thanks go to Alfiya Safina, the co-author of our joint paper; without her invitation, I would not have been part of this project, nor embarked on this learning journey.

I am forever grateful to my supervisors, Patrick Brennan and Mary Rickard for their continuous support throughout these years, reviewing and giving suggestions to guide me through this academic process. My thanks to the rest of the research team, Peter Kench, Elaine Ryan, Mark McEntee, Claudia Mello-Thoms; the regular meetings with them, their suggestions and their tireless work towards our joint paper were really appreciated.

I am also very grateful to John Ryan for designing the Q-perform program, which made this research possible. His assistance and encouragement were an important part in this research. My sincere thanks to the librarian, Elaine Tam, who generously gave her time to assist me in using the library resources, and showed me how to use the EndNote program to facilitate my referencing; Jennifer Kay Peat, consultant biostatistician, who devoted her time in communicating with me through email and taught me how to use the IBM SPSS software to generate the impressive ROC curve.

A big thank you to my workplace, The Sydney Breast Clinic, where the set up for patient examinations enabled easy access for image collection, as well as providing the ultrasound machines and the venue for research meetings. Thanks to my fine colleagues for their participation in the image critique process. Without their participation, this project would be impossible.

Finally to my great family, Po, Heide and Ivan Cheng, for their many and varied forms of support.

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Chapter 1 Literature Review

1.1 Background and introduction

There has been a global increase in the incidence of breast cancer (Parkin & Fernández, 2006). In 2010, breast cancer accounted for 28% of all new cancers in Australian women and was the second leading cause of cancer-related death in 2011 (Australian Government Cancer Australia, 2014). It is estimated that 1 in 8 women will be diagnosed with breast cancer before the age of 85 and that by 2020, the number of women affected will be approximately 13% higher than in 2014 (Australian Government Cancer Australia, 2014).

The implementation of a national mammography screening program in Australia in 1991 has contributed to a significant decrease in breast cancer mortality rate: from 61.5 deaths per 100,000 women in 1996, to 51.8 deaths per 100,000 women in 2005 (BreastScreen Australia Evaluation Advisory Committee, 2009). If cancerous changes are detected earlier, treatment is considered to be more effective and a greater range of treatment options are possible, which includes less aggressive adjuvant therapy and less aggressive surgeries such as lumpectomy rather than mastectomy (Meenalosini & Janet, 2012; Smith,Cokkinides & Brawley, 2012).

Currently, mammography is the most widely used screening test to detect pre-clinical disease and is the only screening test to date which demonstrates a reduction in the breast cancer mortality rate (BreastScreen Australia Evaluation Advisory Committee, 2009; Le-Petross & Shetty, 2011). Ultrasound is an important adjunct to mammography (Dempsey, 2004), and magnetic resonance imaging (MRI) is another widely used imaging modality. All three imaging modalities have an important role in both screening and symptomatic breast cancer diagnosis.

Image quality in terms of contrast and resolution is important in medical imaging as it can facilitate lesion detection and characterisation (Weinstein,Conant & Sehgal, 2006). In ultrasound imaging, the radiologist or

sonographer evaluates the tissue in real-time, and when the image quality is optimised, it facilitates the operator's ability to perceive changes in echotexture, hence facilitating lesion detection. The possibility of non-identification exists in breast ultrasound where changes can be subtle and small in size. Once a change is perceived, the practitioner can evaluate its features such as shape, margin, echotexture and relationship to the surrounding tissue (lesion characterisation), and make a diagnostic decision regarding the nature of the change.

A novel speckle reduction algorithm, 'Precision Imaging' (PI), is used by Toshiba Medical Systems (Toshiba Medical Systems, Otawara-shi, Tochigi-ken, Japan) in some of their ultrasound machines. This research used visual grading analysis (VGA) to evaluate whether the PI algorithm improves the image quality, and used a receiver operating characteristic analysis (ROC) to determine whether PI affects the practitioner's diagnostic decision.

This literature review provides a brief discussion on

1. Breast imaging modalities

2. Visual assessment and interpretation of breast ultrasound

3. Image quality and speckle reduction

4. Precision Imaging

1.2 Most widely used imaging modalities for breast disease investigation

1.2.1 Mammography

Mammography is a low dose X-ray examination of the breast, and the technology is widely available and relatively inexpensive. Over the past ten years, mammogram image acquisition has evolved from film-screen combination or analogue mammography to full field digital mammography using either computed radiography (CR) or direct digital radiography (DR). Both analogue and digital mammography are quick examinations, taking a few minutes per breast, and are relatively easy to perform. Typically the patient has 2 standard mammogram images (craniocaudal and mediolateral oblique projections) of each breast. The images are then interpreted by a radiologist, who looks for signs of cancer such as asymmetrical density, mass, architectural disturbance or microcalcifications. The time taken for this mammographic reading is typically less than 1 minute (Garg et al., 2011).

Mammography sensitivity has been reported to vary widely from 27% to 90%. This variation in sensitivity is mainly due to the breast density related to age and menopausal status (Pinsky, 2012; Pisano et al., 2008; Skaane, 2009; Yankaskas et al., 2010). The actual amount of dense breast tissue, the distribution of density within the breast, and the relative contrast between breast tissue and a lesion can affect its detection (Powell,Obuchowski,Davros & Chilcote, 1999). Various studies have shown that not only does breast density reduce the sensitivity of mammography but also that women with extremely dense breasts have 3-5 times more risk of cancer development compared with women with the least dense breasts (Boyd et al., 2007; Kerlikowske et al., 2007; McCormack & dos Santos Silva, 2006; Ursin et al., 2003; Vacek & Geller, 2004). Full field digital mammography compared with film screen technology has significantly better sensitivity for women with dense breasts, for women younger than 50 years of age and for pre-menopausal women (Pisano et al., 2005).

There are some disadvantages with mammography. First of all, it utilises radiation, so there is a risk of inducing breast cancer, especially in younger women under 25 years of age (D'Orsi & Newell, 2011; Jochelson & Morris, 2011). Secondly, mammography is a 2D technology and the intrinsic superimposition of tissues of similar density in this radiologic examination can reduce the sensitivity and specificity, particularly with dense breasts.

Breast tomosynthesis (DBT) is a relatively new mammographic technique that can reduce the effect of superimposition of breast tissue that occurs in 2D mammography, and has been shown to improve the reader's sensitivity and specificity. It also enables better perception and classification of masses and microcalcifications, especially in dense breasts, and improves accuracy and reduces recall rates in a screening environment (Ciatto et al., 2013; Domingo et al., 2011; Estévez et al., 2010; Friedewald et al., 2014; Houssami & Skaane, 2013; Philpotts, 2011; Skaane et al., 2013; Wallis,Moa,Zanca,Leifland & Danielsson, 2012). Breast tomosynthesis, instead of acquiring a single image from one projection, acquires multiple images from different angles (projections) during a single arc sweep of the X-ray tube. These images from different angles are reconstructed into a series of thin slice images. The radiologist can scroll through the series of images as if viewing a three-dimensional mammogram. This technique has been shown to ameliorate some of the limitations of 2D mammography. However the increase in mean glandular radiation dose in image acquisition, the longer reading time for interpretation, the higher capital cost in implementing the system and the need for greater digital storage capacity due to the larger file size of tomosynthesis images all need to be considered before implementation (Uematsu, 2013).

A further limitation of mammography is the skills and experience needed for accurate interpretation (Rawashdeh et al., 2013). Minimum annual reading requirements have been set at 2,000 reads in the breast screening program in Australia (National Quality Management Committee of BreastScreen Australia, 2008) and 5,000 reads in the UK (NHS cancer screening programmes, 2011).

Finally it should be acknowledged that when breast compression is applied in mammography, the woman may experience discomfort. This can deter her from future repeat mammography (Elwood et al., 1998; Kee,Telford,Donaghy & O'Doherty, 1992; Rutter,Calnan,Vaile,Field & Wade, 1992).

1.2.2 Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) plays an important role in breast imaging and has a high sensitivity for detection of invasive cancer. The sensitivity of MRI for breast cancers is in the range of 71% to 94%. MRI has relatively low specificity (26%-76%) compared to mammography (75%-91%) and ultrasound (34%-89%) (Berg,Blume, et al., 2008; Berg et al., 2004; DeMartini & Lehman, 2008; Kim et al., 2007; Kriege et al., 2004).

MRI gives more accurate tumour staging than a mammogram or an ultrasound examination, and a better assessment of tumour size and of multifocality and multicentricity (Yeh, 2011).

Currently, about 15% to 20% of screening-detected cancers are ductal carcinoma in situ (DCIS). DCIS lesions are most commonly detected due to the presence of microcalcifications, for which the detection by mammography is superior to MRI. MRI can sometimes detect DCIS which is occult on mammogram, but has limited sensitivity in DCIS diagnosis (Gwak et al., 2011).

MRI also has other well-reported disadvantages of long examination time, low availability, contrast reactions, claustrophobia for some individuals and high cost (Le-Petross & Shetty, 2011). In addition, MRI is contraindicated for patients with any metallic devices, clips or fragments in the brain or eye (Berg et al., 2012). In the United States it is recommended for screening women at high risk, as well as for some diagnostic examinations, such as evaluation of extent of disease, or screening of the contralateral breast in patients with a new breast cancer diagnosis (Yeh, 2011). In Australia, Medicare reimbursement is currently available for breast MRI screening only

for women less than 50 years of age who have a high risk due to family history (Australian Government Dept of Health Medical Benefit Online, 2014).

1.2.3 Ultrasound

Ultrasound examination uses high frequency acoustic waves to image breast tissue. The rapid technological advancements in digital high frequency high resolution transducers (in the range of 9-14MHz), colour and power Doppler imaging and harmonic imaging, combined with the increased experience of physicians and technologists in interpreting breast ultrasound, have made ultrasound an important adjunctive imaging tool for breast evaluation (D'Orsi & Newell, 2011; Leconte et al., 2003; Madjar, 2010). Ultrasound has several advantages when compared with other breast imaging modalities:

1. Accessibility, cost and comfort. Ultrasound machines are relatively inexpensive pieces of medical imaging equipment that can be used to examine many different regions of the body. Because of these qualities, they are found in most medical imaging practices, thus being easily accessible to the population. In addition to this, the examination cost is relatively low and similar to that of mammography, the patient lies in a relatively comfortable supine position and the reported median examination time is approximately 19 minutes (Berg et al., 2008).

2. Lack of ionising radiation. Ultrasound does not involve ionising radiation, therefore it is the recommended imaging method for assessing breast disorders in young and pregnant women (Hosny,Eldin & Elghawabi, 2011).

3. Lesion identification and characterisation. Ultrasound imaging can improve lesion identification and characterisation when used in conjunction with mammography (Buchberger,Niehoff,Obrist,DeKoekkoek-Doll & Dünser, 2000; Kaplan, 2001; Mendelson, 2004). Different studies have demonstrated an increase of around 0.4% cancer detection due to additional ultrasound screening (Berg et al., 2008; Buchberger,Niehoff,Orbist,DeKoekkoek-Doll & Dünser, 2000).

From a mammographic perspective, breasts with high density offer a diagnostic challenge, as density makes a mass, asymmetrical density or architectural disturbance more difficult to perceive. These soft tissue abnormalities, both benign and malignant, have a similar density on mammography to that of the background fibroglandular tissue and can be obscured by underlying or overlying tissue on a standard 2D image. In an ultrasound examination, breast tissue is assessed in thin slices from the skin to the chest wall and therefore tissue overlap does not occur. In addition, most pathological processes have different acoustic characteristics from normal fibroglandular tissue, therefore these ultrasound features can be used to differentiate benignity from malignancy and reduce unnecessary biopsies (Costantini et al., 2006; Stavros et al., 1995).

4. Combined screening and early detection. Studies based on the comparison of the screening yield from mammography alone, with the yield from ultrasound in addition to mammography have shown that the cancer yield improved from 7.6/1000 screens for mammography to 11.8/1000 with mammography and ultrasound combined. Ultrasound identified an additional 4.4/1000 screens (Berg,Blume, et al., 2008; Corsetti et al., 2011). It has been reported that in a screening setting, the use of ultrasound screening will lead to detection of small cancers, some at an earlier stage than those identified by mammogram, and mostly node negative (Corsetti,Houssami & Ferrari, 2008; Hooley,Andrejeva & Scoutt, 2011; Kolb,Lichy & Newhouse, 2002). This is beneficial as the survival rate is higher when the breast cancer is detected in the early stage (Australian Institute of Health and Welfare, 2007).

5. Tumour staging. Ultrasound can be used for loco-regional staging to determine the primary tumour size, whether it is unifocal, multifocal or multicentric, and to identify possible disease foci in the contralateral breast as well as regional nodal status (Yang, 2011).

6. Needle biopsy guidance. Ultrasound can facilitate guidance of fine needle cytology and/or core biopsy. In ultrasound guided biopsy, the procedure is monitored in real-time, is easier and quicker to perform, and is more

comfortable than with mammography or MRI guidance (Abe et al., 2013; Destounis et al., 2009; Kornecki, 2011; Philpotts, 2011).

Ultrasound examination also has its limitations: operator dependency for lesion detection, the time required to perform the scan and low specificity (34%-89.9%)(Berg et al., 2012). Low specificity (high false positive rate) may require an invasive procedure to rule out malignancy. Ultrasound also has low sensitivity in microcalcifications detection when compared with mammography. The detection rate of microcalcifications by ultrasound varied between 45% to 75% (Cilotti et al., 1997; Gufler et al., 2000; Moon,Im,Koh,Noh & Park, 2000; Nagashima et al., 2005).

1.3 Visual assessment and interpretation of ultrasound images

In ultrasound, accurate diagnosis requires a process of continuous visual assessment to detect visible changes, subsequently followed by interpretation through cognitive analysis (Kundel & Nodine, 1983).

1.3.1 Interpretation

In order to categorise a lesion identified during an ultrasound examination, the reporting radiologist analyses lesion features. The principal features are summarised in table 1-1.

Table 1-1: Ultrasound features and descriptors (Compiled from Synoptic breast imaging report, ACR BI-RADS pocket guide, and Diagnostic Imaging – Breast by Berg et al 2008.)

Ultrasound feature	Descriptor
Shape	Oval
	Round
	Irregular

Orientation with respect to chest wall	Parallel Not parallel
Margin	Circumscribed Not circumscribed (microlobulate, spiculate, angular, indistinct)
Boundary	Abrupt interface Echogenic halo
Echotexture relative to fatty tissue	Anechoic Hypoechoic Isoechoic Hyperechoic Complex echogenicity
Posterior acoustic features	No posterior features Enhancement Shadowing Combined patterns
Vascularity	None In lesion Adjacent to lesion Diffuse
Presence of calcifications	Macrocalcifications >0.5mm in diameter Microcalcifications within lesions Microcalcifications in surrounding parenchyma Microcalcifications both within lesions and in surrounding parenchyma
Duct changes	Dilated ducts >2mm Focally narrowed ducts Intraductal extension of mass
Architectural distortion	Straightening or thickening of Cooper ligaments Disruption of normal anatomic planes

Skin	Focal or diffuse thickening > 2mm
Oedema	Increased echogenicity of surrounding parenchyma +/- dilated lymphatic channels

Shape, margin and orientation are considered the three most important features for lesion characterisation (Rahbar et al., 1999). A lesion with an ellipsoid or oval shape, which is well circumscribed with gentle and smooth lobulations, parallel to the chest wall, hypoechoic in echotexture and demonstrating the presence of a thin echogenic pseudocapsule is characterised as definitely benign. On the other hand, a lesion with irregular shape, with its long axis perpendicular to the chest wall, not circumscribed and with spiculate or angled margins, heterogeneous in echotexture and with posterior shadowing or presence of halo, is considered suspicious of malignancy (Berg,Birdwell, et al., 2008; Costantini et al., 2006).

However, benign lesions can have some features suggestive of invasive malignancy and vice versa. A landmark study (Stavros et al., 1995) on the characterisation of 750 solid breast lesions had a sensitivity of 98.4% (123 of 125 malignancies) using strict ultrasound features. The negative predictive value was 99.5%, with only 2 of 246 malignancies having been classified as benign. Of the 504 cases which had been classified as indeterminate or malignant, only 123 cases (24.4%) were proven malignant, consistent with the overlap in diagnostic features. This is also true for in situ carcinoma where the ultrasound features of benign conditions, such as papilloma, mammary duct ectasia, fibrocystic change and atypical ductal hyperplasia may appear similar to the findings of DCIS without calcifications (Moon et al., 2002). These overlapping benign and malignant features mean that lesions categorised as indeterminate for diagnostic purposes need either cytology or core biopsy to ascertain their nature.

1.4 Image Quality

In medical imaging, a lot of effort has been devoted to improving image quality, because a good image can facilitate perception and interpretation of findings, reduce operator dependence and improve diagnostic confidence (Birnholz, 2013; Milkowski,Li,Becker & Ishrak, 2003).

In diagnostic ultrasound, image quality is determined by the transducer resolution features, such as the centre frequency and pulse width, the signal acquisition techniques intrinsic to the transducer, the signal processing converter and the physical display.

Recent advances in the transducer array material and elements design, electronic and computational processing power have improved the transmission and acquisition of ultrasound signals. Transducers used in breast ultrasound are generally broad-bandwidth linear arrays, with maximum frequencies of 10-13 MHz and a centre frequency of at least 7 or 7.5 MHz; combined with broadband digital beam-forming technology and dedicated digital signal processing, both axial and lateral resolution have been improved (Stafford & Whitman, 2011).

However, four key intrinsic factors have been identified as causing degradation of the image quality. These are summarised in table 1-2.

Table 1-2: Technical factors negatively affecting ultrasound image quality (compiled from Huber et al. 2002, Stafford and Whitman, 2011)

Intrinsic factor	Cause	Result
Speckle	Constructive & destructive interference of backscattered signal	Granular appearing background noise
Clutter	Signals arising from sidelobes, grating lobes & multipath reverberation & other acoustical phenomena	Spurious signals from objects not in the primary beam
Electronic noise	Electronic component of system	Increased background noise and reduced signal to noise ratio
Phase aberration	Incorrect estimation of speed of sound travelling within breast tissue	Error in focusing, decreased resolution, reduced beam penetration and distortion of speckle pattern

Amongst these factors, speckle has been historically identified as an important cause of degradation of image quality (Burckhardt, 1978). Speckle is a correlated multiplicative noise that is produced due to the constructive and destructive interference of backscattered signal. This signal makes the image appear granular, and decreases the signal to noise ratio, hence affecting the contrast resolution. In breast ultrasound, the different compositions of glandular and fibrous tissue in different breasts and the often subtle alteration in echotexture or architectural change due to pathological processes, can make it a challenging task for sonographers and radiologists to accurately perceive and diagnose the presence of disease. The presence of speckle is undesirable as it can mask small but significant features, which

can reduce the ability of the operator to perceive subtle changes, thus affecting the diagnostic decision. Its presence also reduces the efficiency of further image processing such as edge detection (Hacini,Hachouf & Djemal, 2011).

There have been 2 basic approaches to reducing speckle: the pre-processing approach and post-processing approach (Adam,Beilin-Nissan,Friedman & Behar, 2006).

1.4.1 Pre-processing approach

The pre-processing approach means optimising the emitting ultrasound beam to reduce degradation of image quality. This is achieved through modifying the pulse signal and/or image acquisition. Techniques include frequency compounding, spatial compounding and tissue harmonic imaging (Contreras Ortiz,Chiu & Fox, 2012).

In frequency compounding, by applying a conventional pulsing technique, multiple transmission pulses of different frequency bands are used to acquire images. These different frequency bands produce different speckle patterns, which are averaged or decorrelated after the detection phase, thus reducing the speckle signal. However, there is a trade-off on axial resolution and penetration when different frequencies are used.

A more recent technique for frequency compounding uses a pre-enhanced chirp (frequency coding) to excite the ultrasound transducer, a process known as resolution enhancement compression (REC). The effective impulse response has twice the bandwidth of a conventional pulsing technique, which translates to more sub-band frequencies and more decorrelation of speckle. The summation and averaging of several REC-frequency compounding images with matched filter processing improve not only contrast resolution (reduced speckle), but also penetration and axial resolution when compared to those of a conventional pulsing technique (Chiao & Hao, 2005; Piccoli & Forsberg, 2011; Powers & Kremkau, 2011; Stafford & Whitman, 2011; Ullom,Oelze & Sanchez, 2010).

Spatial compounding, on the other hand, relies on images acquired from different angles of insonation. The received echoes are then combined and averaged to produce a single compound image in real-time. In this way, angle generated noise and speckle artifacts are reduced due to averaging. Several breast ultrasound studies have shown that spatial compounding improves tissue differentiation, provides better delineation of capsular margins and ducts, and increases conspicuity of low contrast lesions (Piccoli & Forsberg, 2011). However, spatial compound imaging also causes a reduction in refractive shadowing and this is potentially a disadvantage as refractive shadowing can be used as a diagnostic feature. Therefore it has been suggested that real-time switching between conventional and spatial compound imaging would be the most effective scanning method (Barr,Maldonado & Georgian-Smith, 2009; Malich,Marx & Sauner, 2003).

Tissue harmonic imaging uses the signal from second harmonics (twice the central emitting frequency) of the backscatter echoes to produce an image. It is routinely used in breast imaging as an option for minimising clutter and clearing internal echoes in cyst-like structures. As the beamwidth is narrower than the fundamental beamwidth, better resolution and less scattering of echoes from superficial layers are achieved (Kremkau, 2012). It also increases lesion and acoustic shadow conspicuity, and potentially improves lesion borders and internal echoes (Leconte et al., 2003; Rosen & Soo, 2001; Stafford & Whitman, 2011).

1.4.2 Post-processing approach

The post-processing approach uses signal processing techniques to enhance the captured images. ‘Speckle-reducing post-processing filters’ (Ullom et al., 2010) are algorithms that analyse the returned echo and adaptively remove speckle whilst preserving the echogenic structures. Some filters also utilise edge-preserving smoothing techniques to enhance sharp edges and smooth homogeneous regions within the image. These filtering algorithms are usually coupled with spatial compounding to give a higher degree of speckle reduction (Stafford & Whitman, 2011). Commercial companies using this technology are GE (commercial name SRI), Philips

(commercial name XRES) and Toshiba (commercial name Precision Imaging) (Piccoli & Forsberg, 2011).

Studies comparing images acquired with spatial compounding and with the addition of the XRES algorithm concluded that this post-processing approach improved overall image quality. Most importantly, all abnormalities seen on original images were also visible after the application of the XRES algorithm (Barr et al., 2009; Meuwly,Thiran & Gudinchet, 2003).

1.4.3 Speckle reduction effects on breast ultrasound

There have been various published papers comparing the quality of breast images obtained with conventional and different speckle reduction techniques (Barr et al., 2009; Clevert,Jung,Jungius,Ertan & Kubale, 2007; Entrekin,Jackson,Jago & Porter, 1999; Huber,Wagner,Medl & Czembirek 2002; Kwak,Kim,You & Oh, 2004; Malich,Marx & Sauner, 2003; Mesurolle et al., 2007; Rosen & Soo, 2001; Seo et al., 2002; Szopinski et al., 2003). These showed speckle reduction techniques have improved image quality through increasing the contrast resolution and edge enhancement, improving the conspicuity of low-contrast lesions, enhancing the delineation of tumour margins and enhancing the depiction of the internal architecture of solid lesions and microcalcifications. These factors are all important in facilitating lesion detection. However, as mentioned above, these speckle reduction techniques have their limitations and therefore the combined use of different speckle reduction techniques has been recommended for lesion evaluation.

Few studies have addressed whether these improvements in image quality affected the final diagnostic assessment of breast lesions and assisted in selecting patients for biopsy. Two studies in 2005 and 2007 compared the diagnostic performance of three experienced radiologists in assessing images using conventional ultrasonography versus spatial compound imaging and in assessing images using conventional ultrasonography versus tissue harmonic imaging respectively (Cha et al., 2005; 2007). Both studies concluded there were no significant improvements in diagnostic performance.

In contrast, another study used lesion-containing breast images processed with an ultrasound image speckle reduction algorithm based on a 2-D textural homogeneity histogram and directional average filters. This study demonstrated that receiver operating characteristics (ROC) scores improved from 78.67% to 92.73%, the sensitivity increased from 88.7% to 94.3%, and the specificity increased from 68.6% to 75.2% (Su et al., 2010). Another group also processed clinical breast ultrasound images with a speckle reduction algorithm using 2-D homogeneity and directional average filters. Their study demonstrated a change in the value of A_z from 0.843 for the original images to 0.955 for the speckle-reduced images, and increased sensitivity from 87.5% to 98.2% (Guo,Cheng,Tian & Zhang, 2009). These studies concluded that the diagnostic accuracy greatly improved with the application of a speckle reduction algorithm. Given the conflicting results of these studies, the impact of speckle reduction techniques on diagnostic performance is currently unclear.

1.5 Precision Imaging

'Precision Imaging' is a fundamental signal processing technique from Toshiba, differing from XRES (Philips) or SRI (GE), which are image processing techniques. According to Toshiba, 'Precision Imaging' (PI) is a multi-resolution signal processing technology, i.e. a real time speckle processing technique powered by 'Intelligent Component Architecture' (Figure 1-1). In PI, instead of creating an image line by line, the information from adjacent lines is considered. Based on the assumption that a received signal comes from a structure, the adjacent lines will have the same signal and are therefore real and useful signals. On the other hand, if the adjacent lines do not have the same signal, then it is highly likely to be noise (speckle). In this way, it identifies diffuse random noise earlier and discounts signals that it considers as noise, leading to a more homogeneous image. Another feature of PI is structure recognition, which looks for a signal that contains edge definition of structure across multiple lines. This structural definition of line data is then enhanced, which results in clearer image data. Noise reduction combined with enhanced image data results in images

containing greater detail (Figure 1-2).

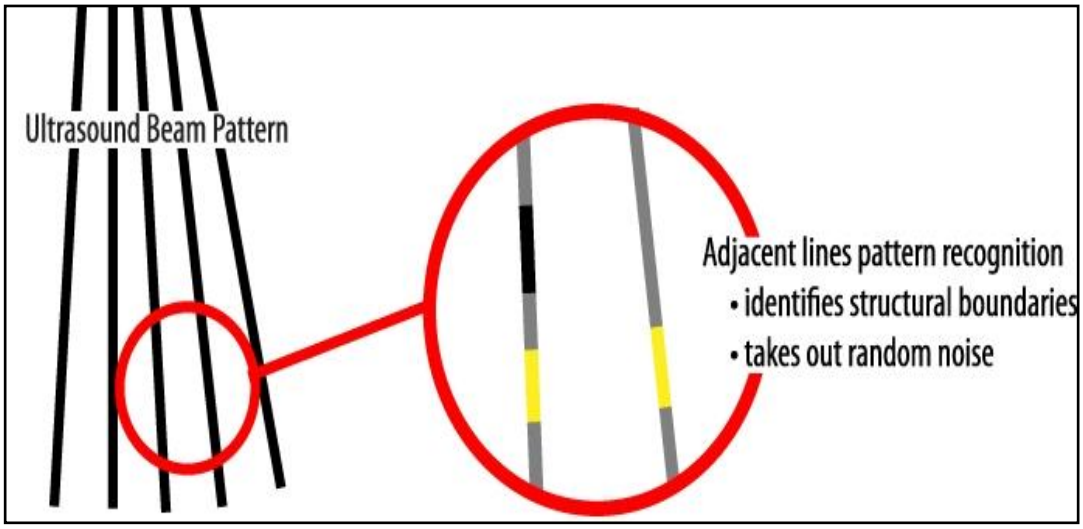


Figure 1-1: Schematic explanation of real time speckle processing technique powered by 'Intelligent Component Architecture' (Courtesy of Toshiba Medical Systems). The coloured sections of the lines within the red circle represent received signals (colour coded to represent same signal) from each ultrasound beam. The yellow colour is present in both lines, therefore they are considered to be real and useful signals, while the black colour signal was absent on the adjacent lines, this would be considered as noise and be discounted.

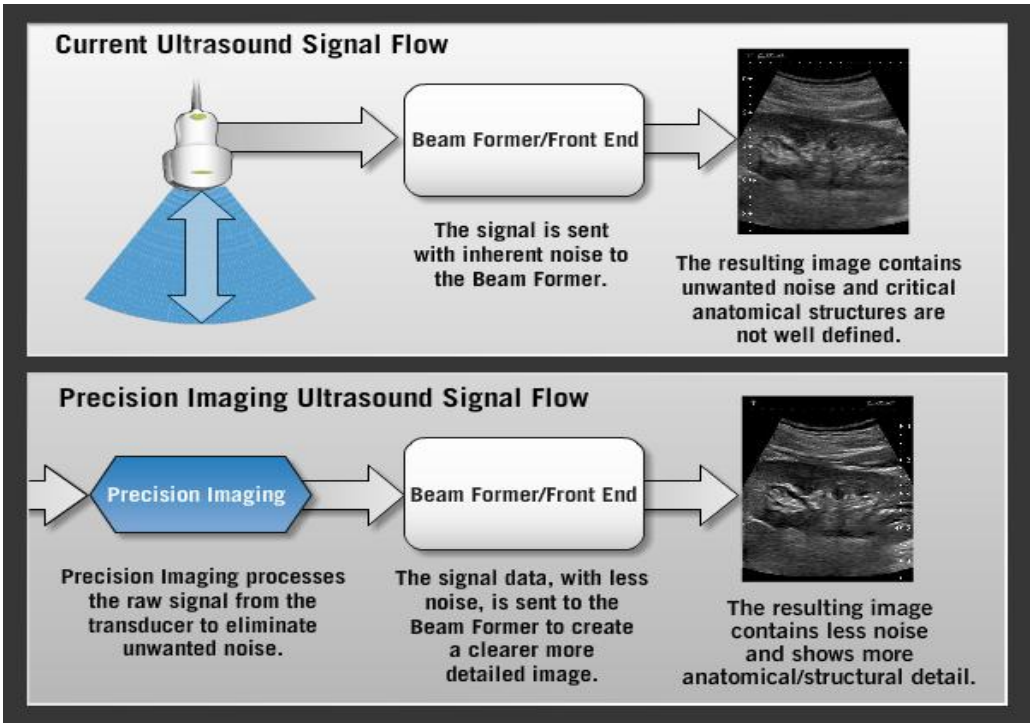


Figure 1-2: Comparison of image processing through conventional and 'Precision Imaging' (Courtesy of Toshiba Medical Systems)

According to Toshiba, this pre-processing of signal has several advantages. Firstly, there is no sacrifice of frame rate (unlike spatial compounding). Secondly, as unwanted noise is eliminated, a sharper image is produced and better contrast between tissue and lesion boundaries is shown. This improvement in clarity will enhance the ability to show subtle tissue differences and delineate small structures better than conventional imaging. This will enable ultrasound operators to view more clinical detail faster, view a clearer image due to less clutter and enhance their capacity to evaluate difficult to image areas which therefore improves diagnoses (Azar, 2011; Toshiba America Medical systems, 2009).

There are 3 levels (L) of PI. Figure 1-3 and 1-4 are images acquired without PI (L0) and with increasing levels of PI (L1-L3). The higher L number signifies an increased PI level. These images show the increase in contrast resolution and edge enhancement and the decrease in speckle with the increase of PI level. It is easy to appreciate the difference when the images are placed side by side.

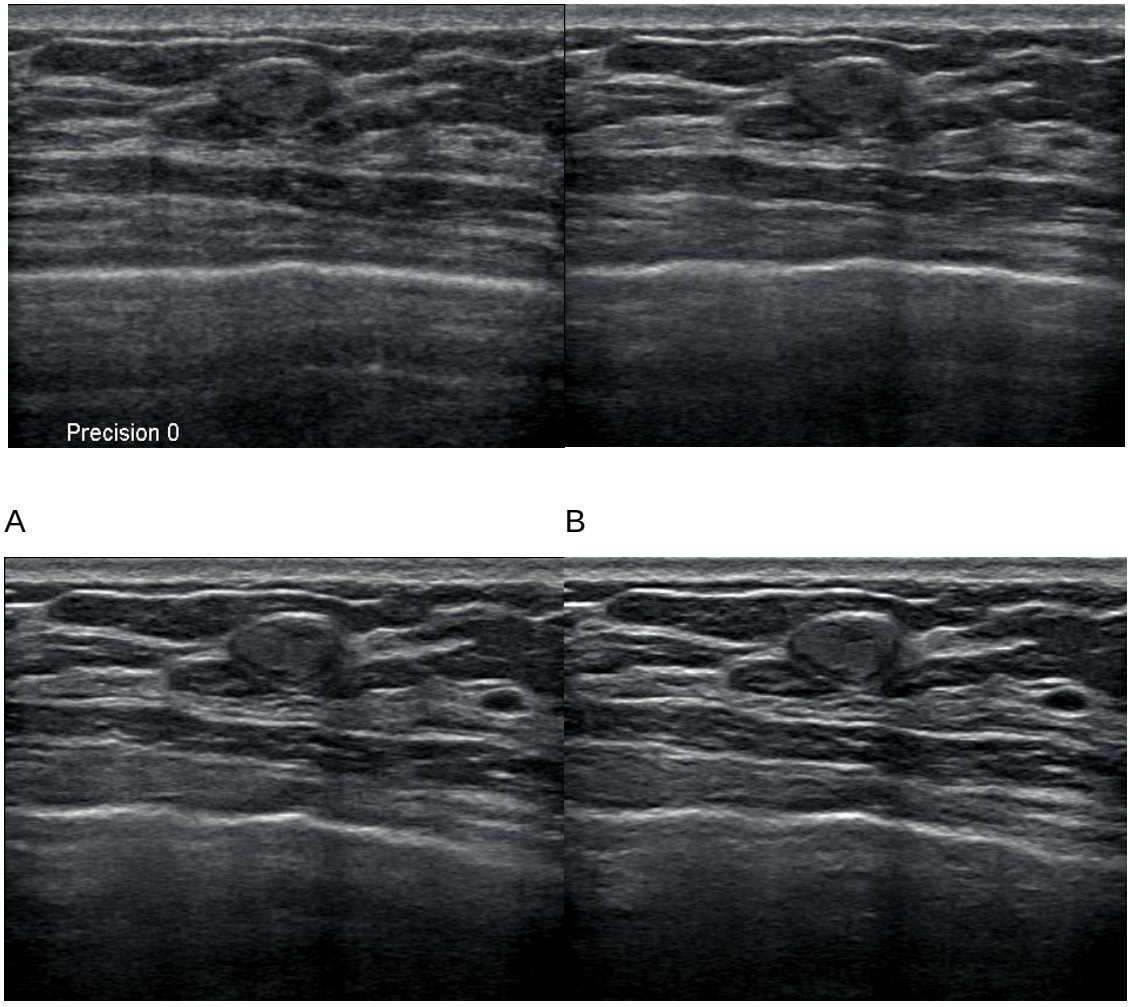
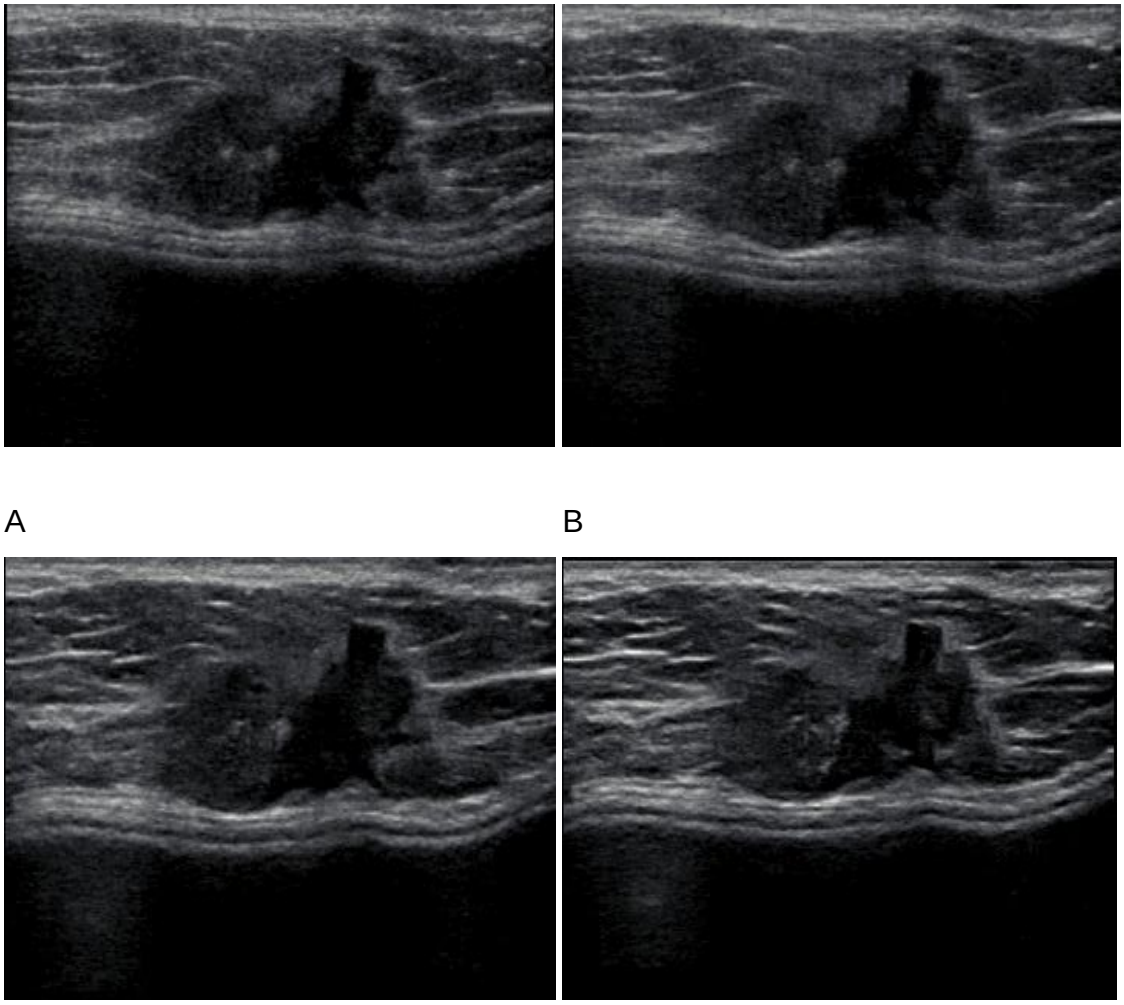


Figure 1-3: Images of the same benign breast lesion with different levels of PI, A-L0, B-L1, C-L2 and D-L3. As PI increases, the border of the lesion in the middle sharpens and the cystic structure to the right is more readily seen, when compared to the conventional image.



A B

C D

Figure 1-4: Images of a malignant breast lesion, A-L0, B-L1, C-L2 and D-L3 . With increase in PI, one can appreciate better margin delineation, more details in lesion echotexture heterogeneity and better demonstration of architectural interruption.

The incorporation of PI in scanning aims to improve clarity and increase the conspicuity of lesions by enhancing the subtle tissue differences and better delineating small structures. In a recent article comparing the image quality in focal liver lesions with and without PI (Yazgan,Akata,Ozmen & Karcaaltincaba, 2013), the author noted that the usual appearance of liver structure changed when using this algorithm without loss of detail in the 'smoothed' image`, and concluded that this algorithm provided better lesion conspicuity and image quality. The author also suggested further research was required to assess whether it would affect lesion characterisation. Until now there has been no published work scientifically evaluating the

usefulness of the PI algorithm on breast ultrasound examination. There is no published evidence that the increased clarity of the lesion, in terms of shape, lesion boundary and margin, increases diagnostic confidence in differentiating benign from malignant characteristics. There is also no published evidence that the PI algorithm works equally well with different breast tissue densities and volumes.

The aim of the current research was to investigate if PI could be shown to improve the ability of clinicians to correctly classify the nature of a breast tumour. This was done by evaluating the image assessment using receiver operating characteristic (ROC) analysis.

Chapter 2 Methodology

The purpose of this research was to investigate whether the application of the speckle reduction algorithm, Precision Imaging (PI), has any impact on breast ultrasound image quality and diagnostic outcome.

There were 2 parts to this research

1. To evaluate the effect of PI on image quality as assessed by the visualisation of breast structures. Visual grading analysis (VGA) was used to assess the effect of different levels of PI application. My colleague, Alfiya Safina, performed this study using anatomic and benign breast markers.

2. To assess the impact of changing PI levels on the breast practitioners diagnostic confidence in assessing solid breast lesions. I performed this study using lesion scoring and receiver operating characteristics (ROC) analysis and this is the focus of this thesis.

The findings of the two parts of this research are discussed in our joint paper submitted for publication and included in this thesis (Appendix 5.5).

2.1 Sample and consent

All patients attending the breast clinic signed a general consent form that gave permission to use their information for research purposes anonymously. Patients scanned with the particular ultrasound machine between October 2010 and June 2011 were automatically recruited in this study, and their age ranged from 20 to 84 years.

The Human Research Ethics Committee of Sydney University approved the study (protocol number 14466) (Appendix 5.1).

2.2 Image acquisition

Between October 2010 to June 2011, a single commercial ultrasound scanner Toshiba AplioMX, Model SSA-780A (Toshiba Medical Systems,

Otawara-shi, Tochigi-ken, Japan) with compact linear transducers 15-7MHz (PLT-1204BT) and 12-5 MHz (PLT-805AT) was used for image acquisition, with the choice of the transducer used being dependant on the size and density of the breast.

The examination was performed with the patient lying supine, with the ipsilateral arm raised above the head and a pillow tucked underneath the shoulder for support, in such way that the breast tissue was evenly spread over the chest wall. The breast was then systematically scanned in both longitudinal and transverse sections and in various radial and oblique scan planes whenever an area needed to be evaluated further. The images were optimised by adjusting the time gain compensation (TGC), centre frequency of transmitting ultrasound, depth of image (field of view), focal range and focal position, compound scanning and tissue harmonic imaging (THI).

Once the standard study was completed, a single projection image that was considered to best represent the lesion was recorded without PI (L0). The ultrasound scanner used in this research had split screen imaging capability. The acquired image without PI was kept to the left hand side of the screen, and the right side screen was activated and images, as close as possible in position to that seen on the left side of the screen, were obtained at different levels of PI, namely, Precision 1 (L1), Precision 2 (L2) and Precision 3 (L3); the higher number signifying greater speckle reduction. The levels of PI used in the images were labelled accordingly and still frames were recorded displaying both single level PI images (L0, L1, L2 and L3) and combined level images (L0/L1, L0/L2, L0/L3).

All images were stored in the hard disc of the ultrasound machine. A log book was used to record patient details and relevant ultrasound findings.

This choice of a single image was based on the recommendation that if a single malignant feature was present in the lesion, it excluded the lesion from benign classification (Stavros et al., 1995). A change in the observer's diagnostic decision with different PI application would imply an effect of PI on the diagnostic features.

2.3 Selection of lesions

In the nine month study period over two hundred patients were scanned. The criteria for lesion selection were based on the clinic's grading for ultrasound images, using the 1-5 classification system developed by National Breast Cancer Centre (NBCC) in collaboration with the Royal Australian and New Zealand College of Radiologists (RANZCR) (National Breast Cancer Centre, 2007).

In this system, the 1-5 breast imaging classifications are:

1. No significant abnormality
2. Benign findings
3. Indeterminate/equivocal findings
4. Suspicious findings of malignancy
5. Malignant findings

According to the clinic's regular practice, all lesions that were given a score of 3, 4 or 5 underwent cytology and/or core biopsy. On the other hand, solid lesions that were scored 2 (benign findings) were proven to be benign either by cytology and/or core biopsy or by stability over a minimum period of 2 years. In this study, lesions in fifty-one patients aged from 29 to 75 were selected based on the ultrasound imaging grading (grade 2-4 in 5-point scoring system).

Image quality may alter lesion features and their classification. Indeterminate lesion features, such as irregular shape or ill-defined/indistinct margins, may be presented differently when using different vendor ultrasound machines. Therefore, when evaluating practitioner diagnostic confidence, lesions with indeterminate features were included to investigate whether adding PI could enhance important benign and malignant lesions features and thus increase reader confidence in the classification of breast lesions.

The 51selected lesions are shown in table 2-1, as follows:

- 20 lesions classified as 2 (benign) with sizes ranging from 5-21mm.

- 14 lesions classified as 3 (indeterminate). Of these 4 were proven to be malignant: a 13mm ductal carcinoma in situ (DCIS); a 14mm infiltrating ductal carcinoma (IDC); a 9mm infiltrating lobular carcinoma (ILC); and a 12mm IDC with DCIS. The other 10 lesions were proven to be benign.

- 17 lesions classified as 4 (suspicious). Of these 16 were proven to be malignant with sizes ranging from 9-28mm. One was a 10mm area of fat necrosis.

Table 2-1: Lesions chosen for ROC analysis

Lesions	Types	No of cases	Size range(mm)
Malignant	invasive ductal carcinoma	17	7-28
	invasive lobular carcinoma	1	9
	ductal carcinoma in situ	2	12
Benign	fat necrosis	3	7-19
	fibroadenoma	8	9-17
	fibrocystic changes	7	7-21
	hyperplasia without atypia	2	7&9
	intraduct papilloma	2	5&7
	fibrosis	1	7
	phyllodes	1	24
	sclerosing lymphocytic lobulitis	1	10
	stable lesions	6	5-13

2.4 Creation and display of test sets

The selected lesions were transferred to a CD in DICOM format, reloaded into a PC, and ImageJ (NIH, Bethesda, Maryland, USA) was used to remove all technical details, which included patient information, time and date of examination, frequency of transducer, depth of ultrasound field, application of compound imaging and tissue harmonic imaging and the level of PI used. The test set was a series of images with featured lesions and surrounding breast tissue, which were then organised into four sets (A, B, C and D), with each set containing images produced at the same PI level.

The 51 images in set A were arranged in sequence from 1-51, then for the second set, these images were randomly moved in blocks. For example, number 13-17 moved to the top, 1-4 moved to the end, 5-7 moved to the middle. No rules were applied and the main purpose was to make the images' sequence different for each set, so that the observer was not familiar with the image sequence when reading the different sets. These were presented using a Q-Perform (Ziltron, Limerick, Ireland) image presentation system. These test sets were stored on two computers within the Sydney Breast Clinic and the image display size, resolution, contrast, brightness and reading conditions were controlled and remained consistent.

2.5 Participants (observers)

An invitation letter (Appendix 5.2) to participate in this study was sent to radiologists, breast physicians and sonographers working in the clinic.

In the current study, each of the six radiologists and six sonographers (all with over 2 years experience in breast imaging) completed an evaluation of all four test sets. Some radiologists completed the study while multitasking (such as reporting on other imaging examinations) while some radiologists and all sonographers completed the study without interruption. Therefore the individual timing of readings could not be measured as not all participants completed the study in the same way. Some other observers (breast

physicians) did not complete the full sets, so their results were not included in the study.

2.6 Evaluation of test sets

The invitation letter also included the instructions informing the observers of the order in which they should review the test sets. They logged into the program, chose the appropriate first test set, entered their user initials and started the image critique. They could start or log out of the review at any time and resume the review at their convenience.

The observers were blinded to all clinical and imaging history and scored lesions based on their diagnostic experience, using a 1-6 scale where 1 indicated definitely benign, 2 - probably benign, 3 - possibly benign, 4 - possibly malignant, 5 - probably malignant and 6 - definitely malignant. There was no time limit on scoring each image. Once an image was scored, the next image would appear for scoring and the scored image would not appear again. Observer scores from this study were rated with 1-3 as negative (indicating the benign nature of the lesion) and 4-6 as positive.

Different observers read the test sets in different orders. Observer performance in terms of ROC was compared to see if the reading order affected the outcome.

2.7 Data analyses

A Wilcoxon signed-rank test was employed to identify any significant differences in sensitivity or specificity between any of the PI pairings. Sensitivity was defined by the true positive (TP) value over the combined value of TPs and false negatives (FN). Specificity was calculated using the ratio of true negative (TN) numbers over the combined value of TNs and false positives (FP).

A receiver operating characteristics analysis (ROC) used the Dorfman, Berbaum, Metz multi-reader multi-case approach (DBMMRMC 2.32 Build 3)

to assess if there were differences in ROC values between individual pairings of PI.

In the current study, six radiologists and six sonographers participated in the study, and a Mann-Whitney U-test was used to determine whether there were statistically significant differences in ROC values between these two groups.

Chapter 3 Data analyses and results

The selection of lesions were not representative of normal distribution, therefore a non-parametric test was used. As stated in the methodology, six radiologists and six sonographers participated in the study. Their individual responses to the image assessment were collected and simultaneously analysed using Q-Perform software (Ziltron, Limerick, Ireland), Wilcoxon signed-rank test, Mann-Whitney U-test, the Dorfman, Berbaum, Metz multi-reader multi-case software (DBMMRMC 2.32 Build 3) and IBM SPSS statistic softwares were also used.

3.1 ROC analysis

The Q-Perform software (Ziltron, Limerick, Ireland) was used to analyse collected data (true positives, false positives, true negatives, false negatives) and to calculate metrics for each reader. These included: receiver operator characteristic (ROC) values, sensitivity (number of malignant lesions correctly identified over the total number of malignant lesions present in the test set) and specificity (number of benign lesions correctly identified over the total number of benign lesions present in the test set). These sets of data were then arranged to facilitate comparison. Observers 1 to 6 are radiologists and observers 7 to 12 are sonographers (Table 3-1).

Table 3-1: Summary of ROC area under the curve (AUC)results (using Q-Perform) for each observer

Observer	L0	L1	L2	L3
1	0.78	0.77	0.83	0.76
2	0.79	0.82	0.75	0.79
3	0.79	0.81	0.83	0.80
4	0.76	0.79	0.79	0.78
5	0.79	0.77	0.86	0.88
6	0.81	0.79	0.85	0.79
7	0.79	0.78	0.80	0.84
8	0.82	0.80	0.88	0.78
9	0.82	0.85	0.84	0.85
10	0.87	0.83	0.81	0.85
11	0.71	0.80	0.81	0.74
12	0.80	0.82	0.67	0.82

It was concluded from the Wilcoxon signed-rank test analyses that there was no statistical difference for the ROC levels with varying levels of PI (statistical significance was determined at $P<0.05$) (Table 3-2).

Table 3-2: Wilcoxon signed-rank test comparing ROC between different PI levels

ROC between PI level	Z-Value*	P-Value*
L0/L1	-0.784	.433
L0/L2	-1.059	.290
L0/L3	-0.800	.424

* rounded to 3 decimal point

A Mann-Whitney U-test was used to determine whether there were statistically significant differences for the ROC between the observer groups (radiologists and sonographers) (Table 3-3).

Table 3-3: Mann-Whitney U-test on ROC between the observer groups (radiologists and sonographers) for different PI levels

ROC for PI level	Z-Value*	P-Value*
L0	-1.361	.174
L1	-1.041	.298
L2	-0.320	.749
L3	-0.721	.471

* rounded to 3 decimal point

As no statistically significant differences were found, this enabled the combination of the two observer groups.

The data (Appendix 5.3) was then reanalysed with a well-established statistical analysis tool, the Dorfman, Berbaum, Metz multi-reader multi-case software (DBMMRMC 2.32 Build 3), which involves jackknifing images and is recognised for its statistical rigour (Dorfman,Berbaum,Lenth,Chen & Donaghy, 1998; Dorfman,Berbaum & Metz, 1992; Hillis, 2007; Hillis & Berbaum, 2004, 2005; Hillis,Berbaum & Metz, 2008; Hillis,Obuchowski,Schartz & Berbaum, 2005).

In this statistical analysis, individual observer's scores (51 cases in this research) for each treatment (L0, L1, L2 and L3) were computed for ROCAUC. Jackknife images meant that the scores were computed with one case systematically removed from the analysis. For example the first case was removed (result in pseudovalue A_{z1}), then case 2 was removed and case 1 returned to be computed (result in pseudovalue A_{z2}). This scenario was repeated across the 51 cases. In this way, 51 sets of data were generated from one set of data. These pseudovalues were used for statistical analysis, and this method of statistical analysis has been found to be more powerful (Dorfman, Berbaum & Meta, 1992).

The resultant ROC (analysis of variance trapezoidal area analysis) values are given in Table 3-4 with the results from the DBMMRMC analysis shown in Table 3-5.

Table 3-4: ROCAUC values (rounded to 2 decimal points) for each observer at different PI levels using DBMMRMC analysis. Mean values are given for radiologists (R) (observers 1-6), sonographers (S) (observers 7-12) and all observers combined. Standard deviation (SD) values are shown in parentheses.

Observer	L0	L1	L2	L3
1	0.78	0.77	0.83	0.76
2	0.79	0.82	0.75	0.79
3	0.79	0.81	0.83	0.80
4	0.76	0.79	0.79	0.78
5	0.79	0.77	0.86	0.88
6	0.81	0.79	0.85	0.77
R means	0.79(0.06)	0.79(0.06)	0.82(0.05)	0.80(0.05)
7	0.79	0.78	0.81	0.84
8	0.82	0.80	0.88	0.78
9	0.82	0.86	0.84	0.85
10	0.87	0.83	0.81	0.85
11	0.71	0.77	0.82	0.74
12	0.80	0.82	0.67	0.82
S means	0.80(0.06)	0.81(0.05)	0.80(0.06)	0.82(0.06)
Overall	0.79(0.05)	0.80(0.05)	0.81(0.05)	0.81(0.05)

Table 3-5: Mean differences between different levels of PI

PI level	Mean differences*	95% Confidence interval*
L0-L1	-0.006	-0.047, 0.035
L0-L2	-0.018	-0.059, 0.023
L0-L3	-0.011	-0.052, 0.029
L1-L2	-0.012	-0.053, 0.029
L1-L3	-0.005	-0.046, 0.036
L2-L3	0.007	-0.034, 0.048

* rounded to 3 decimal points

There were no significant differences found in ROC between different PI levels, with p=0.8408 (significance level set at p<0.05).

The data from the radiologist group and sonographer group were analysed separately using DBMMRMC 2.32 Build 3 software. The ROC values are shown in Table 3-6. Again there was no statistically significant difference between the two groups.

Table 3-6: Comparison of mean ROC values between the radiologist group and sonographer group

PI Level	Radiologists*	Sonographers*
L0	0.786	0.802
L1	0.790	0.810
L2	0.820	0.804
L3	0.795	0.815

* rounded to 3 decimal point

Individual ROC curve across all Precision levels are shown in Figures 3-1 to 3-12 (constructed with IBM SPSS statistical software).

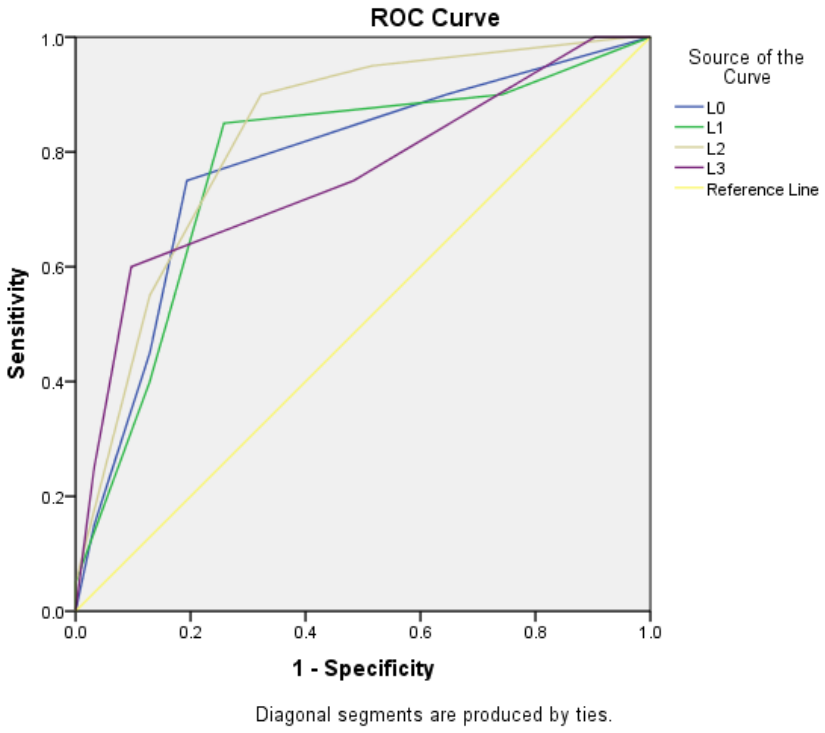


Figure 3-1: ROC curve for observer 1

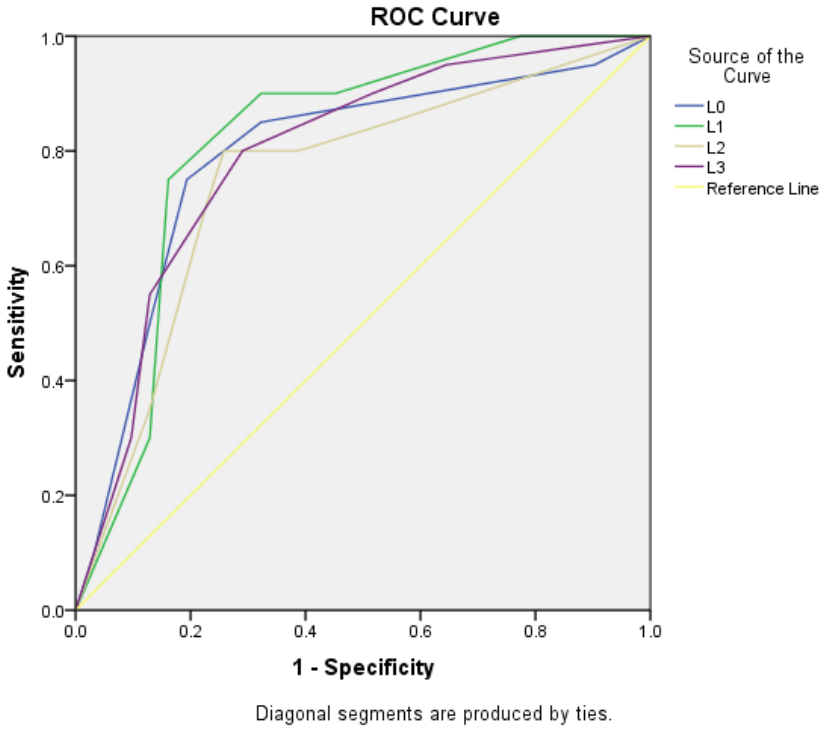


Figure 3-2: ROC curve for observer 2

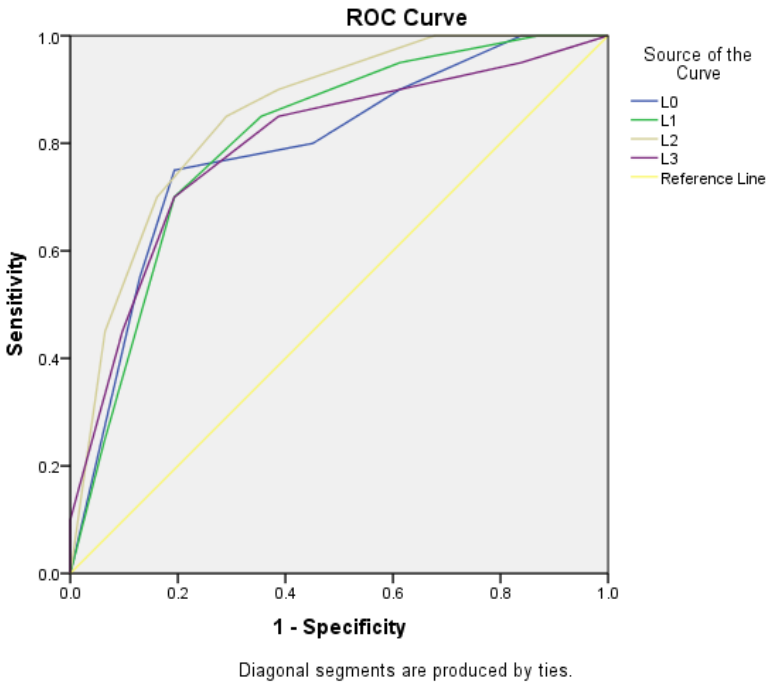


Figure 3-3: ROC curve for observer 3

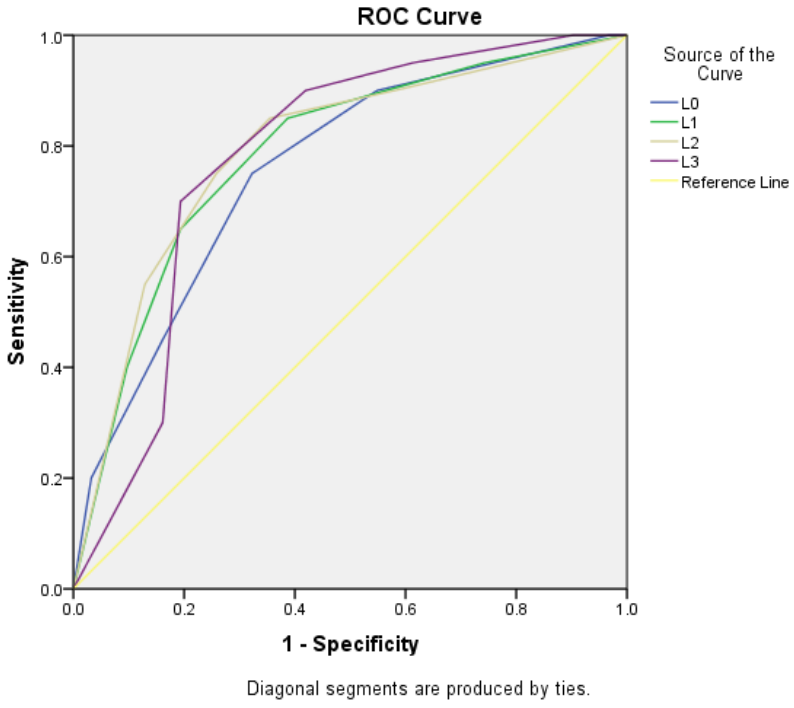


Figure 3-4: ROC curve for observer 4

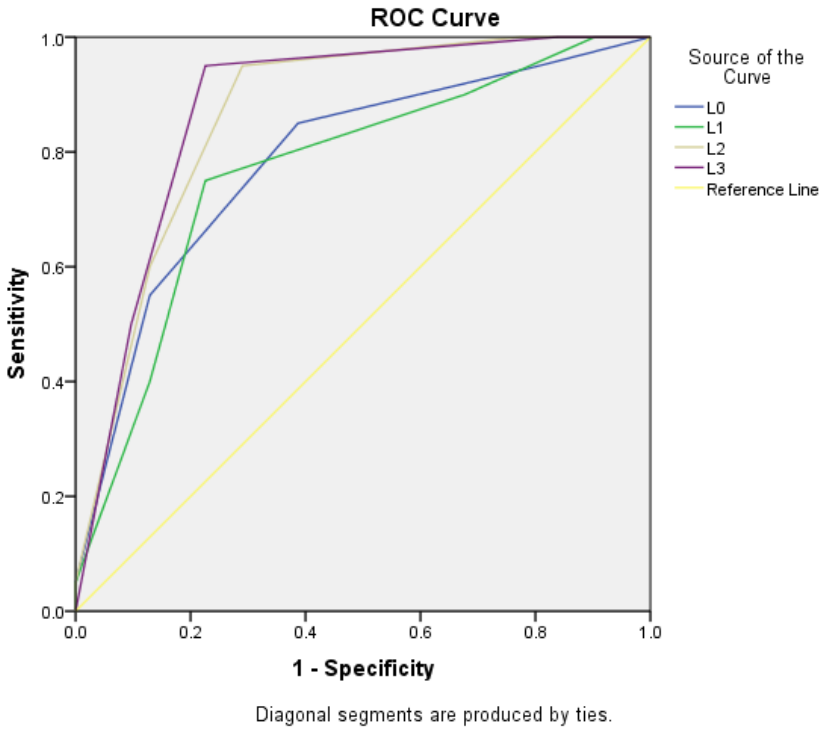


Figure 3-5: ROC curve for observer 5

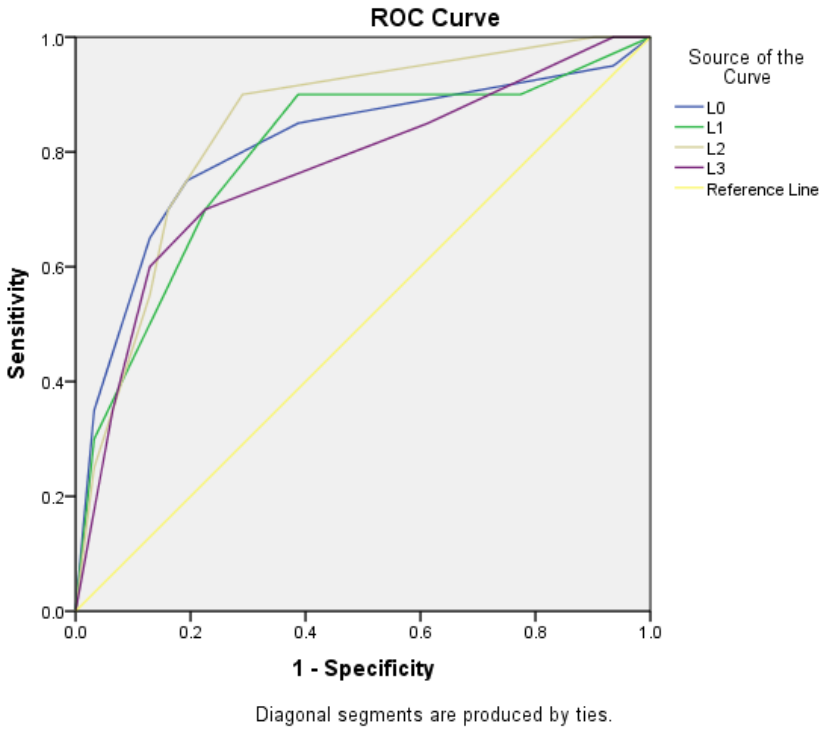


Figure 3-6: ROC curve for observer 6

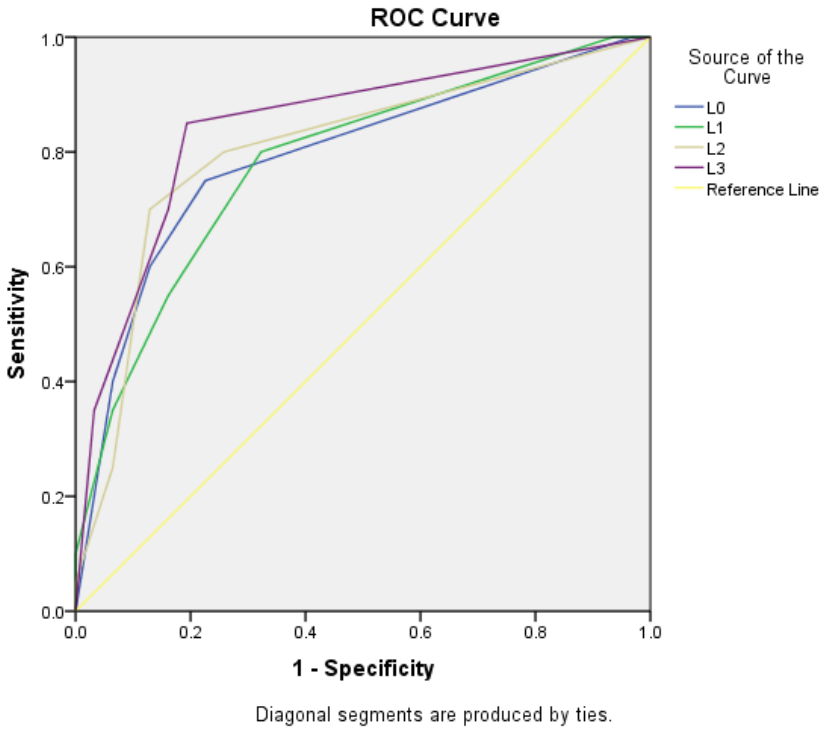


Figure 3-7: ROC curve for observer 7

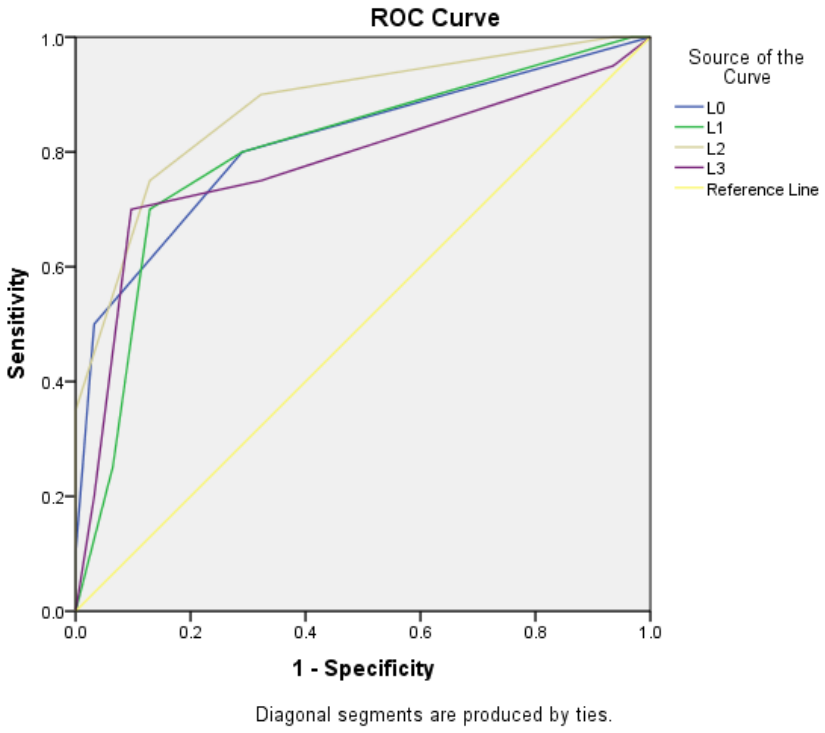


Figure 3-8: ROC curve for observer 8

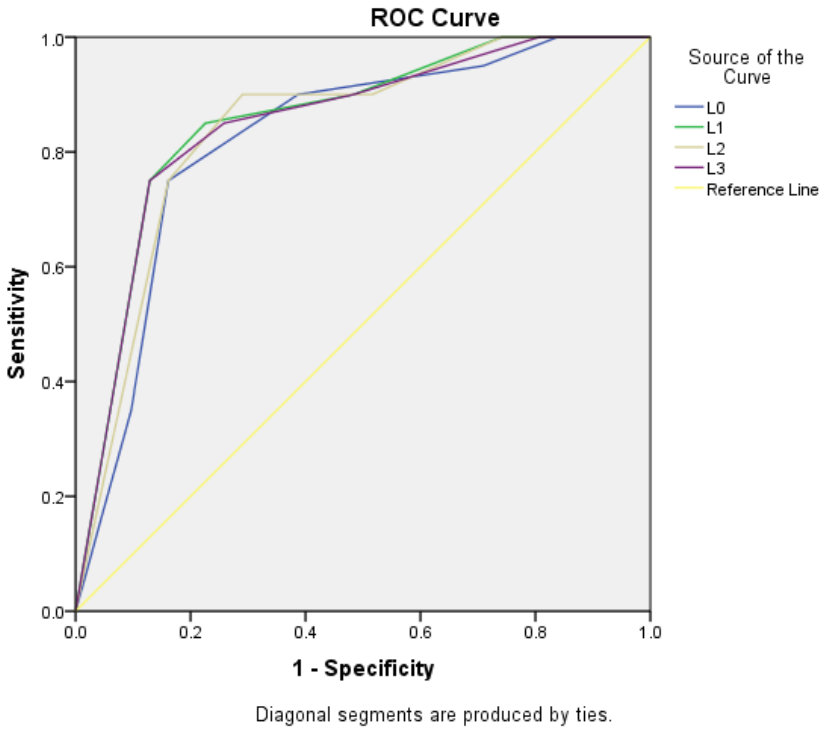


Figure 3-9: ROC curve for observer 9

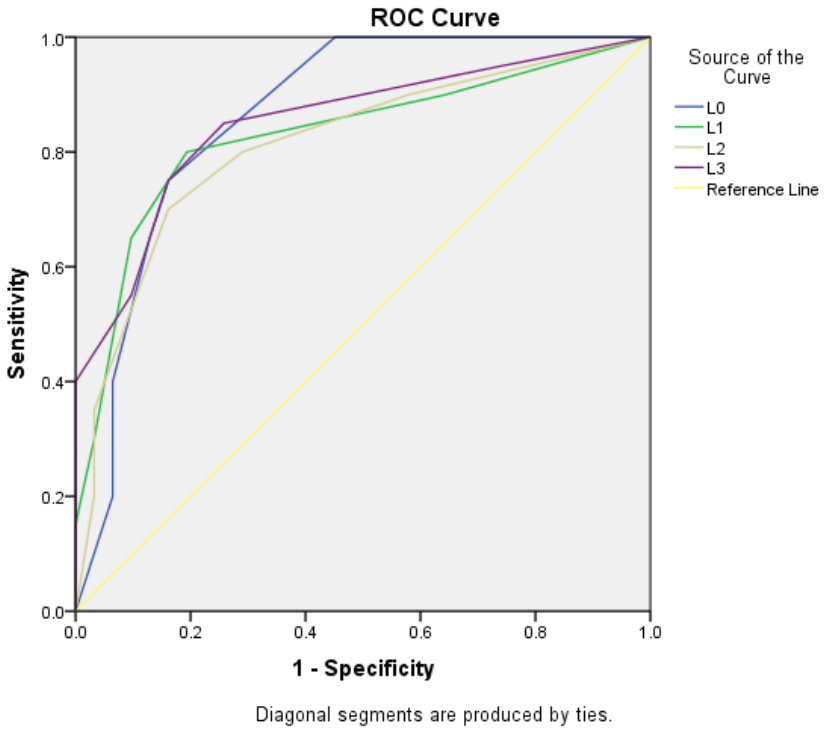


Figure 3-10: ROC curve for observer 10

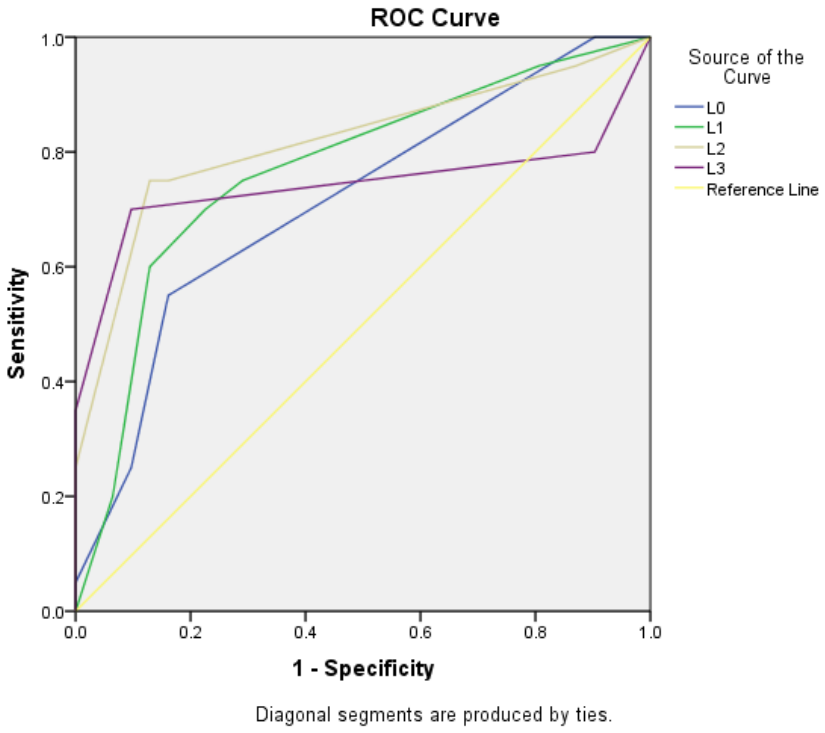


Figure 3-11: ROC curve for observer 11

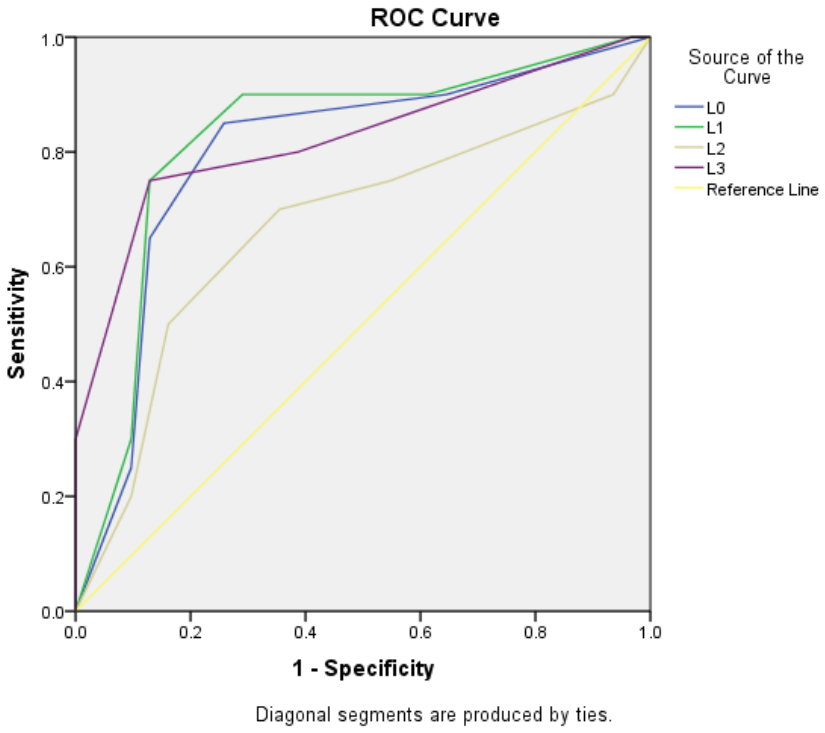


Figure 3-12: ROC curve for observer 12

3.2 Sensitivity and specificity

A summary of the sensitivity and specificity for different PI levels for each observer is presented in Table 3-7.

Table 3-7: Sensitivity and specificity for different levels of PI. Mean values are given for radiologists (R) (observers 1-6) sonographers (S) (observers 7-12) and all observers combined (OM). Standard deviation (SD) values are shown in parentheses.

Observer	Sensitivity				Specificity			
	L0	L1	L2	L3	L0	L1	L2	L3
1	0.75	0.85	0.9	0.75	0.81	0.74	0.68	0.52
2	0.75	0.9	0.8	0.8	0.81	0.68	0.74	0.71
3	0.8	0.85	0.8	0.7	0.55	0.65	0.71	0.81
4	0.75	0.85	0.85	0.9	0.68	0.61	0.65	0.58
5	0.85	0.75	0.95	0.95	0.61	0.77	0.71	0.77
6	0.75	0.7	0.7	0.7	0.81	0.77	0.84	0.77
R means	0.78	0.82	0.83	0.80	0.71	0.70	0.72	0.69
(SD)	(0.04)	(0.08)	(0.09)	(0.10)	(0.12)	(0.07)	(0.07)	(0.12)
7	0.6	0.55	0.7	0.7	0.87	0.84	0.87	0.84
8	0.8	0.8	0.9	0.75	0.71	0.71	0.68	0.68
9	0.9	0.9	0.9	0.9	0.61	0.52	0.48	0.52
10	0.65	0.65	0.7	0.75	0.87	0.9	0.84	0.84
11	0.55	0.75	0.75	0.7	0.84	0.77	0.87	0.9
12	0.85	0.9	0.7	0.8	0.74	0.71	0.65	0.61
S means	0.73	0.76	0.78	0.77	0.77	0.74	0.73	0.73
(SD)	(0.14)	(0.14)	(0.10)	(0.08)	(0.10)	(0.13)	(0.16)	(0.15)
OM	0.75	0.79	0.80	0.78	0.74	0.72	0.73	0.71
(SD)	(0.10)	(0.11)	(0.09)	(0.09)	(0.11)	(0.10)	(0.11)	(0.13)

A Wilcoxon signed-rank test was used to determine whether there were statistically significant differences in either sensitivity or specificity between any of the PI pairings, where sensitivity was the ratio of true positives (TP) over the combined value of TP and false negatives (FN) and specificity was the ratio of true negative (TN) over the combined value of TN and false positive (FP). There were no statistically significant differences (significance level with $p<0.05$) demonstrated in either sensitivity or specificity between any of the PI pairings (Tables 3-8 and 3-9).

Table 3-8: Wilcoxon signed-rank test on sensitivity between PI pairings

PI levels	Z-Value*	P-Value*
L0/L1	-1.362	.173
L0/L2	-1.733	.083
L0/L3	-1.376	.169
L1/L2	-0.560	.575
L1/L3	-0.153	.879
L2/L3	-0.930	.353

* rounded to 3 decimal point

Table 3-9: Wilcoxon signed-rank test on specificity between PI pairings

PI levels	Z-Value*	P-Value*
L0/L1	-0.978	.328
L0/L2	-0.711	.477
L0/L3	-1.020	.308
L1/L2	-0.314	.754
L1/L3	-0.420	.674
L2/L3	-0.612	.541

* rounded to 3 decimal point

3.3 Reading order

Each observer was assigned a different reading order (Table 3-10) in an effort to determine if reading order (rather than the PI values) had any influence on the findings. The consistency of the results suggests that the reading order did not affect the observers' performance.

Table 3-10: Reading order of each observer and the respective ROC results

Observer	reading order	ROC result according to reading order
1	A, C, D, B	0.78, 0.83, 0.76, 0.77
2	A, D, C, B	0.79, 0.79, 0.75, 0.82
3	D, C, A, B	0.80, 0.83, 0.79, 0.81
4	A, D, B, C	0.76, 0.78, 0.79, 0.79
5	B, D, A, C	0.77, 0.88, 0.79, 0.86
6	C, B, D, A	0.85, 0.79, 0.77, 0.81
7	B, C, A, D	0.78, 0.80, 0.79, 0.84
8	B, C, D, A	0.80, 0.88, 0.78, 0.82
9	A, B, C, D	0.82, 0.85, 0.84, 0.85
10	A, C, B, D	0.87, 0.81, 0.83, 0.85
11	D, A, C, B	0.74, 0.71, 0.82, 0.77
12	C, D, B, A	0.67, 0.82, 0.82, 0.80

3.4 Summary

This research was structured to show whether there was an improvement in diagnostic confidence from observers when using different levels of PI and if so, which levels had the best outcome.

In this study, the scores of each observer for the lesions imaged with different PI levels were subjected to Q-Perform software, DBMMRMC 2.32 Build 3 software, Mann-Whitney U-test, Wilcoxon signed-rank test and IBM SPSS statistics for statistical analyses. The data analyses did not demonstrate any statistically significant difference between different PI levels, either for individual observers or for the group (radiologists and sonographers combined). These findings will be discussed in the following discussion chapter.

Chapter 4 Discussion

Precision Imaging (PI) is a speckle reduction algorithm developed by Toshiba Medical Imaging, introduced to Sydney Breast Clinic through the purchase of a new ultrasound machine. The manufacturer recommends using this technology as it claims to provide better image quality. A study was conceived to investigate breast practitioner preferences with PI usage and if 'better quality' images could facilitate lesion characterisation and ultimately increase the breast practitioner's diagnostic confidence. If so, which of the three PI levels was most suitable for breast scanning and how could PI be incorporated into clinical preset scanning programs? The answer to these questions would facilitate more effective clinical implementation of this new technology.

There were several published studies related to the application of speckle reduction technology in breast imaging (Cha et al., 2005; 2007; Mesurolle et al., 2007; Su et al., 2010; Tseng et al., 2012), but a review of the literature did not identify any specific studies related to application of PI in breast ultrasound. Based on the work of Azar (Azar, 2011), it was hypothesised that PI would improve visualisation of anatomically important structures in the breast, improve feature recognition of benign and malignant lesions and hence improve reader confidence in the classification of breast lesions. This could lead to a more effective scanning process, as improved visualisation allows one to perceive structural detail faster, and improvements to feature recognition should improve diagnostic accuracy (sensitivity and specificity).

My colleague, Alfiya Safina, performed the study of observer preference for PI levels using anatomic and benign breast markers. Her findings are discussed in our joint paper submitted for publication and included in this thesis (Appendix 5.5). Whilst her work found significantly different preferences for PI levels in breast imaging, my study of diagnostic efficacy did not reveal any improvements in diagnostic accuracy. The reasons for and the implications of my findings are discussed below.

4.1 Diagnostic performance analysed through receiver operating characteristic (ROC)

Analysis of lesion categorisation using ROC values specific to each observer was first undertaken with the Q-Perform software (Ziltron, Limerick, Ireland) and there were no significant differences between different levels of PI. Another vigorous statistical analysis was undertaken, using multireader-multicase methodology (DBMMRMC 2.32 Build 3), again with no statistical differences. The consistency of our findings, coupled with the rigorous methodological approaches used, would suggest that PI presents limited benefits with regards to diagnostic performance.

In our study, the images with no PI application already demonstrated some level of speckle reduction through spatial compounding and tissue harmonic imaging. These two speckle reduction techniques are routinely used in clinical practice and the observers participating in this work were already familiar with the images obtained with these techniques. While the addition of PI may have produced a sharper image (or a preferred image as demonstrated by the VGA study by Alfiya Safina), this change in image quality did not affect the observers' diagnostic performance, as reflected by the ROC analysis. In two separate studies (Cha et al., 2005; 2007), three radiologists evaluated solid breast lesions. A comparison was made of their diagnostic performance with images acquired by conventional ultrasound technique versus images acquired by speckle reduction techniques, namely spatial compound imaging and tissue harmonic imaging (THI). Both studies indicated an improvement in image quality with reduced speckle artifacts. This resulted in improved conspicuity of low contrast lesions, enhanced delineation of tumour margins, better differentiation of fluid from solid tissue in complicated cysts, improved depiction of the internal architecture of solid lesions and improved identification of microcalcifications. However, both studies concluded that there were no significant improvements in the radiologists' performance when using these speckle reduction techniques. The speckle reduction effects achieved in these studies are similar to those

produced using the PI algorithm and the lack of effect on diagnostic performance is also similar.

Tseng et al. published a study which evaluated breast lesions obtained with speckle reduction imaging (SRI) and no SRI using computer-aided diagnosis (CAD) (Tseng et al., 2012). This study was similar to ours since SRI was achieved through a 'speckle-reducing post-processing filters' algorithm (Piccoli & Forsberg, 2011). The main difference between the work of Tseng et al. and current work is that the former employed a morphology-based CAD system, known as support vector machine (SVM), to classify the breast lesions as benign or malignant rather than human observers. In the Tseng et al. study, the borders of the breast lesions were manually delineated by an experienced breast physician to define their contour. These computerised morphologic features were then extracted, calculated and classified by the SVM. Their study did not demonstrate a significant difference in either ROC value, sensitivity or specificity and they concluded that SRI did not significantly improve the performance of breast ultrasound in characterising solid breast lesions. Although the interpretation methodologies are quite different between the two studies, it is interesting to note that conclusions based on both artificial and human intelligence indicated no advantage in terms of diagnostic efficacy.

There have been studies that processed the clinical breast ultrasound images with a speckle reduction algorithm using 2-D homogeneity and directional average filters. Contrary to the findings of the current study, these studies concluded that the applied algorithm was useful as it improved the ROC, sensitivity and specificity (Guo et al., 2009; Su et al., 2010). In comparing these studies and the current work, there were differences in image processing methods and the number of images used. Firstly, they applied the speckle reduction algorithm to the stored images, whereas in the current study and the studies by Cha et al and Tseng et al, the images were processed in real-time. Secondly, they used several images for each lesion, whilst the current and the previous studies used one to two images per lesion (Cha et al., 2005; 2007; Tseng et al., 2012).

The hypothesis that an improvement in image quality as a result of PI will improve the observer's diagnostic performance was not supported by this study. This finding may be explained by the 'top down theory' (Kundel & Nodine, 1983). These authors concluded that the radiologic perception of experienced radiologists follows this top down approach, which is a parallel processing of the visual image with acquired memories of normal and abnormal appearances. The hypothesis is that an abnormality is identified in a very short time and then a preselected portion of the image is continuously sampled to gain supporting diagnostic feature detail. In a speckle reduced ultrasound image, the lesion may be easier to evaluate as speckle reduced images have better contrast and margin delineation. This is demonstrated in Figures 4-1 and 4-2: when images of different PI levels were placed side by side, the lesion and the surrounding features are seen to be relatively sharper and better delineated with increasing PI levels. However, the lesion maintains its characteristics, such as shape, margin, orientation, echotexture and architectural disturbance, regardless of the PI levels, although these features are progressively enhanced with increasing PI levels. For experienced observers, this change in contrast and margin delineation might not be significant, as the features of the lesion, which ultimately determine characterisation, are maintained despite different PI levels. Therefore, in accordance with the notion of 'top down theory', since there were no major changes to the pattern structure nor to the observer's acquired memories of normal and abnormal appearance, it is reasonable to suggest that the diagnostic decision should not have changed significantly.

The image quality study carried out by my colleague, Alfiya Safina, used the same observers who participated in my study, although my study involved some additional observers. The image quality study showed that the observers considered the images with higher PI to be 'better' quality images. It could be that despite no change in diagnostic performance, the 'better' quality images may have expedited the observer's diagnostic decision by reducing the time taken to evaluate the test set. However the current study cannot address this possibility, as the observers approached the study under different working environments and reporting times were not analysed.

The participants in this research were sonographers and radiologists who specialise in breast imaging and the ROC results from this study suggested a 'good' quality image served the same diagnostic purpose as a 'better' quality image amongst our experts. The question remains whether the ROC results would have been similar to those of the current study had the observers not been specialists, but rather inexperienced observers such as trainee radiologists without expertise in breast ultrasound. In accordance with the 'top down theory', trainee radiologists would have less acquired memory of image characteristics and a 'better' quality image with enhanced features could facilitate lesion detection and recognition, consequently improving the diagnostic efficacy in this group. Such an outcome would indicate the benefit of PI application and its potential use to facilitate training. However, these postulates can only be answered through further work.

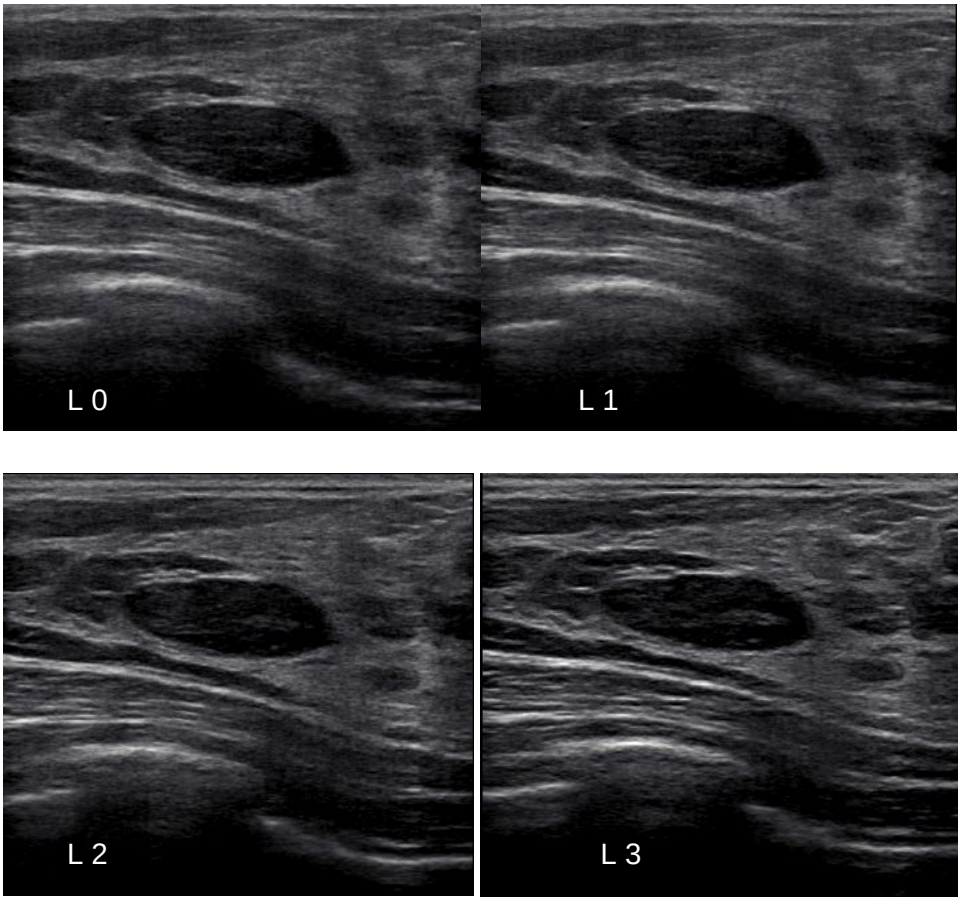


Figure 4-1: Images of a benign breast lesion with different levels of PI. As the PI increases from L0 to L3, the border of the lesion in the centre of the image and the surrounding tissues appear sharper.

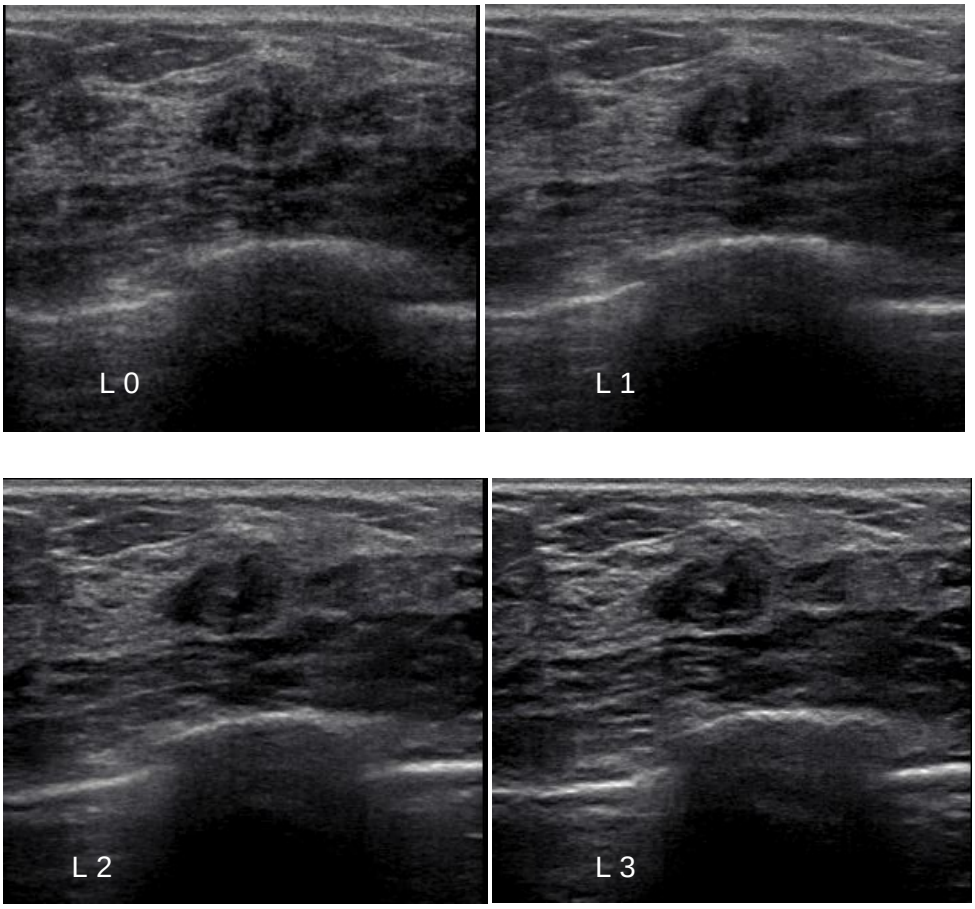


Figure 4-2: Images of a malignant breast lesion with different levels of PI. As the PI increases from L0 to L3, improvements in margin delineation, lesion echotexture heterogeneity and sharpness of surrounding tissues are easily appreciated.

4.2 Specificity

In ultrasound imaging of the breast, it is important to maximise specificity in order to reduce the number of unnecessary invasive investigations. For the patient, any invasive procedure carries potential risks and may induce anxiety, for example while waiting for the results. Other negatives such as the time involved and the financial costs all contribute to the burden on the patient and the health care system.

In the current study, no significant differences were shown with the mean specificity being 0.74 for lesions without any PI level (L0) added and 0.73 for L2. This is consistent with other published studies. In previous work looking

at non-SRI v SRI images, specificity was shown to be 70.8% v 73.6% (Tseng et al., 2012), 63% v 62% (Cha et al., 2007) and 80% v 82% (Cha et al., 2005) respectively. No statistically significant differences in specificity were noted in any of these comparisons.

In this study, while there were no statistically significant differences in specificity, only one radiologist out of six demonstrated an increase in specificity with increasing level of PI (observer 3). This trend was not repeated with other observers. However three out of six radiologists demonstrated increased specificity (0.81) with original images (L0) compared with L3 (specificity 0.52-0.77) and four out of six sonographers had increased or equal specificity (0.61-0.87) with L0 compared with L3 (specificity 0.52-0.84). It could be suggested that some observers were familiar with the L0 image appearance (the image generally used in clinical practice) and therefore performed better when presented with this image. In a study using PI in liver imaging, it was observed that the 'usual' sonographic appearance of structures was altered by the application of PI (Yazgan et al., 2013). It could be argued that the application of PI in the current study may have altered the appearance of some breast lesion features, which could have changed observer interpretation of lesion characterisation, a scenario which might be reflected in the slightly lower group mean specificity for L3 (0.71) when compared with L0 (0.74).

When the current research was carried out, the PI algorithm was new to the observers. It is probable that the observers needed to become familiar with the changed 'uncluttered' image to provide an appropriate interpretation of any perceived abnormality (Kundel & Nodine, 1983). This concept is supported by the work of Yap et al. who concluded that experienced radiologists performed well (with high sensitivity and specificity) when reading images that they are familiar with (Yap,Edirisinghe & Bez, 2010). The observed variation in individual ROC outcomes in the current study is consistent with the 'top-down theory' on visual concept, which postulates that when radiologists are relying on memory and 'stored templates' of normality, a disruption of the familiar image appearance with a 'new improved look',

may also cause disruption of markers of diagnostic efficacy such as specificity.

4.3 Observers

This research also indirectly compared the diagnostic performance of the radiologist and sonographer groups and the data analysis showed there were no statistically significant differences between the two professional groups, meaning the performance of the two groups was comparable. This result is reassuring, as the sonographers serve at the 'frontline', filtering and recording the information on which the radiologists base their diagnoses.

The current research did not evaluate the effect of PI application on the efficacy of any other diagnostic group, such as breast physicians. It would be of value to assess the performance of professionals with a range of different skill levels and experience, to assess any difference in impact of technology changes.

These results may be influenced by intraobserver variability. Intraobserver variability has been recognised (Loizou & Pattichis, 2008), meaning that an expert evaluating the same image may have different opinions on different occasions. However the effect of intraobserver variability was not tested in this study.

4.4 Type of lesions

Different studies have demonstrated that regardless of the type of speckle reducing technology employed, the features of a breast lesion (such as shape, margin, orientation) were observed to be equal or improved when compared with ultrasound images without speckle reduction techniques (Cha et al., 2005; 2007; Clevert et al., 2007; Mesurolle et al., 2007; Rosen & Soo, 2001). In other words, it can be argued that the clearer margin delineation between the lesion and the surrounding structures in speckle reduced images could facilitate its accurate evaluation and possibly increase the observer's diagnostic confidence as evaluated in some studies (J. Cha et al.,

2005; 2007). However the original (L0) images used in this study were optimised with spatial compounding and tissue harmonic imaging prior to the application of PI, meaning that the original image (L0) had little clutter and this could have reduced the potential impact of PI on diagnostic efficacy.

In the current study, around a quarter of selected lesions were graded as indeterminate. These were chosen with the notion that better image quality may facilitate the observer to make more definitive diagnostic decisions. However the results were inconclusive. Anecdotally in our clinical practice, a combination of better quality image and real-time review is believed to assist the radiologists in their diagnostic decision in difficult cases.

4.5 Limitations

In clinical practice it is important to categorise solid breast lesions as benign or malignant based on their characteristic sonographic features and to reduce the number of lesions categorised as indeterminate and thus reduce the number of unnecessary benign biopsies (Baker & Soo, 2000). However due to the significant overlap of the benign and malignant features in ultrasound images and the level of subjectivity in interpretation, an image-guide needle biopsy is used as the next step in the diagnostic process to provide a definitive diagnosis for efficient and proper patient management (Dempsey, 2010). In the usual clinical situation lesions are examined in real-time, multiple views of the same lesion are obtained for evaluation and these findings are combined with an array of prior imaging information and clinical information to allow a better informed diagnostic opinion. A limitation of this study was that the observers were only provided with one image per lesion for evaluation, as well as being blinded to mammographic and clinical information.

In this study, 51 breast lesions were used for evaluation. This number is less than that used in other comparable studies; Cha et al. (2005& 2007) used 75 breast lesions in their spatial compounding study and 91 breast lesions in their tissue harmonic imaging study, and Tseng et al. (2012) used 110 breast lesions in their morphology based CAD study. Whether our study included

sufficient cases to enable statistical significant differences to be revealed between different levels of PI is not certain, an issue discussed by Metz (Metz, 2008). A power calculation demonstrated that the numbers of observers we used (n=12) would allow a difference in ROC of 0.05 to be detected at 79% power.

4.6 Future work

Ultrasound is a dynamic diagnostic procedure, i.e. examination is carried out in real-time. Besides 2-D imaging, other techniques such as Doppler study, mobility and compressibility, are also used to form a diagnostic opinion and freeze frames or static images are largely taken for documentation purposes (Meuwly et al., 2003). The current research compared static images chosen by sonographers and it is acknowledged that in order to comprehensively compare the diagnostic efficacy of PI, multiple real-time dynamic examinations would have been necessary. This method of research would involve repeated scanning of the patient and be extremely demanding of resources. However real-time dynamic breast studies may yield results which vary from those obtained from static images.

One of the challenges in breast ultrasound is to be able to perceive abnormalities of varying size, shape and echotexture despite the presence of numerous normal anatomic interfaces and interactions. The lesion features, along with the operator's experience, are contributing factors for correct detection (Chang,Moon,Cho,Park & Kim, 2011; Drukker,Giger & Mendelson, 2003). Another challenge with breast ultrasound is 'imaginoma', where the combination of altered echotexture and shadowing mislead the operator to perceive the presence of an abnormality that does not exist. In the current study, the lesions were already presented in the images and it was not possible to evaluate if this algorithm could alter lesion detection or alter the detection of the 'imaginoma'. It could be suggested that the impact of PI on lesion detectability, time needed for lesion detection and the effect on diagnostic efficacy could be better assessed by the use of new 3D technology to provide an acquired whole volume data set (continuous video record) of breast images for the observers to evaluate.

In breast imaging, it is important to be able to identify small lesions because if cancerous changes are detected early then treatment is considered to be more effective. Earlier detection also leads to a greater range of treatment options, such as less aggressive adjuvant therapies or surgeries (lumpectomy as opposed to mastectomy) (Meenalosini & Janet, 2012; Smith et al., 2012). However, it is challenging to detect small lesions by ultrasound examination. In one study, the ultrasound detection rate was approximately 53% for malignant lesions less than 7mm and increased to 97% when the mean diameter of the lesion was larger than 11mm (Berg,Blume,Cormack & Mendelson, 2006). Small lesions also make it challenging for characterisation - it was observed that there was lower interobserver agreement for small masses at 7mm or less, which was linked to lower concordance for margin and shape assessment (Abdullah,Mesurolle,El-Khoury & Kao, 2009).

In our study, there were thirteen lesions measuring 7mm or less and ten lesions measuring from 8 to 10mm. A comparison of the observers responses based on lesion size (Appendix 5.4) showed no differences in accuracy of classification. There may not have been enough small lesions present, or enough of the same pathology type, to demonstrate a size-specific impact of PI. In a study by Chang et al., mean diameter, surrounding tissue changes and shape of the lesion were important factors associated with detectability (Chang et al., 2011), therefore future work should consider the effect of PI on small lesions, grouped according to their pathology and background tissue appearances.

4.7 Conclusion

This research investigated the effect of Precision Imaging, a speckle reduction algorithm, on diagnostic efficacy through observer evaluation of solid breast lesions. The data analysis using ROC, sensitivity and specificity did not demonstrate any significant change in diagnostic efficacy with varying PI application amongst expert observers (radiologists and sonographers) in this study. Thus, our results are consistent with other studies by Cha et al. and Tseng et al. (Cha et al., 2005; 2007; Tseng et al., 2012) on speckle

reduction. The main limitation in the study was the provision of a single static image for evaluation which is not a true reflection of clinical practice. The value of the PI algorithm when used by less experienced or trainee clinicians, and the potential of this algorithm to expedite lesion perception, were not evaluated. However, the large number of observers included in this research and rigorous use of methodologies make the results worthy of serious consideration. In addition, the method and protocol used will be of value to clinicians embarking on similar radiologic-type studies. This research serves to complement the study of the PI algorithm on image quality conducted by my colleague and emphasises the importance and difficulties of studies which investigate diagnostic efficacy in the application of advanced technologies in diagnostic imaging.

Chapter 5 Appendices

5.1 Human Research Ethics Committee Documentation

THE UNIVERSITY OF SYDNEY

RESEARCH INTEGRITY
Human Research Ethics Committee
Web: http://sydney.edu.au/ethics/
Email: ro.humanethics@sydney.edu.au

Address for all correspondence:
Level 6, Jane Foss Russell Building - G02
The University of Sydney
NSW 2006 AUSTRALIA

Ref: GD/JM

29th February, 2012

Professor Patrick Brennan
Discipline of Medical Radiation Sciences
The University of Sydney
Email: patrick.brennan@sydney.edu.au

Dear Patrick,

Thank you for your correspondence dated 13 February 2012 addressing comments made to you by the Human Research Ethics Committee (HREC).

On February 29th, 2012 the Chair of the HREC considered this information and approved your protocol entitled **"Whether PRECISION IMAGING (PI) improves image quality and increases confidence in diagnosing breast tumours?".**

Details of the approval are as follows:

Protocol No.:	**14466**
Approval Date:	29 February 2012
First Annual Report Due:	28 February 2013
Authorised Personnel:	Prof. Patrick Brennan Prof. Mary Rickard Dr Peter Kench Ms Louisa Lau Ms Alfiya Safina

Documents Approved:

Document	Version Number	Date
Consent form	1	Submitted 6/1/2012

HREC approval is valid for four (4) years from the approval date stated in this letter and is granted pending the following conditions being met:

Condition/s of Approval

- Continuing compliance with the National Statement on Ethical Conduct in Research Involving Humans.

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CRICOS 00026A

THE UNIVERSITY OF SYDNEY

- Provision of an annual report on this research to the Human Research Ethics Committee from the approval date and at the completion of the study. Failure to submit reports will result in withdrawal of ethics approval for the project.
- All serious and unexpected adverse events should be reported to the HREC within 72 hours.
- All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.
- Any changes to the protocol including changes to research personnel must be approved by the HREC by submitting a Modification Form before the research project can proceed.

Chief Investigator / Supervisor's responsibilities:

1. You must retain copies of all signed Consent Forms (if applicable) and provide these to the HREC on request.
2. It is your responsibility to provide a copy of this letter to any internal/external granting agencies if requested.

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Glen Davis
E

Professor Glen Davis
Deputy Chair
Human Research Ethics Committee

cc. Prof. Mary Rickard mtr2006@bigpond.net.au
Ms. Louisa Lau llau@sydneybreastclinic.com.au
Ms. Alfiya Safina asafina@sydneybreastclinic.com.au

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

5.2 Invitation letter to participate in research

Dear Colleagues

Thank you for giving your time to participate in this research project. Through your responses, I hope to evaluate if *Toshiba Precision Imaging* improves your confidence in deciding whether a lesion is malignant or benign.

How to do the image critique:

There are 4 sets of images in this critique, A-D, representing different levels of precision imaging. For research purposes, I will let each participant know in which order you should review the images e.g. ABCD or BCDA etc.

Step 1 Click the required Q-perform icon (Q-perform A, Q-perform B, etc) on the desk top of the computer.

Step 2 Select “New User” if this is the first time you are starting a Q-perform set; otherwise select “Existing User” if you are returning to the Q-perform set.

Step 3 Enter your initials as your user name.

Step 4 You can do the following to facilitate your viewing:

- Hold the left or right mouse down to pan the image
- Scroll the middle wheel to zoom or minimize the image
- Click on RESET sign on upper right hand corner to reset the image to its original setting

Step 5 Provide your opinion by selecting the appropriate button underneath the image. The image will then automatically proceed to the next one, and you cannot return to the previous image.

Key for the buttons:

1 - the lesion is **definitely benign**

2 - the lesion is **probably benign**

3 - the lesion is **possibly benign**

4 - the lesion is **possibly malignant**

5 - the lesion is **probably malignant**

6 - the lesion is **definitely malignant**

You can always take a break whenever you want to, by clicking the "X" at the top right corner. You can resume the critique at your convenience on the same day or another day.

Step 6 When you have finished the last image in the set, the set of images will automatically close.

Step 7 You can proceed to the next Q-perform set of images. Simply follow the steps 1-6 as above, selecting "New User".

Step 8 Please let me know when you have finished the critique.

I can be contacted on 0425 266 427 or louisasflau@hotmail.com if you require any assistance in this matter.

Once again, thank you for completing the survey.

Yours faithfully

Louisa Lau

5.3 Data entry for DBMMRMC 2.32 BUILD 3 analysis

sample input data

READR1

"P0"	"P1"	"P2"	"P3"	
L	L	L	L	
2	3	2	3	Neg Case 1
2	3	2	2	Neg Case 2
3	3	4	3	Neg Case 3
3	3	2	3	Neg Case 4
6	4	5	4	Neg Case 5
3	5	4	4	Neg Case 6
5	3	4	4	Neg Case 7
4	2	3	4	Neg Case 8
2	3	2	4	Neg Case 9
2	2	1	2	Neg Case 10
5	5	5	6	Neg Case 11
4	3	2	4	Neg Case 12
3	5	5	5	Neg Case 13
2	4	4	4	Neg Case 14
3	4	5	5	Neg Case 15

3	3	3	3	Neg Case 16
5	5	4	4	Neg Case 17
3	2	2	2	Neg Case 18
3	3	3	4	Neg Case 19
3	4	3	4	Neg Case 20
2	2	2	3	Neg Case 21
2	2	2	3	Neg Case 22
3	2	2	3	Neg Case 23
2	3	2	3	Neg Case 24
2	3	2	3	Neg Case 25
3	2	2	3	Neg Case 26
3	3	3	3	Neg Case 27
2	3	3	3	Neg Case 28
2	2	2	3	Neg Case 29
3	3	2	4	Neg Case 30
3	3	4	4	Neg Case 31

*

4	4	5	6	Pos Case 1
2	2	3	3	Pos Case 2
5	5	5	5	Pos Case 3

5	5	5	5	Pos Case 4
6	4	5	5	Pos Case 5
5	6	5	6	Pos Case 6
5	4	4	5	Pos Case 7
4	4	5	3	Pos Case 8
2	2	2	3	Pos Case 9
6	5	4	5	Pos Case 10
4	4	4	3	Pos Case 11
5	4	5	6	Pos Case 12
5	4	5	5	Pos Case 13
3	3	4	4	Pos Case 14
6	5	6	6	Pos Case 15
3	4	4	4	Pos Case 16
4	4	5	5	Pos Case 17
4	4	5	6	Pos Case 18
4	5	4	3	Pos Case 19
3	4	4	4	Pos Case 20

*

READR2

2	3	3	2	Neg Case 1

2	2	1	1	Neg Case 2
2	1	5	2	Neg Case 3
2	2	1	1	Neg Case 4
5	6	5	4	Neg Case 5
3	4	3	3	Neg Case 6
5	4	6	6	Neg Case 7
3	4	2	3	Neg Case 8
3	3	1	3	Neg Case 9
1	2	1	1	Neg Case 10
4	5	6	6	Neg Case 11
2	2	2	2	Neg Case 12
5	6	6	6	Neg Case 13
3	4	5	5	Neg Case 14
4	6	1	4	Neg Case 15
2	2	2	1	Neg Case 16
6	6	6	4	Neg Case 17
2	1	1	1	Neg Case 18
2	1	2	2	Neg Case 19
2	3	3	4	Neg Case 20
2	3	3	3	Neg Case 21

1	2	1	1	Neg Case 22
2	2	1	3	Neg Case 23
2	2	1	1	Neg Case 24
2	1	1	1	Neg Case 25
2	2	2	3	Neg Case 26
2	2	1	3	Neg Case 27
2	1	1	1	Neg Case 28
1	1	1	1	Neg Case 29
2	1	1	1	Neg Case 30
2	4	4	4	Neg Case 31

*

4	6	5	5	Pos Case 1
1	2	1	1	Pos Case 2
5	6	6	6	Pos Case 3
4	5	5	5	Pos Case 4
6	5	6	4	Pos Case 5
6	6	6	6	Pos Case 6
4	5	5	4	Pos Case 7
2	4	2	3	Pos Case 8
3	2	1	2	Pos Case 9

5	5	5	6	Pos Case 10
5	5	5	4	Pos Case 11
5	6	6	6	Pos Case 12
5	5	6	6	Pos Case 13
2	5	4	5	Pos Case 14
5	6	6	6	Pos Case 15
3	4	4	3	Pos Case 16
5	6	6	5	Pos Case 17
5	5	1	5	Pos Case 18
4	5	5	4	Pos Case 19
4	4	5	4	Pos Case 20

*

READR3

5	3	2	2	Neg Case 1
4	3	2	2	Neg Case 2
3	3	5	3	Neg Case 3
4	2	2	2	Neg Case 4
6	4	4	3	Neg Case 5
3	3	2	3	Neg Case 6
6	5	6	5	Neg Case 7

3	3	1	1	Neg Case 8
4	3	3	2	Neg Case 9
1	1	1	1	Neg Case 10
6	5	5	5	Neg Case 11
3	4	2	3	Neg Case 12
5	6	5	4	Neg Case 13
4	5	4	3	Neg Case 14
4	5	3	4	Neg Case 15
4	4	4	2	Neg Case 16
6	6	6	5	Neg Case 17
1	1	1	1	Neg Case 18
3	3	3	2	Neg Case 19
2	4	4	2	Neg Case 20
2	3	2	2	Neg Case 21
2	2	1	2	Neg Case 22
2	1	2	1	Neg Case 23
1	2	1	1	Neg Case 24
4	2	1	2	Neg Case 25
1	2	2	2	Neg Case 26
2	2	1	2	Neg Case 27

2	1	1	3	Neg Case 28
2	2	1	2	Neg Case 29
4	4	2	4	Neg Case 30
1	2	1	2	Neg Case 31

*

6	5	6	4	Pos Case 1
2	2	2	1	Pos Case 2
6	6	6	5	Pos Case 3
4	4	4	3	Pos Case 4
6	5	6	5	Pos Case 5
6	6	6	5	Pos Case 6
6	5	6	4	Pos Case 7
3	3	2	3	Pos Case 8
2	5	2	2	Pos Case 9
6	5	5	5	Pos Case 10
5	4	6	4	Pos Case 11
6	6	6	6	Pos Case 12
6	6	5	6	Pos Case 13
5	3	4	2	Pos Case 14
6	6	5	5	Pos Case 15

3	4	3	3	Pos Case 16
6	5	5	5	Pos Case 17
5	5	6	5	Pos Case 18
5	5	6	4	Pos Case 19
6	5	4	4	Pos Case 20

*

READR4

3	3	2	2	Neg Case 1
2	4	3	3	Neg Case 2
3	3	5	4	Neg Case 3
2	4	2	2	Neg Case 4
5	5	5	4	Neg Case 5
3	5	5	6	Neg Case 6
5	5	6	6	Neg Case 7
4	4	3	4	Neg Case 8
4	4	2	3	Neg Case 9
2	2	2	2	Neg Case 10
6	6	6	6	Neg Case 11
3	2	2	2	Neg Case 12
5	6	6	6	Neg Case 13

3	4	5	4	Neg Case 14
4	4	4	5	Neg Case 15
4	3	2	2	Neg Case 16
5	6	6	6	Neg Case 17
2	2	2	2	Neg Case 18
4	2	3	4	Neg Case 19
3	2	4	4	Neg Case 20
2	3	3	3	Neg Case 21
2	2	2	1	Neg Case 22
2	2	2	1	Neg Case 23
2	3	2	2	Neg Case 24
2	3	3	2	Neg Case 25
2	3	3	3	Neg Case 26
2	3	2	3	Neg Case 27
3	3	2	3	Neg Case 28
1	3	2	1	Neg Case 29
2	2	3	2	Neg Case 30
2	3	4	4	Neg Case 31

*

6	6	6	5	Pos Case 1

2	3	2	4	Pos Case 2
5	5	6	5	Pos Case 3
5	6	6	6	Pos Case 4
5	5	5	5	Pos Case 5
4	4	3	4	Pos Case 6
4	6	6	6	Pos Case 7
4	4	5	4	Pos Case 8
3	2	2	2	Pos Case 9
4	5	5	5	Pos Case 10
4	6	6	5	Pos Case 11
6	6	6	6	Pos Case 12
6	6	6	6	Pos Case 13
2	3	4	5	Pos Case 14
6	6	6	6	Pos Case 15
3	4	5	3	Pos Case 16
5	5	6	6	Pos Case 17
4	6	6	5	Pos Case 18
5	5	6	5	Pos Case 19
3	4	4	4	Pos Case 20

*

READR5

3	3	3	3	Neg Case 1
3	1	1	1	Neg Case 2
3	2	3	3	Neg Case 3
3	3	3	3	Neg Case 4
5	5	4	4	Neg Case 5
4	4	4	3	Neg Case 6
5	4	5	5	Neg Case 7
4	3	3	3	Neg Case 8
3	3	2	3	Neg Case 9
3	2	2	3	Neg Case 10
4	4	5	5	Neg Case 11
3	3	3	3	Neg Case 12
5	5	5	4	Neg Case 13
4	3	4	3	Neg Case 14
4	5	4	4	Neg Case 15
2	3	3	2	Neg Case 16
5	5	5	5	Neg Case 17
4	3	4	4	Neg Case 18
3	3	3	3	Neg Case 19

3	3	3	3	Neg Case 20
3	3	3	3	Neg Case 21
2	3	2	3	Neg Case 22
2	1	2	2	Neg Case 23
2	3	3	3	Neg Case 24
4	3	3	2	Neg Case 25
3	2	3	3	Neg Case 26
3	1	2	3	Neg Case 27
3	2	3	3	Neg Case 28
2	2	2	2	Neg Case 29
4	2	3	3	Neg Case 30
2	2	3	3	Neg Case 31

*

5	6	5	5	Pos Case 1
3	3	3	3	Pos Case 2
5	4	5	5	Pos Case 3
5	5	5	5	Pos Case 4
5	4	5	4	Pos Case 5
5	5	5	5	Pos Case 6
4	4	5	5	Pos Case 7

4	2	4	4	Pos Case 8
4	3	4	4	Pos Case 9
5	4	5	5	Pos Case 10
5	5	4	4	Pos Case 11
6	5	6	4	Pos Case 12
5	5	5	5	Pos Case 13
2	2	4	4	Pos Case 14
5	5	5	5	Pos Case 15
3	4	5	4	Pos Case 16
5	4	4	5	Pos Case 17
4	3	4	4	Pos Case 18
4	5	5	5	Pos Case 19
4	4	4	4	Pos Case 20

*

READR6

2	2	2	3	Neg Case 1
2	3	2	4	Neg Case 2
2	2	3	3	Neg Case 3
2	2	2	3	Neg Case 4
5	3	2	2	Neg Case 5

4	4	3	3	Neg Case 6
5	5	4	5	Neg Case 7
3	2	2	4	Neg Case 8
3	4	2	4	Neg Case 9
2	1	2	1	Neg Case 10
2	4	5	5	Neg Case 11
2	3	2	2	Neg Case 12
6	6	6	6	Neg Case 13
3	3	3	3	Neg Case 14
4	5	5	3	Neg Case 15
2	1	2	2	Neg Case 16
5	5	5	6	Neg Case 17
1	2	1	2	Neg Case 18
2	1	1	2	Neg Case 19
2	2	3	2	Neg Case 20
3	3	2	3	Neg Case 21
3	1	2	2	Neg Case 22
2	2	2	3	Neg Case 23
2	2	2	2	Neg Case 24
1	1	1	1	Neg Case 25

2	2	2	3	Neg Case 26
2	2	2	3	Neg Case 27
2	1	2	2	Neg Case 28
2	2	2	2	Neg Case 29
3	2	2	3	Neg Case 30
2	1	2	3	Neg Case 31

*

5	4	4	6	Pos Case 1
1	3	2	3	Pos Case 2
5	4	5	5	Pos Case 3
5	6	5	5	Pos Case 4
6	6	6	6	Pos Case 5
5	4	4	4	Pos Case 6
6	6	6	6	Pos Case 7
2	1	3	2	Pos Case 8
2	3	2	2	Pos Case 9
6	5	5	5	Pos Case 10
5	5	5	6	Pos Case 11
6	6	6	6	Pos Case 12
6	6	6	6	Pos Case 13

3	1	3	3	Pos Case 14
6	6	6	6	Pos Case 15
4	3	3	4	Pos Case 16
5	4	4	5	Pos Case 17
3	5	3	2	Pos Case 18
4	3	5	5	Pos Case 19
6	5	5	3	Pos Case 20

*

READR7

2	2	2	2	Neg Case 1
2	2	2	2	Neg Case 2
3	3	3	2	Neg Case 3
2	2	2	2	Neg Case 4
2	3	2	2	Neg Case 5
2	4	2	3	Neg Case 6
3	3	4	4	Neg Case 7
2	2	2	2	Neg Case 8
2	2	2	2	Neg Case 9
2	2	2	2	Neg Case 10
4	5	4	4	Neg Case 11

2	2	2	2	Neg Case 12
5	4	5	4	Neg Case 13
3	2	3	2	Neg Case 14
4	2	2	4	Neg Case 15
2	2	3	2	Neg Case 16
5	5	5	5	Neg Case 17
2	2	2	2	Neg Case 18
2	2	2	2	Neg Case 19
2	2	2	2	Neg Case 20
2	3	2	2	Neg Case 21
2	1	2	2	Neg Case 22
1	2	2	2	Neg Case 23
2	2	2	2	Neg Case 24
2	4	2	2	Neg Case 25
2	3	2	2	Neg Case 26
2	2	2	2	Neg Case 27
2	2	2	2	Neg Case 28
2	1	3	2	Neg Case 29
2	2	2	2	Neg Case 30
2	2	2	2	Neg Case 31

*

3	4	4	5	Pos Case 1
2	3	2	2	Pos Case 2
5	5	5	5	Pos Case 3
4	5	4	4	Pos Case 4
4	3	4	4	Pos Case 5
5	5	5	5	Pos Case 6
5	4	4	4	Pos Case 7
3	2	2	4	Pos Case 8
2	2	2	2	Pos Case 9
5	5	4	5	Pos Case 10
5	4	4	4	Pos Case 11
5	6	6	5	Pos Case 12
3	3	4	3	Pos Case 13
2	2	3	2	Pos Case 14
5	6	5	5	Pos Case 15
2	2	3	3	Pos Case 16
5	5	4	5	Pos Case 17
4	3	5	4	Pos Case 18
4	4	4	4	Pos Case 19

2	3	2	3	Pos Case 20

*

READR8

3	3	3	3	Neg Case 1
3	3	2	2	Neg Case 2
3	3	3	4	Neg Case 3
3	3	3	3	Neg Case 4
4	3	3	3	Neg Case 5
3	4	5	3	Neg Case 6
4	5	5	5	Neg Case 7
4	3	4	3	Neg Case 8
3	3	3	3	Neg Case 9
3	3	3	3	Neg Case 10
4	4	4	4	Neg Case 11
3	3	3	3	Neg Case 12
4	6	5	5	Neg Case 13
4	3	4	4	Neg Case 14
4	5	3	4	Neg Case 15
3	3	3	3	Neg Case 16
5	6	5	6	Neg Case 17

4	4	4	4	Neg Case 18
3	3	2	2	Neg Case 19
3	3	3	3	Neg Case 20
3	3	3	3	Neg Case 21
3	3	3	3	Neg Case 22
3	3	3	3	Neg Case 23
3	3	3	3	Neg Case 24
3	3	3	3	Neg Case 25
3	3	4	3	Neg Case 26
3	2	3	3	Neg Case 27
3	3	3	3	Neg Case 28
3	4	3	4	Neg Case 29
3	3	3	3	Neg Case 30
3	4	4	4	Neg Case 31

*

5	5	5	5	Pos Case 1
3	3	4	3	Pos Case 2
5	6	5	5	Pos Case 3
5	5	6	5	Pos Case 4
4	5	5	5	Pos Case 5

5	6	6	6	Pos Case 6
4	5	6	5	Pos Case 7
4	3	3	3	Pos Case 8
3	3	3	2	Pos Case 9
4	5	5	5	Pos Case 10
5	5	6	6	Pos Case 11
6	6	6	6	Pos Case 12
5	6	5	5	Pos Case 13
4	5	5	5	Pos Case 14
6	6	6	5	Pos Case 15
3	5	4	3	Pos Case 16
5	5	5	5	Pos Case 17
4	4	4	4	Pos Case 18
5	4	6	6	Pos Case 19
3	3	5	3	Pos Case 20

*

READR9

3	4	4	3	Neg Case 1
4	3	4	3	Neg Case 2
3	2	6	4	Neg Case 3

3	4	5	4	Neg Case 4
5	4	5	3	Neg Case 5
3	4	4	5	Neg Case 6
6	6	6	6	Neg Case 7
3	5	3	5	Neg Case 8
1	3	3	3	Neg Case 9
1	2	2	1	Neg Case 10
5	5	5	6	Neg Case 11
3	3	4	4	Neg Case 12
6	6	6	6	Neg Case 13
4	5	5	5	Neg Case 14
4	6	6	5	Neg Case 15
2	3	4	4	Neg Case 16
6	6	6	6	Neg Case 17
3	2	2	2	Neg Case 18
2	3	3	3	Neg Case 19
3	4	3	4	Neg Case 20
4	4	4	3	Neg Case 21
1	4	3	4	Neg Case 22
2	2	2	3	Neg Case 23

1	2	2	2	Neg Case 24
2	3	2	2	Neg Case 25
4	4	3	2	Neg Case 26
4	3	2	3	Neg Case 27
3	3	4	3	Neg Case 28
1	2	2	1	Neg Case 29
3	2	1	4	Neg Case 30
4	2	3	3	Neg Case 31

*

6	6	6	6	Pos Case 1
3	4	3	3	Pos Case 2
6	6	6	6	Pos Case 3
6	6	6	6	Pos Case 4
5	6	6	6	Pos Case 5
6	6	6	6	Pos Case 6
5	6	6	6	Pos Case 7
4	5	6	6	Pos Case 8
2	3	3	3	Pos Case 9
5	6	6	6	Pos Case 10
5	6	6	6	Pos Case 11

6	6	6	6	Pos Case 12
6	6	6	6	Pos Case 13
4	3	5	4	Pos Case 14
6	6	6	6	Pos Case 15
4	5	5	5	Pos Case 16
5	6	6	6	Pos Case 17
5	6	6	6	Pos Case 18
5	6	6	6	Pos Case 19
5	6	5	5	Pos Case 20

*

READR10

1	1	1	2	Neg Case 1
1	3	2	2	Neg Case 2
1	1	1	1	Neg Case 3
2	2	2	2	Neg Case 4
4	2	4	3	Neg Case 5
2	2	2	2	Neg Case 6
2	4	3	5	Neg Case 7
2	2	2	2	Neg Case 8
2	2	2	2	Neg Case 9

1	1	1	1	Neg Case 10
3	3	4	3	Neg Case 11
1	1	1	2	Neg Case 12
6	5	6	5	Neg Case 13
2	2	3	3	Neg Case 14
4	2	4	4	Neg Case 15
2	2	2	2	Neg Case 16
6	4	3	5	Neg Case 17
1	2	1	2	Neg Case 18
2	2	1	1	Neg Case 19
1	2	3	2	Neg Case 20
1	2	2	1	Neg Case 21
1	1	1	1	Neg Case 22
1	2	1	2	Neg Case 23
1	1	2	1	Neg Case 24
1	1	1	1	Neg Case 25
1	2	2	2	Neg Case 26
1	1	1	2	Neg Case 27
1	1	1	2	Neg Case 28
1	1	1	1	Neg Case 29

2	1	1	2	Neg Case 30
1	3	4	4	Neg Case 31

*

6	6	6	6	Pos Case 1
2	1	1	1	Pos Case 2
4	4	5	5	Pos Case 3
3	3	3	3	Pos Case 4
4	4	4	5	Pos Case 5
4	5	4	6	Pos Case 6
5	4	4	5	Pos Case 7
5	4	4	4	Pos Case 8
2	1	1	2	Pos Case 9
6	5	3	6	Pos Case 10
5	5	4	6	Pos Case 11
5	4	6	6	Pos Case 12
6	6	5	6	Pos Case 13
2	3	5	4	Pos Case 14
6	6	6	6	Pos Case 15
3	2	2	2	Pos Case 16
2	4	4	4	Pos Case 17

4	3	4	4	Pos Case 18
4	4	6	6	Pos Case 19
2	2	2	3	Pos Case 20

*

READR11

3	1	1	3	Neg Case 1
3	2	2	3	Neg Case 2
3	2	2	3	Neg Case 3
2	1	1	3	Neg Case 4
4	1	1	2	Neg Case 5
3	4	2	3	Neg Case 6
5	5	5	4	Neg Case 7
3	2	2	4	Neg Case 8
3	2	2	3	Neg Case 9
3	1	2	3	Neg Case 10
3	2	4	3	Neg Case 11
3	2	2	3	Neg Case 12
5	5	5	4	Neg Case 13
3	4	2	3	Neg Case 14
2	6	2	3	Neg Case 15

2	2	2	2	Neg Case 16
5	6	4	3	Neg Case 17
3	1	2	3	Neg Case 18
3	2	2	3	Neg Case 19
3	4	2	3	Neg Case 20
3	2	2	3	Neg Case 21
3	2	2	3	Neg Case 22
3	3	2	3	Neg Case 23
3	1	2	3	Neg Case 24
3	2	2	2	Neg Case 25
3	2	2	3	Neg Case 26
4	2	2	3	Neg Case 27
3	2	1	3	Neg Case 28
3	2	2	3	Neg Case 29
3	2	2	3	Neg Case 30
3	3	3	3	Neg Case 31

*

4	5	4	5	Pos Case 1
3	2	2	2	Pos Case 2
3	5	5	5	Pos Case 3

4	6	6	4	Pos Case 4
4	5	4	3	Pos Case 5
3	2	5	5	Pos Case 6
5	5	4	4	Pos Case 7
3	3	2	4	Pos Case 8
3	2	1	2	Pos Case 9
5	5	5	4	Pos Case 10
4	4	5	5	Pos Case 11
6	6	6	5	Pos Case 12
5	5	5	4	Pos Case 13
3	2	4	4	Pos Case 14
5	6	6	5	Pos Case 15
3	1	2	2	Pos Case 16
4	5	6	5	Pos Case 17
3	4	2	2	Pos Case 18
4	6	6	4	Pos Case 19
3	5	4	3	Pos Case 20

*

READR12

3	4	2	3	Neg Case 1

4	3	2	4	Neg Case 2
3	3	4	4	Neg Case 3
3	3	2	3	Neg Case 4
4	4	4	4	Neg Case 5
3	4	4	4	Neg Case 6
6	6	5	5	Neg Case 7
3	4	4	4	Neg Case 8
2	3	2	2	Neg Case 9
2	2	1	1	Neg Case 10
4	4	5	4	Neg Case 11
3	2	2	2	Neg Case 12
6	6	6	5	Neg Case 13
3	3	4	4	Neg Case 14
5	5	4	5	Neg Case 15
2	2	3	2	Neg Case 16
6	6	6	5	Neg Case 17
2	2	2	2	Neg Case 18
4	2	2	3	Neg Case 19
3	3	3	4	Neg Case 20
3	3	3	3	Neg Case 21

2	2	2	2	Neg Case 22
2	2	2	3	Neg Case 23
2	3	2	2	Neg Case 24
2	2	6	2	Neg Case 25
3	2	3	3	Neg Case 26
2	2	2	3	Neg Case 27
3	2	2	2	Neg Case 28
2	1	1	2	Neg Case 29
3	3	3	3	Neg Case 30
2	3	3	3	Neg Case 31

*

5	5	5	5	Pos Case 1
2	2	2	2	Pos Case 2
6	6	6	6	Pos Case 3
5	5	6	5	Pos Case 4
4	5	4	5	Pos Case 5
6	6	2	6	Pos Case 6
5	5	5	5	Pos Case 7
4	4	1	4	Pos Case 8
2	2	3	2	Pos Case 9

5	6	5	6	Pos Case 10
6	5	5	5	Pos Case 11
6	6	6	6	Pos Case 12
5	5	4	5	Pos Case 13
4	4	4	5	Pos Case 14
6	6	5	6	Pos Case 15
3	4	1	3	Pos Case 16
5	6	6	6	Pos Case 17
5	5	2	3	Pos Case 18
5	5	4	5	Pos Case 19
4	5	5	5	Pos Case 20

*

READR1 - observer 1, READR2 - observer 2 etc
"P0" - L0
"P1" - L1
"P2" - L2
"P3" - L3
Neg Case - Negative case, benign lesion
Pos Case - Positive case, malignant lesion

Observers response from L0-L3 based on lesion size

US Code	Lesion size mm	Cytology	Ob 1 L0-L3	Ob2	Ob 3	Ob 4	Ob 5	Ob 6	Ob 7	Ob 8	Ob 9	Ob 10	Ob 11	Ob12
4	9	IDC	5445	4554	6665	4666	4455	6666	5444	4565	5666	5445	5544	5555
4	8	IDC	2223	3212	2522	3222	4344	2322	2222	3332	2333	2112	3212	2232
4	7	IDC	6545	5556	6555	4555	5455	6555	5545	4555	5666	6536	5554	5656
3	9	ILC	3444	3443	3433	3453	3454	4334	2233	3543	4555	3222	3122	3413
4	10	IDC	4455	5665	6555	5566	5445	5445	5545	5555	5666	2444	4565	5666
4	7	IDC	4456	5515	5565	4665	4344	3532	4354	4444	5666	4344	3422	5523
2	9	HWA	2323	2332	5322	2322	3333	2223	2222	3333	3443	1112	3113	3423
3	7	HDT	3343	2152	3353	3354	3233	2233	3332	3334	3264	1111	3223	3344
2	7	FCC	3323	2211	4222	2422	3333	2223	2222	3333	3454	2222	2113	3323
3	6	B9	6454	5654	6443	5554	5544	5322	2322	4333	5453	4243	4112	4444
4	10	FN	5344	5466	6565	5566	5455	5545	3344	4555	6666	2435	5554	6655
2	7	FN	4234	3423	3311	4434	4333	3224	2222	4343	3535	2222	3224	3444
2	5	IP	2324	3313	4332	4423	3323	3424	2222	3333	1333	2222	3223	2322
3	7	FI	5556	4566	6555	6666	4455	2455	4544	4444	5556	3343	3243	4454
2	7	IP	4324	2222	3423	3222	3333	2322	2222	3333	3344	1112	3223	3222
3	10	SLL	3455	4614	4534	4445	4544	4553	4224	4534	4665	4244	2623	5545
3	5	OC	3333	2221	4442	4322	2332	2122	2232	3333	2344	2222	2222	2232
2	10	ST	2223	2333	2322	2333	3333	3323	2322	3333	4443	1221	3223	3333
2	5	ST	2223	1211	2212	2221	2323	3122	2122	3333	1434	1111	3223	2222
2	9	FA	3223	2223	1222	2333	3233	2223	2322	3343	4432	1222	3223	3233
2	9	FCC	2333	2111	2113	3323	3233	2122	2222	3333	3343	1112	3213	3222
2	6	B9	2223	1111	2212	1321	2222	2222	2132	3434	1221	1111	3223	2112
2	6	B9	3324	2111	4424	2232	4233	3223	2222	3333	3214	2112	3223	3333

B9, benign; FA, fibroadenoma; FCC, fibrocystic changes; FI, fibrosis; FN, fat necrosis; HDT, hyperplastic ductal tissue; HWA, hyperplasia without atypia; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IP, intraduct papilloma; Ob, observer; OC, oil cyst; SLL, sclerosing lymphocytic lobulitis; ST, stable lesion

5.5 Joint paper submitted to British Journal of Radiology for publication

BLIND TITLE PAGE

Title:

Precision Imaging – Its impact on image quality and diagnostic confidence in breast ultrasound examinations

Short title:

Does PI affect image quality and diagnostic efficacy in breast ultrasound?

Abstract

OBJECTIVES:

To determine the effect of a noise reducing innovation, Precision Imaging, on image quality and diagnostic efficacy in breast ultrasound.

MATERIALS AND METHODS:

The study, which assessed 4 levels of Precision Imaging from zero to three, consisted of two parts: image quality assessment and diagnostic efficacy evaluation. For the first part, 247 sets of ultrasound images displayed at each Precision Imaging level were evaluated by six experienced breast imaging observers, by rating image quality using visual grading analysis on a 1-4 scale. For the diagnostic efficacy part, 51 breast lesions were displayed at each Precision Imaging level and scored 1 to 6 to generate a receiver operating characteristic (ROC) curve. These images were evaluated by six radiologists and six sonographers dedicated to breast imaging. Analyses were performed using non-parametric Friedman and Wilcoxon signed-rank tests as well as a multi-reader multi-case methodology.

RESULTS :

Statistically higher scores of image quality were observed with increased levels of Precision Imaging compared with the zero setting ($P < 0.001$). The ROC analysis did not demonstrate any significant change in diagnostic efficacy with mean scores for all observers being 0.79, 0.80, 0.81 and 0.81 for settings zero, one, two and three respectively.

CONCLUSION :

This study suggested a perceived improvement in image quality with increasing levels of Precision Imaging however no changes in diagnostic efficacy were noted. The importance of looking at the impact of new imaging technologies in a multifaceted way is emphasised.

ADVANCES IN KNOWLEDGE :

To our knowledge, this is the first paper investigating the impact of the Precision Imaging algorithm on ultrasound image quality and breast lesion characterisation.

Main text

INTRODUCTION

Ultrasound is a highly useful but operator-dependent imaging modality for breast disease diagnosis. The variation in composition of glandular and other tissues, in addition to the subtlety of alterations in echotexture or architectural change which occur due to pathological processes, can make detection and interpretation of breast lesions difficult. Accurate diagnosis of malignancies requires a process of competent visual search, recognition of potential abnormalities, and accurate cognitive assessment (Kundel & Nodine, 1983).

Good image quality is reported to reduce operator dependence and improve diagnostic confidence (Birnholz, 2013; Milkowski et al., 2003). There have been many major improvements in ultrasound image quality since its initial clinical use in the 1970s, thanks to advancements in electronic and computational capabilities, as well as significant developments in transducer design: lateral resolution has been enhanced through the use of a higher centre frequency and an increased number of transducer elements; higher axial resolution has been achieved by increased scanner bandwidth. These improvements have led to more effective pre- and post- processing of ultrasound signals and images with higher signal to noise ratios (Contreras Ortiz et al., 2012).

Optimal image quality is highly subjective, but, in general, operators and those who interpret images prefer low noise levels (Yoon,Kim,Yoo,Song & Chang, 2013). There are a number of factors that affect noise, a major one of these being sub-resolution scatter, which causes coherent interference of backscattered ultrasound signals. This results in a type of granular noise known as speckle, which degrades spatial and contrast resolution and reduces the detection of small, low-contrast targets of critical importance in breast imaging. One study looking at speckle reduction algorithms using a two-dimensional textural homogeneity histogram and directional averaging filters, demonstrated improved diagnostic accuracy, sensitivity and specificity

by approximately 15%, 6% and 9% respectively (Su et al., 2010). However, other studies focusing on tissue harmonics and spatial compounding methods to reduce speckle, have demonstrated that even though there is a quantifiable improvement in image quality, there was no measurable difference in diagnostic performance (Cha et al., 2005; 2007). The current picture regarding the efficacy of speckle reduction technology remains unclear. The current work investigates a speckle reduction algorithm, Precision Imaging (PI). According to the manufacturer (Toshiba Medical Systems Corporation, Tochigi-ken, Japan), this algorithm can differentiate between random noise inputs and signals critical to patient information. It modifies the data to construct images that are less noisy and which demonstrate sharpened contours or boundaries at important interfaces (Piccoli & Forsberg, 2011). The technology can be applied in conjunction with other ultrasound techniques, such as spatial and frequency image compounding, tissue harmonic imaging and colour Doppler imaging, without affecting frame rate or increasing image delay. A study focussed on focal liver lesions concluded that PI software produced images with better lesion conspicuity, sharper margins and overall improved image quality (Yazgan et al., 2013). However the efficacy of the PI algorithm in breast imaging is unknown.

The aim of this work was to explore the impact of PI on breast image quality and lesion characterisation using expert observers. To this end we used two analytic methods: visual grading analysis (VGA) to investigate image quality appearances of normal breast tissue and benign lesions; receiver operating characteristic (ROC) analysis, to determine observers' ability to discriminate between malignant and benign conditions.

MATERIALS AND METHODS

Patient and case selection

Patients aged from 20 to 84 years examined at the Sydney Breast Clinic between October 2010 and June 2011 were included in the study. The Human Research Ethics Committee of Sydney University approved (protocol number 14466) the study and patients provided consent.

Cases were selected based on their clinical grading using the Royal Australian and New Zealand College of Radiologists (RANZCR) 5-point scoring system(National Breast Cancer Centre, 2007): 1 normal; 2 definitely benign; 3 indeterminate/equivocal; 4 suspicious of malignancy; 5 definitely malignant. According to the clinic's regular practice, the nature of all lesions that were given a score of 3, 4 or 5 was determined by fine needle aspiration (FNA) and/or core biopsy pathology. Lesions with a score of 2, definitively benign, were a mix of cysts and solid lesions. Some benign lesions with appearances of solid lesions were biopsied if they were the patient's presenting symptom and the rest were shown to be stable over time.

Two sets of cases were chosen, one for each of the two parts of the study (study 1: VGA; study 2: ROC). For study 1, two hundred and forty-seven cases (scored 1 or 2) were chosen, of which ninety two cases showed normal breast parenchyma, one hundred and forty cases contained benign fluid-filled lesions and a further fifteen demonstrated benign solid lesions. For study 2, fifty one cases were selected: 4 and 16 were lesions given scores of 3 and 4 respectively in the clinic and later proven to be malignant; 20, 10 and 1 were lesions originally scored 2, 3 and 4 and later proven to be benign. Details on the lesion type and size are given in Table 1.

Table 1. Type of Lesion Chosen for Study 2 – ROC analysis

Lesions	Types	Number of cases	Size range (mm)
Malignant	invasive ductal carcinoma	17	7-28
	invasive lobular carcinoma	1	9
	ductal carcinoma in situ	2	12
Benign	fat necrosis	3	7-19
	fibroadenoma	8	9-17
	fibrocystic changes	7	7-21
	hyperplasia without atypia	2	7&9
	intraduct papilloma	2	5&7
	fibrosis	1	7
	phyllodes	1	24
	sclerosing lymphocytic lobulitis	1	10
	stable lesions for $\geq$2 years without FNA	6	5-13

Image acquisition and processing

The commercial ultrasound scanner Toshiba AplioMX, Model SSA-780A, (Toshiba Medical Systems, JAPAN) with compact linear transducers 15-7MHz (PLT-1204BT) and 12-5MHz (PLT-805AT) were used for image acquisition, with the choice of transducer depending on the size and density of the breast. The breast was first scanned using the standard departmental protocol, which included optimising each of the following: time gain compensation (TGC), centre frequency of transmitting ultrasound, and depth of image. Tissue harmonic imaging (THI) was applied to all images.

Once the standard imaging was completed, a single projection image that was considered to best represent the lesion or normal breast parenchyma was captured four times, once as a baseline with no additional algorithm applied (L0), then with each of three PI levels - L1, L2 and L3, with the higher number signifying greater speckle reduction. All other pre- or post-processing settings remained the same and the collected images were cropped so that patients' identity and all technical factors including the PI level were removed.

Observer studies

Study 1 - Visual Grading Analysis (VGA)

For the VGA analysis the four images (L0, L1, L2 & L3) for each case were displayed simultaneously as shown in figures 1 and 2 using ViewDex (Sahlgrenska University Hospital, Gőteborg, Sweden). The allocation of images with different PI levels to specific quadrants was randomized in each case. The images were reviewed by one radiologist and five sonographers, all with at least five years experience in breast imaging. All observers were asked to rank each of the four images within each case from 1 to 4 in order of image quality, with a score of 1 indicating the highest quality.

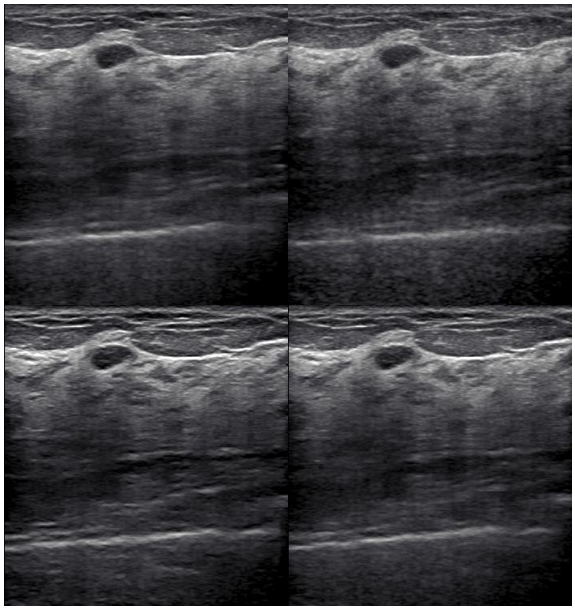

Figure 1. An example of a typical image showing a fluid filled lesion as presented to the observers. In this case the order was: Top left - L1, top right - L0, lower left - L3 and lower right - L2.

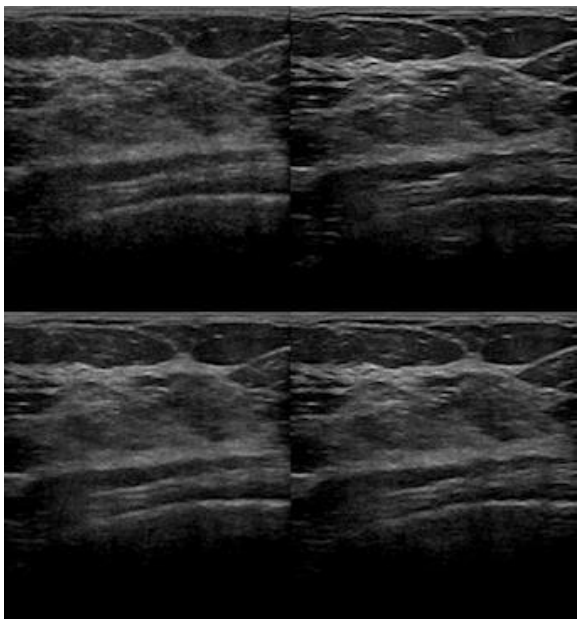

Figure 2. An example of a typical image showing a normal breast parenchyma as presented to the observers. In this case: Top left - L0, top right - L3, lower left - L1 and lower right - L2.

Study 2 - Receiver Operating Characteristic (ROC) analysis

For the ROC analysis, four sets of images were created, each set consisted of all 51 lesions with the same level of applied PI, and images were randomly arranged within each set using Q-Perform software (Ziltron, Limerick, Ireland). Six radiologists and six sonographers read all images with the order in which image sets were presented being different for each observer. Each lesion was scored using a 1-6 scale: 1 - definitely benign; 2 - probably benign; 3 - possibly benign; 4 - possibly malignant; 5 - probably malignant; 6 - definitely malignant. The observers were blinded to all clinical and imaging history.

For both VGA and ROC analyses, there was no time limit on scoring, all images were displayed at full native resolution, and zooming was available.

Statistical Analysis

Non-parametric Friedman test was used for the overall VGA analyses with the Wilcoxon tests being employed for paired comparisons between L0 and each of the other three PI levels.

For the ROC analysis, scores 1-3 were defined as negative and 4-6 were defined as positive. ROC analysis used the Dorfman, Berbaum, Metz multi-reader multi-case (DBMMRMC 2.32 Build 3) approach, and again paired comparisons between L0 and each of the other three pairings were performed. A Mann-Whitney U-test was also used to determine whether there were statistically significant differences for ROC values between the observer groups (radiologists and sonographers) and since no statistically significant inter-group differences were found, observers were (for part of the analysis) then combined as a single group. A Wilcoxon signed-rank test was also used to determine whether there were statistically significant differences in sensitivity or specificity between any of the PI pairings, where sensitivity was the ratio of true positive (TP) over the combined value of TP and false negative (FN), and specificity was the ratio of true negative (TN) over the combined value of TN and false positive (FP).

RESULTS

Study 1 - VGA analysis

Observer VGA scores at specific PI values for all images grouped together, along with Friedman test ranking are shown in table 2. Statistically significant differences can be observed for all participants between PI levels. The paired testing demonstrated significant findings for a number of observers for each pairing with most significant outcomes being noted for the L0 V L3 comparison (Table 3). All significant findings at this specific comparison demonstrated lower scores (increased quality) at the higher compared with lower level of PI.

When images were broken into normal and benign groups, significant findings were demonstrated for both groups of images for observers 2-6 (including the radiologist observer). Observer 1 demonstrated a difference for only benign images (Table 4). The paired testing again showed a number of significant differences with most of these occurring at the L0 V L3 pairing (Table 5). Again lower scores (higher quality) were generally shown at the higher rather than lower level of PI.

Table 2. VGA assessment of image quality for all images grouped together. Note that the lower score implies a higher level of image quality. Asterisks highlight significant findings.

	L0	L1	L2	L3	χ^2	p
Observer 1	2.52	2.68	2.34	2.46	8.443	0.04*
Observer 2	2.8	2.36	2.6	2.23	28.56	<0.001*
Observer 3	2.64	2.7	2.38	2.28	18.543	<0.001*
Observer 4	2.54	2.87	2.34	2.24	34.789	<0.001*
Observer 5	2.73	2.72	2.42	2.12	37.366	<0.001*
Observer 6	2.81	2.65	2.52	2.02	53.049	<0.001*
Median	2.69	2.69	2.40	2.24		

Table 3. Wilcoxon signed-rank test results for all images grouped together. Asterisks highlight significant findings.

	L1-L0		L2-L0		L3-L0	
	Z	P	Z	p	Z	p
Observer 1	-1.70	0.09	-1.30	0.19	-0.82	0.41
Observer 2	-4.43	<0.001*	-1.46	0.15	-4.63	<0.001*
Observer 3	-0.68	0.50	-1.89	0.06	-3.28	0.01*
Observer 4	-3.44	0.001*	-1.59	0.11	-2.87	0.004*
Observer 5	-0.30	0.77	-2.40	0.02*	-5.75	<0.001*
Observer 6	-0.94	0.35	-2.54	0.01*	-6.15	<0.001*

Table 4. VGA assessment of image quality for normal and benign images considered separately. Note that the lower score implies a higher level of image quality. Asterisks highlight significant findings.

		L0	**L1**	**L2**	**L3**	**χ^2**	**p**
Observer 1	Normal	2.59	2.63	2.40	2.38	4.47	0.21
	Lesion	2.54	2.74	2.28	2.44	10.27	0.02*
Observer 2	Normal	2.77	2.55	2.53	2.15	18.81	<0.001*
	Lesion	2.81	2.32	2.57	2.31	15.93	0.001*
Observer 3	Normal	2.63	2.79	2.39	2.19	17.91	<0.001*
	Lesion	2.70	2.62	2.36	2.33	9.51	0.02*
Observer 4	Normal	2.54	2.88	2.30	2.28	21.43	<0.001*
	Lesion	2.63	2.81	2.37	2.19	21.25	<0.001*
Observer 5	Normal	2.71	2.78	2.45	2.05	30.19	<0.001*
	Lesion	2.76	2.66	2.35	2.22	17.91	<0.001*
Observer 6	Normal	2.84	2.65	2.47	2.04	32.99	<0.001*
	Lesion	2.76	2.67	2.5	2.07	26.62	<0.001*
Median	Normal	2.67	2.72	2.43	2.17		
	Lesion	2.73	2.67	2.37	2.27		

Table 5. Wilcoxon signed-rank test results for all images for normal and benign images considered separately. Asterisks highlight significant findings.

		L1-L0		L2-L0		L3-L0	
		Z	p	Z	p	Z	p
Observer 1	Normal	-0.38	0.71	-1.13	0.26	-1.68	0.09
	Lesion	-1.79	0.07	-1.58	0.11	-0.94	0.35
Observer 2	Normal	-1.47	0.14	-1.54	0.12	-4.05	<0.001*
	Lesion	-4.01	<0.000*	-1.36	0.18	-3.16	0.002*
Observer 3	Normal	-1.53	0.13	-1.47	10.14	-3.05	0.002*
	Lesion	-0.43	0.67	-1.98	0.05*	-2.57	0.01*
Observer 4	Normal	-2.95	0.003*	-1.47	0.14	-1.88	0.06
	Lesion	-1.60	0.11	-1.65	0.10	-3.24	0.001*
Observer 5	Normal	-0.91	0.36	-1.70	0.09	-4.67	<0.001*
	Lesion	-0.46	0.64	-2.39	0.02*	-3.97	<0.001*
Observer 6	Normal	-0.80	0.42	-2.60	0.01*	-4.79	<0.001*
	Lesion	-0.29	0.77	-1.71	0.09	-4.39	<0.001*

Study 2 - ROC, sensitivity and specificity analyses

ROC Area Under Curve (AUC) values are given in Table 6 and sensitivity and specificity values are shown in Table 7. No statistically significant differences were found for any of the observer groups (radiologists, sonographers or all grouped together).

Table 6. ROC values for each observer at different PI levels. Mean values are given for radiologists (R) (observers 1-6) , sonographers (S) (observers 7-12) and all observers. Standard deviation (SD) values are shown in parentheses.

Observer	L0	L1	L2	L3
1	0.78	0.77	0.83	0.76
2	0.79	0.82	0.75	0.79
3	0.79	0.81	0.83	0.80
4	0.76	0.79	0.79	0.78
5	0.79	0.77	0.86	0.88
6	0.81	0.79	0.85	0.77
R means (SD)	0.79 (0.06)	0.79 (0.06)	0.82 (0.05)	0.80 (0.05)
7	0.79	0.78	0.80	0.84
8	0.82	0.80	0.88	0.78
9	0.82	0.85	0.84	0.85
10	0.87	0.83	0.81	0.85
11	0.71	0.77	0.82	0.74
12	0.80	0.82	0.67	0.82
S means (SD)	0.80 (0.06)	0.81(.05)	0.80(.06)	0.82(.06)
Overall means (SD)	0.79 (0.05)	0.80 (0.05)	0.81 (0.05)	0.81 (0.05)

Table 7. Sensitivity and specificity values for each observer at different PI levels. Mean values are given for radiologists (R) (observers 1-6) , sonographers (S)(observers 7-12) and all observers . Standard deviation (SD) values are shown in parentheses.

	Sensitivity				Specificity			
	L0	L1	L2	L3	L0	L1	L2	L3
1	0.75	0.85	0.9	0.75	0.81	0.74	0.68	0.52
2	0.75	0.9	0.8	0.8	0.81	0.68	0.74	0.71
3	0.8	0.85	0.8	0.7	0.55	0.65	0.71	0.81
4	0.75	0.85	0.85	0.9	0.68	0.61	0.65	0.58
5	0.85	0.75	0.95	0.95	0.61	0.77	0.71	0.77
6	0.75	0.7	0.7	0.7	0.81	0.77	0.84	0.77
R means (SD)	0.78 (0.04)	0.82 (0.08)	0.83 (0.09)	0.80 (0.10)	0.71 (0.12)	0.70 (0.07)	0.72 (0.07)	0.69 (0.12)
7	0.6	0.55	0.7	0.7	0.87	0.84	0.87	0.84
8	0.8	0.8	0.9	0.75	0.71	0.71	0.68	0.68
9	0.9	0.9	0.9	0.9	0.61	0.52	0.48	0.52
10	0.65	0.65	0.7	0.75	0.87	0.9	0.84	0.84
11	0.55	0.75	0.75	0.7	0.84	0.77	0.87	0.9
12	0.85	0.9	0.7	0.8	0.74	0.71	0.65	0.61
S means (SD)	0.73 (0.14)	0.76 (0.14)	0.78 (0.10)	0.77 (0.08)	0.77 (0.10)	0.74 (0.13)	0.73 (0.16)	0.73 (0.15)
Overall means (SD)	0.75 (0.10)	0.79 (0.11)	0.80 (0.09)	0.78 (0.09)	0.74 (0.11)	0.72 (0.10)	0.73 (0.11)	0.71 (0.13)

DISCUSSION

Previous studies have shown that speckle reduction improves the visual perception of tissue differentiation, delineation of tissue boundaries and depiction of internal architecture (Huber et al., 2002; Piccoli & Forsberg, 2011; Rosen & Soo, 2001; Stafford & Whitman, 2011; Ullom et al., 2010). Whilst these image quality benefits are known, there has been less emphasis in the literature on the impact of these technologies on diagnostic efficacy. This study addresses this deficiency by determining the impact of a novel speckle reduction method on both image quality and diagnostic efficacy in one of the most challenging radiologic environments – breast imaging.

Given the importance of identification of subtle pathological tissue changes, maximization of image quality is vital to facilitate perception of abnormalities. This is particularly critical in a clinical breast-screening environment, where only about 5 in 1000 images will contain pathology and a quick decision is needed (Zanca et al., 2012). Our evaluation of image quality used visual grading analysis (VGA) of paired comparisons of anatomic and benign structures. It demonstrated increasing observer preference for images with higher PI levels (greater speckle reduction) with statistically significant differences.

As noted previously, all images were initially obtained using THI, a speckle reduction technique, which decreases artefacts from shallow structures as well as overall image clutter in the near field (Powers & Kremkau, 2011). However, when this is used in combination with PI, additional image quality improvement can be demonstrated. The benefits of combining different types of technologies have been shown previously in similar contexts, when compounding techniques and computer enhancement (XRES, Philips Ultrasound, Bothell, Wash) together produced superior images to compounding alone (Barr et al., 2009).

Although our VGA analysis presented promising findings, no improvements in diagnostic efficacy were detected using ROC assessment. Whilst speckle reduction can increase the conspicuity of low contrast lesions (Entrekin et al.,

1999; Huber et al., 2002) and improve perception of subtle image details (Nicolae,Moraru & Onose, 2010; Yoon et al., 2013), the absence of an effect of PI on performance in the current study is in line with the findings of Cha et al (Cha et al., 2005; 2007). In their studies using the alternate speckle reduction techniques of THI or spatial compounding, they did not show any significant improvement in the characterisation of breast lesions. On the other hand, Su et al (Su et al., 2010) did find increases in diagnostic accuracy when breast images were reprocessed by a speckle reduction algorithm based on a two-dimensional textural homogeneity histogram and directional averaging filters. A limitation of the current study may be the number of ultrasound images presented for evaluation. Su et al used up to 6 images for each lesion, unlike the work presented here, where a single image was chosen to best represent the lesion and its features.

There are seemingly three possible explanations for an improvement in image quality not impacting on diagnosis. Firstly, lesions with indeterminate features were selected for ROC analysis. Some indeterminate features, such as irregular shape or microlobulation, will remain indeterminate whatever speckle reducing technology is employed, and diagnostic opinion will not change regardless of differing image quality. Secondly, multiple speckle reduction techniques were used synchronously. Tissue harmonic imaging was used to enhance the image prior to the application of PI, therefore the image without PI had very little clutter, and this could have reduced the potential impact of PI on diagnostic efficacy. Thirdly and possibly most importantly, all observers were experienced breast radiologists and sonographers. With expertise it has been shown that image abnormality perception follows the 'top down theory', which means that there is parallel processing of the entire retinal image with acquired knowledge about normal and abnormal appearances (Kundel & Nodine, 1983). Therefore a 'good' quality image probably serves the same purpose as an 'even better' quality image amongst experts. A further study examining the confidence of professionals with lower levels of expertise may show a greater impact on diagnostic efficacy.

CONCLUSION

A significant increase in the perception of improved image quality was achieved with increasing levels of Precision Imaging, a novel speckle reduction technology. However this improvement did not translate into increased diagnostic efficacy amongst expert observers in this study. The importance of assessing new technologies using a variety of analytic approaches has been shown.

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Author Contribution Statement

Candidate Name: Siu Fong Louisa Lau

Degree Title: Master of Applied Science

Paper Title: Precision Imaging - Its impact on image quality and diagnostic confidence in breast ultrasound examinations

As the corresponding author of the above paper, I confirm that the above candidate has made the following contributions:

Conception and design of the research

Analysis and interpretation of the findings

Writing the paper and critical appraisal of content

Signed _____ Name ALFIYA SAFINA Date 9/07/2015

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