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Horizon Scanning Technology Horizon Scanning Report

Intraoperative ultrasound for breast lesion localisation during breast conserving surgery (lumpectomy)

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Breast cancer is the most common invasive cancer diagnosed in females and is widely known as one of the leading causes of cancer death in females. The widespread use of mammography in the last 20 years as a means of screening has resulted in significantly higher detection rates for suspicious, non-palpable breast lesions (Bennett et al. 2005). The localisation and excision (lumpectomy) of these non-palpable lesions is usually performed with the guidance of preoperative percutaneous mammographically-guided wire/needle localisation procedures such as needle localisation breast biopsy (NLBB). Although wire-guided localisation is generally recognised as an effective method; it is nevertheless associated with several drawbacks. The key concerns linked to the use of preoperative wire localisation are: *a)* accurate localisation and resection of the target lesion within a 3-dimensional space with the aid of a 2-dimensional localisation technique and *b)* the incidence of wire/clip migration. Studies have demonstrated that the miss rates of preoperative wire-guided localisation procedures vary from 0% to 22% (Klimberg 2003), and clip migration up to 1cm from the target lesion can occur in up to 50% of patients (Kass et al. 2002). Approximately 20% of patients with malignant non-palpable breast lesions who underwent wire-guided localisation undergo a second surgical intervention to attain adequate margins (Rahusen et al. 2002).

Recently, intraoperative ultrasound (IOUS) is emerging as an alternative technique of localising nonpalpable breast lesions for excision and has been touted as an effective technique without the drawbacks associated with preoperative wire-guided localisation. IOUS does not require the insertion of a wire/clip and therefore eliminates the risk of wire/clip transection or migration while sparing the patient from the discomfort/distress associated with wire-insertion. More importantly, IOUS provides the surgeon with real-time imaging of the target lesion therefore may potentially increase accuracy and ensure adequate margins in malignant cases.

One of the risks associated with the use of IOUS is its ability to reliably detect lesions. Studies have shown that approximately 40% to 60% of mammographically-detected lesions are visible with ultrasound (Potterton et al. 1994, Kaufman et al. 2002); this therefore limits its applicability across a range of nonpalpable lesions. The second risk associated with the use of IOUS is inaccuracy resulting from the inexperience of surgeons with the use of ultrasound imaging. Researchers have proposed that surgeons who are at the early stages of their experience with ultrasound should be guided by a radiologist in the operating theatre until they are able to reliable detect all lesions themselves (Harlow et al. 1999). With adequate training, surgeons can achieve comparable accuracy in localising and identifying lesions as trained radiologists (Whitehouse et al. 2001).

Most of the included studies within this report demonstrate that the use of IOUS localisation achieves better negative margin rates (Moore et al. 2001, Rahusen et al. 2002, Bennett et al. 2005, Buman and Clark 2005, Rahusen et al. 1999, Thompson et al. 2007, Rahman et al. 2007) compared to wire-guided excision. Only one study did not observe better margin clearance when utilising IOUS, but the results were comparable to conventional wire-guided localisation (Snider et al. 1999). Several studies also demonstrated that IOUS is associated with lower excision weight/volume compared to wire-guided excision (Moore et al. 2001, Snider et al. 1999, Rahman et al. 2007). In addition, the use of ultrasound for *ex vivo* specimen analysis during surgery has been shown to be a more accurate method of determining adequate margins compared to specimen mammography (Tan et al. 2006).

The applicability of IOUS localisation was extended to non-ultrasound visible lesions with the introduction of a novel visualisation method that uses iatrogenically-induced haematomas (Smith et al. 2001). Both of the included studies which utilised this technique reported encouraging results, with IOUS attaining better negative margin rates (Thompson et al. 2007) and margin clearance (Rahman et al. 2007) while achieving similar (Thompson et al. 2007) or lower (Rahman et al. 2007) specimen resection volumes compared to conventional wire-guided excision.

At the time of writing, no cost-effectiveness studies on the utilisation of IOUS for nonpalpable breast lesion localisation have been conducted. Some of the included studies indicate that IOUS-guided lesion localisation does not result in substantially longer operative times compared to wire-guided localisation (Moore et al. 2001, Rahusen et al. 2002), while one study stated that operating room expenses did not differ significantly to standard excision in cases of palpable lesions (Moore et al. 2001). However, the cost of surgeon training and the required presence of a guiding radiologist in the early stages of utilising IOUS localisation were not discussed in the studies retrieved.

The evidence currently available on the use of IOUS-guided localisation of nonpalpable breast tumours lends substantial support to this technique and appears to be a potentially better technique to conventional wire-guided localisation. However, it is imperative that adequate training and supervision is provided to breast surgeons before this technique can be utilised effectively in patients.

HealthPACT Advisory

The utility of intra-operative ultrasound as an adjunct in the excision of non-palpable breast lesions has been demonstrated in a limited number of high quality studies. The benefit is confined to a specific subset of such lesions and therefore clear protocols for the use of the modality, along with appropriate skills-training, credentialing and device standards need to be developed by the appropriate professional body (i.e. the Royal Australasian College of Surgeons perhaps in conjunction with the Royal Australian and NZ College of Radiologists).

Introduction

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S), on behalf of the Medical Services Advisory Committee (MSAC), has undertaken a Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of intraoperative ultrasonography for breast cancer surgery.

Intraoperative ultrasonography provides an alternative technique of localising breast lesions among patients undergoing breast conserving surgery/lumpectomy. This technique is offered through breast surgeons and is currently in limited use in Australia.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of intraoperative ultrasonography for breast cancer surgery, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with intraoperative ultrasonography for breast cancer surgery.

Description of the technology

The surgical treatment of breast cancer typically involves the excision of the tumour, either via mastectomy (removal of the breast) or breast conserving surgery (lumpectomy). In the last decade, breast conserving surgery has gained widespread acceptance and is considered to be as effective as mastectomy in treating early breast cancers (Harlow et al. 1999). In order to achieve effective and complete excision during breast conserving surgery, the lesion must be localised accurately and excised with adequate margins[1].

The medical community has exerted substantial resources to enhance breast cancer survival by early detection with screening. The widespread availability and use of mammography in the past 20 years has resulted in the increased detection of suspicious, non-palpable, and benign radiographically visualised lesions (Nurko and Edwards 2005, Bennett et al. 2005). In fact, studies have shown that the average size of detected breast cancer has decreased substantially with the advent of mammography, with half the cases smaller than 15mm in diameter (Kaufman et al. 2002).

Until recently, methods of localising these lesions have largely been limited to percutaneous mammographically-guided wire/needle localisation procedures (i.e. needle localisation breast biopsy [NLBB]). However, despite being the current gold-standard for non-palpable lesion localisation; the preoperative percutaneous insertion of a needle or hookwire into the breast by mammographic or ultrasound guidance is associated with several drawbacks. Adequate resection of a non-palpable breast lesion is dependant on the accuracy of wire/needle placement by the radiologist as well as the experience and ability of the surgeon to accurately locate the tumour utilising a 2-dimensional localisation technique. Previous studies have shown that the up to 20% of wire localisation procedures fail to determine the location of the lesion accurately (Rissanen et al. 1993, Snider et al. 1996). Jackson and Marzoni (1997) conducted a retrospective literature review and compiled a total of 12,563 localised needle biopsies from 49 studies; the review reported that the overall miss rate for needle localisation varied from 0% to 18% for all lesions and 0% to 8% for cancers. In addition to this, there is the possibility of wire transection and migration (Hasselgren et al. 1993, Theriault et al. 2002, Rissanen et al. 1993), a situation that is further exacerbated by the transfer of the patient from the radiology department to the operating theatre. The miss rates of wire-guided localisation may be secondary to surgical error, but are more commonly believed to be a result of wire or clip migration. One study has shown that median clip migration in 50% of patients after stereotactic breast biopsy was approximately 1 cm and that the clips migrated greater than 2 cm (range: 0 to 8 cm) from the core biopsy site nearly 20% of the time (Kass et al.

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[1] No cancer cells within the margin area

2002). Overall, these issues essentially contribute to inadequate excision of the tumour and inadequate margins. Evidence indicates that approximately 20% of patients who underwent wire-guided excision of breast tumours are required to undergo a second surgical intervention to attain adequate margins (Rahusen et al. 2002).

An emerging technique for localising nonpalpable lesions is intraoperative ultrasonography (IOUS); a technique previously limited to radiologic characterisation and core needle biopsy or preoperative needle localisation (Klimberg 2003, Henry-Tillman et al. 2001). Considering the fact that ultrasonography can be utilised to guide the placement of a localising needle in the radiology department prior to surgery, logic alludes that it can therefore be used in the operating theatre to guide the surgeon in the excision of the same lesion (Henry-Tillman et al. 2001). It is important to note that the target nonpalpable lesion must be visible with ultrasonography; some lesions can only be detected with mammography and therefore localisation with ultrasound is not feasible (Kaufman et al. 2003).

In some centres, clinicians have utilised ultrasonography to localise nonpalpable breast lesions within the operating theatre without the use of preoperative techniques such as needle/guide-wire insertion (Smith et al. 2000). In addition to this, studies have also examined the feasibility of IOUS-guided excisional biopsy (IUGE), a procedure developed to address the problem of false negative rates in needle biopsy techniques and at the same time obviating wire-localisation breast biopsy with the added benefit of lesion removal (essentially an ultrasound –guided lumpectomy with pathological assessment after lesion excision) (Chen et al. 2003).

Although the use of IOUS for breast surgery is not entirely new, the first use being documented in 1988 (Schwartz et al. 1988), it has garnered considerable interest among clinicians in recent years and has been utilised more frequently for breast surgery. With the technological advances in ultrasound imaging, portable ultrasound machines with high resolution and the emergence of small-footprint probes; the interest among clinicians to use IOUS is expected to increase markedly (Buman and Clark 2005).

The procedure

The technique of IOUS-guided lesion localisation and excision has evolved and modified over time by various groups of researchers. Therefore, the technique for intraoperative localisation and excision of nonpalpable lesions varies to an extent in the studies examined within this report. However the basic principles are similar in all studies utilising to this procedure.

Intraoperative breast ultrasonography is performed with a 7.5MHz or 10MHz linear array transducer with the arm abducted. After administration of general anaesthesia, the involved breast will be prepared and draped while the ultrasound

probe is encased in a sterile plastic sleeve. Ultrasound gel is placed within the sleeve over the head of the probe, and sterile gel is placed on the breast over the target region; if the ultrasound probe has been sterilised chemically or via gas sterilisation, the use of the sterile plastic sleeve is not necessary (Bennett et al. 2005). The lesion is localised in the standard two planes, longitudinal and transverse (Smith et al. 2001a). Once the lesion is identified by ultrasound, a pen is used to mark two axes at 90º to each other overlying the lesion; meanwhile the site for skin incision is marked as well (Bennett et al. 2005). Incision of the skin is carried down to below the subcutaneous fat towards the chest wall using a 'line of site' technique. Following this, the ultrasound probe is repositioned *into* the wound, perpendicular to the lesion and parallel to the chest wall to assess the adequacy of the deep margin (Smith et al. 2001a). Following this, the lesion is excised in a block fashion with occasional ultrasound review to ensure the lesion in question is encompassed within the lines of excision.

The excised specimen is then marked with orientation sutures and *ex vivo* specimen ultrasonography is conducted in a basin filled with water to confirm that the sonographic abnormality/lesion in question was contained within the excised tissue (Henry-Tillman et al. 2001). In instances involving the excision of a *malignant tumour*, the ultrasound probe may be placed over the specimen at various angles to determine the adequacy of the margins of excision in each plane. Therefore if the lesion was found to be close to a margin, immediate re-excision of that area of the cavity can be performed (Bennett et al. 2005, Henry-Tillman et al. 2001).

Figure 1: Intraoperative technique of excising a suspicious lesion within a breast with assessment of margins.

A: Ultrasound probe tilted demonstrating 1cm margins
B: Placement of probe in incision to assess depth
C: Tissue excised in block fashion, with corresponding *ex vivo* ultrasound measurement of the margins.
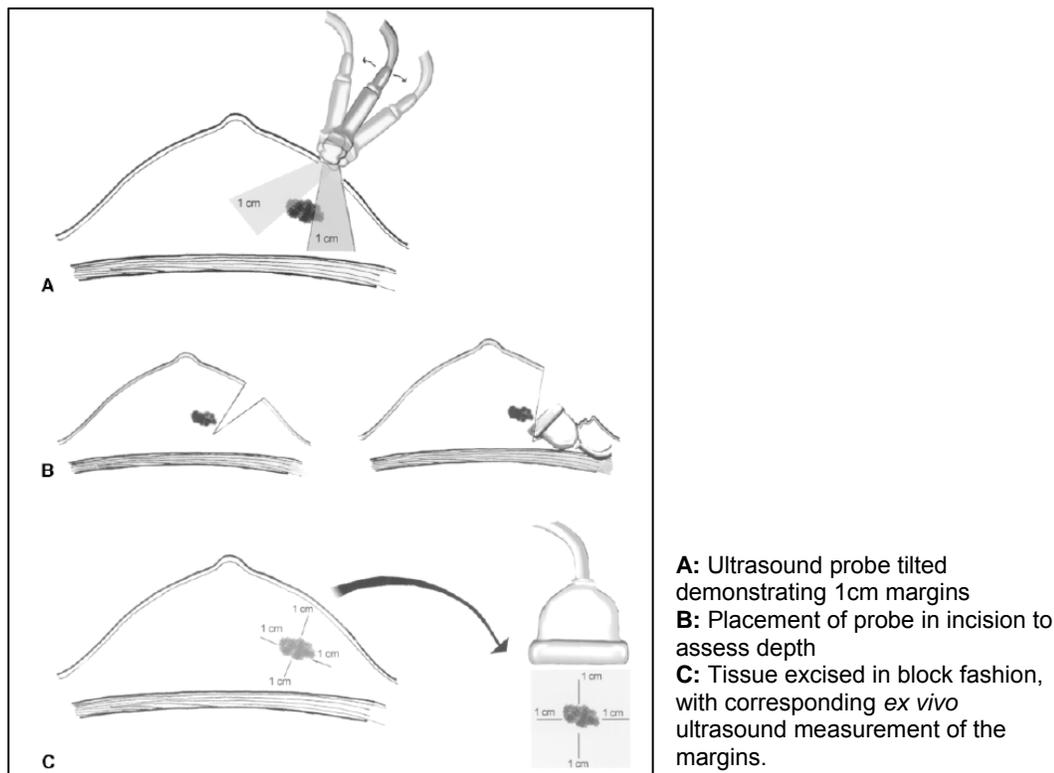
Henry-Tillman et al. (2001)

Intended purpose

IOUS for breast cancer surgery was developed with the intention of streamlining the process of lesion localisation and excision while addressing the inherent disadvantages associated with preoperative wire localisation. The key purported advantages of IOUS for breast cancer surgery are: 1) allows for immediate documentation of removal of the suspect lesion; 2) causes no additional discomfort to the patient; 3) does not require preoperative localisation techniques, entire procedure conducted within the operating theatre; 4) no radiation required and 5) can be utilised to assess margin status immediately after excision (i.e. specimen ultrasound) (Rubio et al. 2003).

Clinical need and burden of disease

In Australia, breast cancer is the most common invasive cancer diagnosed in females and the leading cause of cancer death in females. Breast cancer is rare in males and is reflected by the low incidence rates of 1 per 100,000 population.

In females, the number of new breast cancer cases has increased from 5,318 in 1983 to 12,027 in 2002. It is projected that there will be 14,818 new cases of breast cancer among females in 2011. The age-standardised incidence of breast

cancer in women increased from 80 per 100,000 population in 1983 to 98 per 100,000 population in 2002. However, it should be noted that the substantial rise in the incidence of breast cancer may have been spurred by the utilisation of mammography. In 1991, BreastScreen Australia commenced a population-based mammography screening program causing a sharp rise in incidence in the early 1990s. The age-standardised rate is projected to remain at about 117 new cases per 100,000 females through to 2011. It is estimated that is 2002, there were 114,000 women alive who had been diagnosed with breast cancer in the previous 20 years (Australian Institute of Health and Welfare & National Breast Cancer Centre 2006).

As stated previously, breast cancer is the leading cause of death in females in Australia. In 2004, there were 2,641 female deaths due to breast cancer with an average of 601 additional cases per year from 2000-2004 where breast cancer was an associated cause[2] and not the underlying cause[3] of death. Based on mortality data from the Australian Bureau of Statistics, the age-standardised rate of death due to breast cancer among women increased steadily in the early part of the century, from 21.8 deaths per 100,000 females in 1907 to 35.0 deaths per 100,000 females in 1943. The age-standardised rate was fairly steady until the early 1990s, and has reduced substantially since then; from 31.0 deaths per 100,000 females in 1990 to 23.4 deaths per 100,000 females in 2004. Mortality rates are highest in the older age groups; women 80 to 84 years of age had an age-specific mortality rate of 125.0 deaths per 100,000 women in 2004. The data shows that death in women aged 25 and younger are very rare, with no deaths due to breast cancer within this age group in 2004 (Australian Institute of Health and Welfare & National Breast Cancer Centre 2006).

In New Zealand, a total of 2364 new registrations for breast cancer were reported in 2002. This equates to an age standardised rate[4] of 86.0 and accounts for 27.7% of female cancer registrations (New Zealand Health Information Service 2002). The cumulative mortality and incidence rates per 1000 women (age 0-74 years) was 27.4 (1991-1995) and 83.1 (1989-1993), respectively. The average number of deaths due to breast cancer was 580 per year and the average number of new breast cancer cases was 1605 per year (Gavin et al. 2001). As with Australia, the number of new registrations of breast cancer has increased recently due to the increased detection of breast cancer among women age 50 to 64 participating in the National breast Screening Programme (Gavin et al. 2001).

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[2] Associated cause of death – any other condition or event that is not the underlying cause but is still considered to contribute to death
[3] Underlying cause of death – the disease or injury that initiated the train of events leading directly to death.
[4] Age standardised rate: Rates per 100,000 and age-standardised to Segi's world population.

Stage of development

At the time of writing, the extent of use of IOUS for lesion localisation and margin determination in Australia is unclear. It should be noted that the equipment required for this procedure are readily available in most specialist medical centres and therefore there is a strong likelihood that a substantial proportion of clinicians may be utilising this technique.

Australian Therapeutic Goods Administration approval

Therapeutic Goods Administration approved portable ultrasound systems are available in various medical centres across Australia.

Treatment Alternatives

Existing comparators

The comparators of IOUS-guided lesion localisation for nonpalpable breast lesions are:

a) Preoperative wire-guided localisation
The key comparator to IOUS-guided lesion localisation is preoperative wire/needle localisation under mammographic guidance, which is the current standard practice for localising non-palpable breast lesions in Australia and New Zealand.

b) MRI-guided NLBB
Advances within the field of magnetic resonance imaging (MRI) have resulted in the development of preoperative MRI-guided NLBB procedures. Due to the early stages of investigation with regard to this procedure, data on the miss rate associated with MRI-guided NLBB is limited. It should be noted that as with mammographically-only detected lesions, MRI-only detected lesions have only been amenable to removal by NLBB (Rubio et al. 2003).

c) Carbon injection method
The carbon injection method is essentially a dye procedure consisting of an injection of a 3% sterile charcoal suspension into the site of the lesion under stereotactic mammography or sonography (Canavese et al. 1995). Although the technique can be utilised to successfully localise nonpalpable breast lesions (Cavanese et al. 1995), the injection of charcoal is difficult in patients with dense breasts.

d) Radio-guided occult lesion localisation (ROLL)
The ROLL technique involves the injection of technetium-labelled colloid into a breast lesion 24 hours preoperatively, taking plantar scintigraphy images with a gamma camera, superimposing this image onto the mammogram, at which the

'hot spot' is then shown to correspond to the lesion (Gennari et al. 2000). In a comparative study, Zgajnar et al. (2004) stated that ROLL obtained wider surgical margins compared to NLBB but with a lower average specimen weight; therefore demonstrating that ROLL was more accurate than NLBB.

Clinical Outcomes

Safety

One comparative study (Level III-2 intervention evidence) and three case series studies (Level IV intervention evidence) were included for discussion within this section.

Risks of intraoperative ultrasonography
One of the main concerns with the intraoperative use of ultrasonography is its ability to reliably detect lesions. In studies of both palpable and nonpalpable breast cancers, false-negative rates for ultrasonography have been shown to have large variations, ranging from 0.3% to 47% (Jackson 1990). In addition to this, ultrasonography is not able to reliably demonstrate microcalcifications or small tumours in predominantly fatty breasts (Jackson et al. 1986). Potterton et al. (1994) examined the ability of ultrasonography (7.5 MHz linear array probe) in demonstrating small breast cancers (<10mm diameter; mostly impalpable) that were initially detected with mammography. The investigators reported that approximately 39% (31/79) of breast cancers were not visible during ultrasound examination; with a large majority of these being cancers presenting as microcalcification alone (25 cancers) (Potterton et al. 1994). Overall, it appears that ultrasound is capable of imaging approximately 40% to 60% of non-palpable breast lesions, increasing to approximately 75% when microcalcific lesions are excluded (Potterton et al. 1994, Kaufman et al. 2002).

These results highlight that ultrasonography is not suitable as a sole imaging procedure for breast lesions. Considering the limitations of ultrasonography, it is therefore prudent to ensure that the lesion is visible with ultrasound before utilising IOUS for lesion localisation. Recently, an innovative new method (haematoma-guided ultrasound localisation) has been investigated as a means of increasing the applicability of IOUS; even in cases where the lesion is not visible with ultrasound (Smith et al. 2001a, Smith et al. 2001b).

Another key risk of this procedure is the accuracy of intraoperative breast ultrasonography when performed in the operating theatre by a surgeon instead of a radiologist. Whitehouse et al. (2001) examined the accuracy of breast ultrasound scans performed by a surgeon in outpatients compared to radiologists and found that there was concordance between surgeons and radiologists in 96% (197/231) of patients and discordance in 3.6% (8/231) of patients. Although the results of this study were encouraging, it should be noted that the surgeons conducting the

ultrasound scans in this study were experienced with its use and the scans were not conducted within the operating theatre on a patient undergoing lumpectomy/ excisional biopsy (Whitehouse et al. 2001). Nevertheless, the data presented by Whitehouse et al. (2001) demonstrated that surgeons can achieve similar rates of accuracy to radiologists; given the opportunity to familiarise themselves with the technique. Gittleman (2003) noted that developing confidence in the use of intraoperative breast sonography for the placement of a localisation device took less than 3 months, and complete conversion to IOUS localisation can be achieved within 6 months. Harlow et al. (1999) stated that surgeons who are at the early stages of their experience with ultrasound should be guided by a radiologist until they are able to reliably identify all lesions themselves. The number of procedures required to gain this level of experience is between 10 and 25; but this is obviously dependant on the surgeon's prior experience with the use of ultrasound (Harlow et al. 1999).

In addition to this, there is concern that with the use of ultrasound gel in the wound and the extra manipulations required for IOUS, the wound infection rates may be higher compared to traditional wire localisation. Despite this, most of the included studies did not report on surgical infection rates after the use of intraoperative breast ultrasonography, with the exception of Buman and Clark (2005); where the authors claimed that no substantial increase in infection rates were noted in comparison to wire-guided localisation.

Effectiveness

Two randomised controlled trials (Level II intervention evidence), eight comparative studies (Level III-2 intervention evidence) and one case series study (Level IV intervention evidence) were included for discussion in this section. Studies were selected for inclusion based on the quality of evidence; case reports were excluded due to the low level of evidence.

Lesion localisation and margin status

In all of the included studies, patients underwent preoperative mammography and/or ultrasonography to ensure that the breast lesion would be visible intraoperatively with ultrasound. Consequently, *all* target breast lesions were identified/localised and excised (Moore et al. 2001, Rahusen et al. 2002, Bennett et al. 2005, Buman and Clark 2005, Rahusen et al. 1999, Snider et al. 1999).

The key measure of effectiveness for IOUS-guided excision of breast lesions is the success of attaining adequate negative margins[5] in patients with malignant

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[5] Positive margins (i.e. margins containing cancer cells) are associated with local recurrence and decreased survival. Although there is no dispute in the importance of achieving negative margins, the width of margins necessary for breast cancer removal is highly debated (Swanson et al. 2002). In most of the studies discussed within this report, a 10mm margin was adopted as an adequate margin.

lesions. To date, two randomised controlled trials (Level II intervention evidence) have been published on the use of IOUS for the excision of malignant breast lesions (Moore et al. 2001, Rahusen et al. 2002). The design and outcomes from these trials are presented in Table 1.

Moore et al. (2001) evaluated the efficacy of IOUS in obtaining adequate surgical margins in women (n = 27) undergoing lumpectomy for *palpable* breast cancer; the results were compared to a control group which underwent standard excision[6] (n = 24) (Table 1). The investigators reported that IOUS yielded significantly better rates of negative margins compared to standard excision for palpable infiltrating ductal breast cancer (96.5% vs. 71%, respectively; $p < 0.05$); while the margin of uninvolved breast tissue was greater for IOUS patients as well (7.6 ± 2.0mm vs. 4.8 ± 1.4mm). In addition to this, the use of IOUS resulted in a smaller, but not statistically significant, volume of excised tissue (104 ± 8cm^3 vs. 114 ± 6cm^3). When specimen volume was compared with preoperative mammographically determined parenchymal density, Moore et al. (2001) noted that patients with dense breasts (n = 24) had an increased volume of surgically removed tissue. Ten of these patients (with dense breasts) underwent IOUS while 14 underwent standard excision; the specimen volume was substantially smaller in the ultrasound group (127 cm^3 vs. 180 cm^3). If the breast tissue was not dense, IOUS made little difference to the volume excised (90 cm^3 vs. 102 cm^3). This suggests that the use of IOUS appears more beneficial in patients with dense breast parenchyma surrounding the lesion (Moore et al. 2001).

The second randomised controlled trial (Rahusen et al. 2002) aimed to determine if IOUS localisation enables a better margin clearance compared to preoperative wire-guided localisation in patients with *non-palpable* breast cancers. The investigator noted that a greater proportion of IOUS patients achieved adequate margins (≥1mm) compared to wire-guided patients (89% vs. 55%; $p > 0.001$). In contrast to Moore et al. (2001), Rahusen et al. (2002) did not notice any difference in specimen weight between the two techniques.

Table 1: Surgical outcomes of randomised controlled trials utilising intraoperative ultrasonography for breast conserving surgery.

Study	Study details	Operating time and specimen size	Outcomes
Moore et al. (2001)	Level II intervention evidence Intraoperative ultrasound 27 patients Control (standard excision) 24 patients All lesions were	*Operating time* (Mean ± SD) Intraoperative ultrasound 106±37 minutes Control (standard excision) 121±39 minutes Average time for re-excision (8 patients): 75±26 minutes *Tumour size* (Mean ± SD) Intraoperative ultrasound	*Margin status* Intraoperative ultrasound 3.5% (1/27) had a positive margin. Margin of uninvolved breast tissue, Mean ± SD: 7.6±2.0mm. Control (standard excision) 29% (7/24) had a positive margin.

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[6] Standard excision in this study (Moore et al. 2001) does not involve preoperative wire-guided localisation as the target lesions are palpable.

	palpable, biopsy proven infiltrating ductal carcinoma, stage T1 or T2 Transducer: 7.5 MHz	Specimen size: 104±8cm^3 Control (standard excision) Specimen size: 114±6cm^3	Margin of uninvolved breast tissue, Mean ± SD: 4.8±1.4mm.
Rahusen et al. (2002)	Level II intervention evidence Wire-guided excision 22 patients Intraoperative ultrasound 27 patients Nonpalpable cancer visible with mammography and ultrasound Transducer: 10 MHz	*Operating time* [Mean (range)] Wire-guided excision 65 (40-105) mins Intraoperative ultrasound 66 (30-110) mins *Tumour size* [Mean (range)] Wire-guided excision 1.36 (0.4-2.3) cm Intraoperative ultrasound 1.34 (0.5-2.5) cm	*Margin status* Wire-guided excision Margins ≥ 1 mm: 12 (55%) Margins < 1mm: 6 (27%) Involved margins: 4 (18%) Intraoperative ultrasound Margins ≥ 1 mm: 24 (89%) Margins < 1mm: 2 (7%) Involved margins: 1 (4%)

Overall, both randomised controlled trials demonstrated that IOUS yielded superior results with regards to negative margin rates and margin status. However, there is some inconsistency with regards to the advantage incurred with the use of IOUS and the size of the excised specimen. Moore et al. (2001) reported significantly lesser volume of excision while Rahusen et al. (2002) did not.

Four non-randomised comparative studies (Level III-2 intervention evidence) were retrieved, and the results are outlined in Table 2. All these four comparative studies examined the efficacy of IOUS compared to preoperative wire localisation for lesion excision during breast conserving surgery. It should be noted that one of these comparative studies (Buman and Clark 2005) utilised a slightly modified technique where ultrasonography was performed in *combination* with wire localisation intraoperatively before the excision of the target lesion.

Table 2: Surgical outcomes of comparative studies utilising intraoperative ultrasound-guided excision of lesions for breast conserving surgery.

Study	Study details	Operating time and specimen size	Outcomes
Bennett et al. (2005)	Level III-2 intervention study Intraoperative ultrasound 103 patients (115 excisions, nonpalpable) Preoperative wire localisation 43 patients (43 excisions) Nonpalpable lesions	*Operating time* Not stated *Tumour size* Intraoperative ultrasound group Mean specimen size: 47.2mm Preoperative wire localisation Mean specimen size: 59.0mm	Intraoperative ultrasound All lesions were identified and localised, specimen sonography confirmed excision in 100% of cases. 96% sensitivity, 96% specificity. 48 breast malignancies were excised in 46 patients. In 4/46, excision was performed as open biopsies; 42/46 had excision to achieve clear margins as part of lumpectomy. 93% (39/42) achieved clear margins at the first procedure. Overall 9.7% (10/103) of patients underwent re-

	Note: A number of ultrasound-guided excisions were diagnostic biopsies, most were for therapeutic complete local resection Transducer: 7.5 MHz		excision, 3 cases were due to residual disease. Preoperative wire localisation 28 breast malignancies in this group; 24 underwent lumpectomy (4 had multifocal extensive disease). 83% (19/24) achieved clear margins at the first procedure. *Margin status* <table><tr><td>**Margin**</td><td>**Wire excision no.**</td><td>**%**</td><td>**Ultrasound excision no.**</td><td>**%**</td></tr><tr><td><2mm</td><td>16</td><td>66.7</td><td>8</td><td>19.0</td></tr><tr><td>2-5mm</td><td>5</td><td>20.8</td><td>22</td><td>52.4</td></tr><tr><td>>5mm</td><td>3</td><td>12.5</td><td>12</td><td>28.6</td></tr><tr><td>Total</td><td>24</td><td>100</td><td>42</td><td>100</td></tr></table>
Buman and Clark (2005)	Level IV intervention evidence Intraoperative ultrasound 112 patients (130 lesions) *(Intraoperative ultrasonography used in combination with intraoperative needle placement. If the lesion was to be widely-excised for cancer, it was needle localised intraoperatively and excised with a 10mm margin.)* Preoperative wire guided 50 patients (50 lesions) Nonpalpable lesions Transducer: 5-10 MHz	*Operating time* Not stated *Tumour size* Not stated	Successful removal of lesions achieved in all 112 patients. Intraoperative ultrasound Complete local excision was attempted in 28 patients with proven carcinoma. Of these, 85% (24/28) achieved histologically clear margins. Preoperative wire localisation 72% (36/50) of patients attained clear margins in a separate cohort which underwent preoperative hookwire localisation.
Rahusen et al. (1999)	Level III-2 intervention evidence Intraoperative ultrasound 19 patients (20 non-palpable lesions) Preoperative wire localisation 43 patients Nonpalpable lesions (15 had preop diagnosis of invasive malignancy) Transducer: 7.5 MHz or 10 MHz	*Operating time* Not stated *Tumour size* [Mean (range)] Intraoperative ultrasound 12mm (range: 4-26mm) Preoperative wire localisation 12mm (range: 4-40mm)	Intraoperative ultrasound 89% (17/20) achieved histologic margins of at least 1mm. Preoperative wire localisation 40% (17/43) achieved adequate margins of at least 1mm.

Snider et al. (1999)	Level III-2 intervention evidence Intraoperative ultrasound 29 patients (22 patients had malignant lesions) Preop wire localisation 22 patients Nonpalpable lesions Transducer: 10 MHz	*Operating time* Not stated *Tumour size* (Mean ± SD) Intraoperative ultrasound Mean infiltrating lesion size: 11±3.2mm Mean specimen size: 62.6±54.2 cm^3 Preop wire localisation Mean infiltrating lesion size: 5.5±3.1mm Mean specimen size: 81.1±119.3 cm^3	Intraoperative ultrasound Targeted lesion removed in all patients. 18% (4/22) had microscopically involved margins (positive margins) 82% (18/22) had disease-free margins ranging from 3-20mm (mean: 6.6mm). Preop wire localisation Targeted lesion removed in all patients. 18% (4/22) had margins microscopically involved with DCIS (positive margins). 82% (18/22) had microscopically disease-free margins ranging from 2 to 14 mm (mean: 6.7mm).

Negative margins were achieved in 82% to 93% of patients with the use of IOUS localisation. Meanwhile, negative margins were achieved in 40% to 82% of patients who underwent preoperative wire guided localisation (Table 2). In three of the four comparative studies (Bennett et al. 2005, Buman and Clark 2005, Rahusen et al. 1999), the proportion of patients with negative margins was substantially higher for the IOUS group compared to the preoperative wire localisation group (Bennett et al. 2005, Buman and Clark 2005, Rahusen et al. 1999, Snider et al. 1999). In one study (Bennet et al. 2005), patients who underwent wire localisation had a higher proportion of ductal carcinoma *in situ* (DCIS) cases (36%, 10/28 patients) compared to the ultrasound group (10%, 5/28 patients); so the surgical outcomes may have been skewed in favour of IOUS. However, subgroup analysis revealed that only 2/5 wire excisions that had failed clear margins at first resection were cases of DCIS and did not have significant influence on surgical outcome (Bennet et al. 2005).

In contrast to the other comparative studies, Snider et al. (1999) did not observe significantly better margin status in IOUS patients compared to wire-guided patients. Both patient groups attained similar proportions of negative margins (IOUS: 82%; wire localisation: 82%) and the extent of negative margins (IOUS: 6.6mm; wire localisation: 6.7mm) were similar as well (Snider et al. 1999). However, it should be noted that the two patient groups of this study were not well matched in terms of their clinical, mammographic, and histological findings[7].

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[7] Demographics of patients with malignant lesions (Snider et al. 1999):

Characteristics	Intraoperative ultrasound (n=22)	Preoperative wire localization (n=22)
Infiltrating carcinoma	21 (95%)	12 (55%)
Pure ductal carcinoma in situ	2 (5%)	10 (45%)
Mammographic findings		
Mass lesion	16 (73%)	6 (27%)
Mass with calcification	5 (22.5%)	7 (32%)
Calcification only	0	7 (32%)
Architectural distortion	1 (4.5%)	2 (9%)

Nevertheless, Snider and colleagues (1999) stated that the patient groups provide an accurate representation of patients routinely encountered in surgical practice, despite their differences. When patients with pure DCIS were excluded (only infiltrating tumours were considered), the proportion of positive margins (IOUS: 20%, wire localisation: 17%) and the extent of negative margins (IOUS: 7.0mm, wire localisation: 7.5mm) remained similar. However, it should be noted that less tissue was excised in patients who received IOUS (62.6 ± 54.2 cm^3) compared to those who received wire localisation (81.1 ± 119.3 cm^3) despite the fact that the mean infiltrating lesion size was substantially larger for IOUS patients. This sub-group analysis suggests that the use of IOUS resulted in more direct targeting and removal of the lesion (Snider et al. 1999). Similar results for excised specimen size were reported by Bennett et al. (2005).

Haematoma-guided intraoperative ultrasound localisation
As stated previously, a substantial proportion of breast lesions are not visible with ultrasound (Potterton et al. 1994, Kaufman et al. 2002). This therefore limits the applicability of IOUS-guided excision to the subgroup of lesions that are visible with ultrasound. Three non randomised comparative studies evaluated different forms of haematoma guided IOUS.

The study by Smith et al. (2001b) attempted to utilise IOUS to localise and detect breast lesions that were only visible with magnetic resonance imaging (MRI). Smith and colleagues proposed that iatrogenically induced haematomas (which are clearly visible with ultrasound) could be used to guide the excision of nonpalpable MRI-detected lesions using ultrasound.

A haematoma consisting of 2ml to 5ml of the patient's own blood was injected (preoperatively) into the breast to target nonpalpable lesions in 19 patients. Following this, IOUS was utilised to locate the lesion for excision. In the first 13 of these, wires were placed *in addition* to haematomas[8]. The intraoperative ultrasound localization method used was similar that used by Buman and Clark (2005).

The investigators reported that this procedure successfully localised the lesions in all patients (100% localisation rate); and *ex vivo* ultrasound or direct visualisation of the haematoma confirmed the removal of the haematoma and hence the target lesion in all cases. Of the eight patients with malignant lesions, two had margins that were either positive or <1 mm and subsequently underwent complete mastectomy; resulting in a negative margin rate of 75% (6/8 patients) (Smith et al. 2001b). The 100% success rate of localising breast lesions utilising this novel

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[8] In initial cases, wires were placed *in addition* to haematomas in 13 patients. In several of these patients, the wire was noted to have migrated substantially from the haematoma and lesion. The intraoperative ultrasound localization method utilised by Smith et al. (2001) is similar to the procedure described earlier in this report.

method may potentially extend the applicability of IOUS-guided excision to lesions that are conventionally not visible with ultrasound.

Based on the principle of utilising haematomas for IOUS localisation, Thompson et al. (2007) investigated the use of naturally-occurring haematomas present after vacuum-assisted breast biopsy (VABB)[9] as a physiological surrogate marker for breast lesions. When patients who underwent haematoma-guided excision (HUG) were compared to patients who underwent needle localised breast biopsy (NLBB), the investigators noted that margins[10] were negative in 67% (39/58), close in 10% (6/58) and positive in 22% (13/58) of patients who underwent HUG. Meanwhile, margins were negative in 27% (5/19), close in 0%, and positive in 73% (13/19) of patients who underwent NLBB. Overall, the proportion of patients with positive margins was significantly larger for NLBB patients compared to HUG patients (p = 0.0001) (Table 3), a result which corresponds to several other previously discussed comparative studies (Bennett et al. 2005, Buman and Clark 2005, Rahusen et al. 1999). The mean tissue volume excised and mean tissue weight excised with HUG was similar to NLBB (Table 3).

Table 3: Surgical characteristic of malignant patients undergoing haematoma ultrasound-guided excision (HUG) and needle localisation breast biopsy (NLBB).

	HUG (n=58)	NLBB (n=63)
Mean no. of days to surgery	19±3	42±20
Mean tissue volume excised (cm^3)	96±16	88±21
Mean weight excised (g)	56±12	51±18
No. of patients requiring additional margin excision during surgery	71(57%)	24(38%)
Mean invasive tumour size (mm)	9±5	10±7
Positive margins on final pathology report	13(22%)	14(73%)

Thompson et al. (2007)

Thompson et al. (2007) reported that patients who underwent HUG had a substantially higher rate of additional margin excision during surgery after main mass removal (Table 3). Initially, this appears to indicate that HUG was *less* accurate/precise compared to NLBB. However, the investigators attributed this to the use of direct real-time ultrasound that enabled the surgeon to visualise close margins or additional suspicious tissue; which facilitated the immediate removal of potentially malignant satellite lesions. This may have largely been responsible for the significantly lower positive margins on final pathology for HUG than for NLBB (Thompson et al. 2007). Conversely, the higher rates of immediate

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[9] The biopsy cavity after VABB naturally fills with a haematoma that can be visualized with ultrasound.

[10] In this study by Thompson et al. (2007), *positive margins* were defined as <1mm, *close margins* as between 1mm to 3mm, and *negative margins* as those >3mm.

additional excision may have been caused by bias of the operating surgeon to ensure that patients who underwent HUG attained better margin status.

In another comparative study, Rahman et al. (2007) investigated if the use of haematoma-guided ultrasound lumpectomy (HGL; n = 29) results in better margin status compared to wire-guided lumpectomy (WGL; n = 34) (Table 4). The median closest margin was significantly larger in HGL patients compared to WGL patients (p = 0.01) (Table 4).

Table 4: Surgical outcomes of patients undergoing haematoma-guided lumpectomy and wire-localised lumpectomy.

Main outcome measure	Wire-localised lumpectomy (n=34)	Haematoma-guided lumpectomy (n=29)	p-value
Closest margin, median (interquartile range), mm	3.5 (1-7)	5.0 (5-8)	0.01
Resection volume, median (interquartile range), cm3	143.4 (54-229)	85.0 (60-128)	0.048
Resection index, median (interquartile range)*	315.9 (89-3025)	77.1 (51-220)	0.003
Patients with margin revision, No. (%)	5 (14.7)	1 (3.4)	0.20

* The resection index is calculated as the resection volume divided by the tumour volume.

Rahman et al. (2007)

Median resection volume and median resection index was significantly lower for HGL patients; despite that fact that tumour volume was substantially larger in HGL patients[11]. These results indicate that HGL was significantly more accurate compared to WGL. Margin reexcision was performed (during the same surgery) in 3.4% of HGL patients and 14.7% of WGL patients, but this was not statistically significant (Rahman et al. 2007).

Intraoperative specimen ultrasound
In instances where IOUS was utilised for the localisation and excision of lesions, ex vivo specimen sonography could be an appropriate technique to provide conclusive confirmation of complete target lesion excision. This is supported by the fact that all included studies[12] have utilised specimen ultrasound intraoperatively to ensure total excision of the target lesion and the presence of adequate margins.

Vujovic et al. (2002) retrospectively reviewed the use of specimen ultrasonography and specimen mammography in 53 patients (55 lesions) who underwent ultrasound guided breast excisional biopsies. It should be noted that specimen ultrasonography in this study was conducted mostly within the radiology department and *not* intraoperatively (only 3 cases of IOUS).

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[11] Tumour volume - HGL: $1.1 cm^3$; WGL: $0.3 cm^3$ (p = 0.07)
[12] Included studies within the 'Effectiveness section': Moore et al. 2001, Rahusen et al. 2002, Bennett et al. 2005, Buman and Clark 2005, Rahusen et al. 1999, Snider et al. 1999, Smith et al. 2001, Thompson et al. 2007, Rahman et al. 2007.

Nevertheless, the investigators noted that from 1998-1999, specimen ultrasonography was utilised effectively in 39% (21/53) of patients to confirm the excision of the target lesion; while specimen mammography was utilised in 62% (33/53) of patients. In 10.9% (6/53) of cases, the lesion was only visible with ultrasound and would have been missed if specimen mammography was utilised. Vujovic and colleagues (2002) highlighted that specimen ultrasonography should be the preferred method of confirming total excision in patients undergoing ultrasound guided breast excisions (Vujovic et al. 2002).

Tan et al. (2006) compared the accuracy of intraoperative specimen ultrasonography to specimen mammography in the prediction of achieving adequate histologically disease-free margins during breast conserving surgery. The investigators reported that intraoperative specimen ultrasonography overestimated the margin 58.9% of the time, while specimen mammography overestimated the margin 66.7% of the time. The mean difference in width of minimum margin on intraoperative specimen ultrasonography compared with histopathological measurement of minimum margin was 2.1mm, while specimen mammography was 3.8mm (p = 0.03); indicating that intraoperative specimen ultrasonography was more accurate than specimen mammography in assessing the absolute width of the margin. In addition to this, the efficacy of intraoperative specimen ultrasonography and specimen mammography was examined with the use of histological measurements of margin as the gold standard with each margin considered separately (Table 5).

Table 5: Rates of achieving at least 10, 5 and 2 mm histologically tumour-free margins with at least 10-, 15- and 20-mm margins with intraoperative specimen ultrasonography, specimen mammography and combined imaging.

Imaging method	Margin achieved (%)		
	10 mm	5 mm	2 mm
Minimum margin (10mm)			
Intraoperative specimen US	81.1	92.2	96.7
Specimen mgm	81.1	91.1	95.6
Intraoperative specimen US + specimen mgm	84.4	92.2	96.7
Minimum margin (15mm)			
Intraoperative specimen US	85.1	94.0	98.5
Specimen mgm	82.9	88.6	94.3
Intraoperative specimen US + specimen mgm	87.1	94.0	98.5
Minimum margin (20mm)			
Intraoperative specimen US	93.3	95.6	100
Specimen mgm	86.0	91.2	96.5
Intraoperative specimen US + specimen mgm	93.3	95.6	100

Tan et al. (2006)

The overall positive predictive value of achieving 2mm, 5mm and 10mm margins were 96.7%, 92.2% and 81.1%, respectively (Table 5) when the minimum margin of intraoperative specimen US adopted is 10mm. The results also indicate that the wider the margin as measured on intraoperative specimen ultrasonography or mammography, the chance of achieving a histologically disease-free margin is

higher. Therefore, if the margin measured on intraoperative specimen ultrasound is at least twice the desired histological margin, this will achieve the desired result in >90% of cases (Tan et al. 2006).

Potential Cost Impact

Cost Analysis

Portable ultrasound machines utilised for IOUS-guided breast lesion localisation are generally available in most specialist hospitals and are therefore unlikely to be an additional cost.

The studies retrieved indicated that IOUS-guided breast lesion localisation does not add significantly to the operative time compared to wire-guided localisation (Moore et al. 2001, Rahusen et al. 2002). After the diagnostic work-up, Rahusen et al. (2002) stated that ultrasound-guided excision only adds a single ultrasound investigative procedure (€64.68) to the total cost of the procedure, while wire localisation adds the cost of wire localisation placement (€154.00) and specimen radiogram (€51.97) (Rahusen et al. 2002). Meanwhile, Moore et al. (2001) reported no significant difference in operating room expenses when comparing ultrasound guided localisation to standard excision of palpable tumours (ultrasound: US$2191 ± 752; standard excision: US$2438 ± 777).

Based on the evidence presented, patients who undergo IOUS are generally associated with higher negative margin rates and better margin status. Some researchers have stated that this is likely to translate to lower rates of second operations for reexcisions; but this has not been proven clinically. However, if this is proven to be correct, IOUS could potentially confer substantial cost-savings to the healthcare system. Moore et al. (2001) reported that the average time for a second operation in patients who required reexcision was 75 ± 26 minutes; this generated an additional average cost of US$1788 ± 688 per case, which could be avoided if adequate margins were achieved in the initial operation.

There will also be additional costs if a radiologist is required in the operating theatre to perform the ultrasonography. Therefore, the cost of training a breast surgeon to the point where he/she is comfortable and experienced with the use of IOUS should be considered.

Ethical Considerations

Informed Consent

Patients who choose to undergo IOUS-guided excision of breast lesions should be made aware of the surgeon's experience with this procedure. If the surgeon is not familiar with the use of ultrasound, the presence of a radiologist should be mandatory. In addition, patients should be informed that IOUS is not the current gold-standard practice for breast lesion localisation and the risks of this procedure should be outlined clearly.

Access Issues

As breast surgery should be conducted in specialist medical centres under trained clinicians, it is likely that IOUS-guided excision of breast lesions will be confined to major cities.

Training and Accreditation

Training

Ultrasonic localisation of breast lesions requires detailed knowledge of anatomy, physiological changes and benign/malignant pathology. The accuracy and confidence of interpretation requires experience, therefore breast surgeons are required to familiarise themselves with the use of ultrasonography and be guided by a radiologist intraoperatively until adequate training has been attained.

Clinical Guidelines

At the time of writing, guidelines for the use of IOUS for breast lesion localisation and excision in Australia and New Zealand have not been produced. If this procedure is proven to be significantly better compared to wire-guided localisation, new guidelines will have to be developed.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In

many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of 'Intraoperative ultrasound for breast lesion localisation during breast conserving surgery', its present and potential use in the Australian public health system, and future implications for the use of this technology.

Search Strategy used for the Report

The sources utilised in this assessment are listed in Table 6. The medical literature was searched with the search terms outlined in Table 10 to identify relevant studies up to January 2007 in English only. In addition to this, major international health technology assessment databases and clinical trial registers were searched.

Table 6: Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University of Adelaide library
Australian Medical Index	University of Adelaide library
CINAHL	University of Adelaide library
Cochrane Library – including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Databese, the NHS Economic Evaluation Database	University of Adelaide library
Current Contents	University of Adelaide library
Embase	Personal subscription
Pre-Medline and Medline	University of Adelaide library
PyscINFO	Personal subscription
RACS electronic library	Personal subscription
Internet	

Blue Cross and Blue Shield Association's Technology Evaluation Center	http://www.bcbs.com/tec/
Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca
Current Controlled Trials metaRegister	http://www.controlled-trials.com/
EuroScan	http://www.euroscan.bham.ac.uk/
Health Technology Assessment International	http://www.htai.org/
International Network for agencies for Health Technology Assessment	http://www.inahta.org
Medicines and Healthcare products Regulatory Agency (UK)	http://www.mhra.gov.uk/
US Food and Drug Administration, Center for Devices and Radiological Health	http://www.fda.gov/cdrh/index.html
US Food and Drug Administration, Manufacturer and User Facility Device Experience Database	http://www.fda.gov/cdrh/maude.html
UK National Research Register	http://www.nrr.nhs.uk/
National Breast Cancer Centre	http://www.nbcc.org.au/

Table 7: Search terms utilised

Search terms
MeSH
Breast Neoplasms/radiography*, Breast Neoplasms/ultrasonography*, Ultrasonography, Mammary*
Text words
Intraoperative ultraso*, specimen ultraso*, ultraso* localization
Limits
English, Human

Availability and Level of Evidence

The medical literature (Table 6) was searched utilising the search terms outlined in Table 7 to identify relevant studies and reviews, until July 2007. In addition, major international health assessment databases were searched.

A total of two randomised controlled trial (Level II intervention evidence), seven comparative studies (Level III-2 intervention evidence) and five case series studies (Level IV intervention evidence) were retrieved for assessment in this report. Note that studies were included based on the quality of evidence, i.e. randomised controlled trials and comparative studies were preferred over case series studies; however several case series studies were hand-picked for inclusion within the 'Safety' section due to the lack of higher level evidence. The profiles of the included case series studies are summarised in Appendix B.

Sources of Further Information

A search of the UK National Research Register and the Current Controlled Trials metaRegister revealed no ongoing trials on the use of IOUS for breast cancer surgery.

However, readers should note that a 3-dimensional ultrasound imaging navigation system has been developed in Japan. The system consists of a workstation, a 10MHz linear probe (Aloka SSD-5500), a small video camera (SUN camera II) and a 3-D locating sensor (Polaris System). A preliminary study has been conducted in 40 patients with primary breast cancer in order to determine the precision of this system intraoperatively (Inoue et al. 2005). Overall, the investigators noted a strong correlation between tumour size in the 3-D ultrasound images with pathological size (r = 0.898) and the difference in size between the images and pathological analysis was <1cm in 76.3% and <2cm in 94.6% of cases. Further studies on this new system are required before its effectiveness can be determined. At the time of writing, it is not known if this system offers significant benefits over conventional ultrasound machines in the context of lesion localisation and margin determination.

Conclusions

Until recently, the method of localising nonpalpable breast lesions for breast conserving surgery/lumpectomy have largely been limited to percutaneous mammographically-guided needle localisation procedures (e.g. NLBB). However, despite the fact that wire-guided excision of lesions is the current gold-standard of lesion localisation, the procedure has several persistent problems. Adequate resection of breast lesions, especially non-palpable lesions, is highly dependant on the accurate placement of the wire; however, studies have shown that the miss rates of wire-guided procedures vary from 0% to 22% (Klimberg 2003). Researchers have also highlighted the difficulty faced by breast surgeons when utilising wire-guided localisation, particularly the fact that the surgeon is expected to accurately excise the malignant lesion with adequate margins within a 3-dimensional space with the aid of a 2-dimensional localisation technique. The miss rates of wire-guided excision may be a result of wire or clip migration, with one study demonstrating median clip migration of 1cm from the target lesion (Kass et al. 2002). The potential for wire/clip migration or displacement is further exacerbated by the fact that the patient has to be transferred from the radiology department to the operating theatre. In addition to this, approximately 20% of patients experience vasovagal reactions when subjected to preoperative wire localisation (Klimberg 2003).

In view of these issues, IOUS has been proposed as a potential alternative to wire-guided localisation. It has several desirable traits that address some of the shortfalls related wire-guided localisation: 1) IOUS does not require the patient to

undergo uncomfortable preoperative wire insertion, therefore reducing patient anxiety; and 2) IOUS enables real-time visualisation of the lesion, and its accuracy if not subject to the placement of wires/clips which are prone to displacement and migration. Nevertheless, it is important to realise that IOUS is not without risks. Studies have demonstrated that ultrasound is only capable of visualising approximately 40% to 60% of mammographically-detected lesions (Potterton et al. 1994, Kaufman et al. 2002), which markedly hinders its applicability as an intraoperative localisation technique in a large proportion of lesions. Meanwhile, breast surgeons who are not experienced with the use of ultrasound will require guidance from a radiologist during the procedure as a precautionary step to prevent inaccuracy and misinterpretation of ultrasound images.

Randomised controlled trials utilising IOUS for excision of breast lesions have demonstrated that it is superior to wire-guided localisation (non palpable lesions) and standard excision (palpable lesions) in terms of achieving negative margins (Moore et al. 2001, Rahusen et al. 2002). This is further supported by non-randomised comparative studies, where 81% to 93% of patients who underwent IOUS-guided excision achieved negative margins compared to 40% to 82% of patients who underwent preoperative wire-guided localisation (Bennett et al. 2005, Buman and Clark 2005, Rahusen et al. 1999, Snider et al. 1999). In addition to this, IOUS localisation is also associated with equal (Rahusen et al. 2002, Thompson et al. 2007) or lower excision volumes (Snider et al. 1999, Moore et al. 2001, Rahman et al. 2007) while attaining superior margin status compared to wire-guided localisation (Moore et al. 2001, Rahusen et al. 2002, Bennett et al. 2005, Rahusen et al. 1999, Thompson et al. 2007, Rahman et al. 2007). It is interesting to note that IOUS appears to be more beneficial in patients with dense breast parenchyma (Moore et al. 2001)

In an effort to extend the applicability of IOUS-guided localisation, researchers have developed a novel method of visualising lesions that are otherwise not visible with ultrasound. Smith et al. (2001) proposed that iatrogenically induced haematomas within the target lesion will enable the use of IOUS in lesions that are only visible with MRI. Thompson et al. (2007) and Rahman et al. (2007) extended this principle by utilising ultrasound-visible haematomas caused by preoperative biopsy techniques (e.g. VABB) as a physiological surrogate for localising non-ultrasound-visible lesions intraoperatively. Both studies presented encouraging results, with IOUS attaining better negative margin rates (Thompson et al. 2007) and margin clearance (Rahman et al. 2007) while maintaining similar (Thompson et al. 2007) or lower (Rahman et al. 2007) resection volumes compared to wire-guided localisation.

When ultrasound was utilised for ex vivo specimen analysis to ensure adequate margins, investigators noted that specimen ultrasonography is less likely to overestimate the margin than specimen mammography (59.9% vs. 66.7%); further consolidating the claim that it is a more accurate technique of margin

determination. An interesting outcome of the analysis by Tan et al. (2006) is that if the margin measured with intraoperative specimen ultrasound is at least twice the desired histological margin, the desired result will be achieved in >90% of cases.

Overall, most of the included studies reported that the use of IOUS localisation results in better negative margin rates (Moore et al. 2001, Rahusen et al. 2002, Bennett et al. 2005, Buman and Clark 2005, Rahusen et al. 1999, Thompson et al. 2007, Rahman et al. 2007) and is associated with lower excision weight/volume compared to wire-guided excision or standard excision (Moore et al. 2001, Snider et al. 1999, Rahman et al. 2007). One study did not observe better margin clearance with IOUS localisation (Snider et al. 1999); nevertheless the procedure was still associated with lower resection weight/volume. The application of haematoma-guided ultrasound excision has demonstrated encouraging results as well (Thompson et al. 2007, Rahman et al. 2007), and introduces a novel technique of visualising non-ultrasound-visible tumours without the need for wire or clip insertion. There is some concern that the extra manipulations with the use of IOUS may result in higher would infection rates, this issue should be carefully monitored due to the paucity of evidence (only one study reported that wound infection rates were not elevated with IOUS, Buman and Clark 2005).

The evidence available provides considerable support for the use of IOUS-guided localisation of nonpalpable breast lesions. It appears to be an attractive alternative to preoperative wire-guided localisation, and addresses many of the inherent shortfalls of wire localisation. However, it is important to caution the fact that breast surgeons should receive adequate training before utilising this procedure. Otherwise, the presence of a radiologist in the operating theatre is highly recommended; at least until the surgeon acquires adequate experience and confidence with the use of ultrasound.

Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention [§]	Diagnosis [**]	Prognosis	Aetiology [†††]	Screening
I [*]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among consecutive patients with a defined clinical presentation [††]	A prospective cohort study [***]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among non-consecutive patients with a defined clinical presentation [††]	All or none [§§§]	All or none [§§§]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial [†] Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study [‡] Interrupted time series without a parallel control group	Diagnostic case-control study [††]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) [‡‡]	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*).*

† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C).

‡ Comparing single arm studies ie. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au .

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

†† Well-designed population based case-control studies (eg population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

‡‡ Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; Lijmer et al 1999; Phillips et al 2001; Bandolier editorial 1999)

Appendix B: Profiles of studies

Study	Location	Study design	Study population	Outcomes assessed
Bennett IC, Greenslade J, Chiam H. (2005)	Brisbane, Australia	Level III-2 intervention evidence	Wire-guided: 43 patients Intraop US: 103 patients Nonpalpable lesions	Margin status, reexcision rate, margins of excision, specimen size.
Buman SJ and Clark DA. (2005)	New South Wales, Australia	Level III-2 intervention evidence	Wire-guided: 50 patients Intraop US: 112 patients Nonpalpable lesions	Margin status.
Harlow SP, Krag DN, Ames SE, Weaver DL. (1999)	Vermont, United States	Level IV intervention evidence	62 patients with biopsy-proved nonpalpable breast cancer	Margin status, distance of tumour from closest margin, reexcision rate.
Moore MM, Whitney LA, Cerilli L, Imbrie JZ, Bunch M, Simpson VB, Hanks JB. (2001)	Florida, United States	Level II intervention evidence	Standard excision: 24 patients Intraop US: 27 patients Palpable lesions, biopsy proven infiltrating ductal carcinoma	Margin status, nearest margin location, specimen volume and density, operating time, cost, cosmetic outcome.
Potterton AJ, Peakman DJ, Young JR. (1994)	Newcastle, United Kingdom	Level IV intervention evidence	Patient records and hard copy images of 79 screen-detected cancers measuring 10mm or less	Visibility of tumours with US.
Rahman RL, Iuanow W, Crawford S, Quinlan R. (2007)	Massachusetts, United States	Level III-2 intervention evidence	Wire-guided: 34 patients Haematoma-guided US: 29 patients	Median closest margin, median resection volume, median resection index, margin reexcision rate.
Rahusen FD, Bremers AJA, Fabry HFJ, can Amerongen T, Boom RPA, Meijer S. (2002)	Amsterdam, The Netherlands	Level II intervention evidence	Wire-guided: 22 patients Intraop US: 27 patients Nonpalpable cancer visible with mammography and ultrasound	Margin status, mean operating time, cost.
Rahusen FD, van Amerongen AHMT, van Diest PJ, Borgstein PJ, Bleichrodt RP, Meijer S. (1999)	Amsterdam, The Netherlands	Level III-2 intervention evidence	Wire-guided: 43 patients Intraop US: 19 patients Nonpalpable lesions	Margin status, lesion size.

			(15 had preoperative diagnosis of invasive malignancy)	
Smith LF, Henry-Tillman R, Harms S, Hronas T, Mancino AT, Westbrook KC, Korourian S, Jones MP, Klimberg VS. (2001b)	Arkansas, United States	Level IV intervention evidence	Hematoma-guided US: 19 patients	Localisation rate
Snider HC and Morrison DG. (1999)	Alabama, United States	Level III-2 intervention evidence	Wire-guided: 22 patients Intraop US: 29 patients Nonpalpable lesions	Margin status.
Tan KY, Tan SM, Chiang SH, Tan A, Chong CK, Tay KH. (2006)	Singapore	Level III-2 intervention evidence	Margin status of 25 patients determined used intraop specimen US and specimen mammography	Accuracy of intraop specimen US compared to specimen mammography, efficacy compared to histological measurements.
Thomson M, Henry-Tillman R, Matgulies A, Thostenson J, Bryant-Smith G, Fincher R, Korourian S, Klimberg VS. (2007)	Arkansas, United States	Level III-2 intervention evidence	NLBB: 63 patients Hematoma-guided US: 58 patients	Margin status, specimen volume, specimen weight, margin reexcision rate.
Vujovic P, Gianduzzo T, Archibald C, Bennett I. (2002)	Brisbane, Australia	Level III-2 intervention evidence	Specimen mammography: 33 patients Specimen US: 20 patients	Lesion size, efficacy of visualising lesion.
Whitehouse PA, Baber Y, Brown G, Moskovic E, King DM, Gui GPH. (2001)	London, United Kingdom	Level IV intervention evidence	302 patients with symptomatic breast cancer	Accuracy of US compared to histology, accuracy of US scans by surgeons.

Appendix C: HTA Internet Sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
  http://www.med.monash.edu.au/healthservices/cce/evidence/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit
  http://www.oeaw.ac.at/ita/welcome.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
  http://www.cadth.ca/index.php/en/

- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI)
  http://www.dsi.dk/engelsk.html

FINLAND

- Finnish Office for Health Technology Assessment (FINOHTA)
  http://finohta.stakes.fi/FI/index.htm

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)
  http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) /
  HTA
  http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad
  http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA)
  http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM)
  http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III" / Health Technology Assessment Agency (AETS)
  http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp

- Catalan Agency for Health Technology Assessment (CAHTA)
  http://www.aatrm.net/html/en/dir394/index.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU)
  http://www.sbu.se/www/index.asp

- Center for Medical Health Technology Assessment
  http://www.cmt.liu.se/

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)

http://www.snhta.ch/

UNITED KINGDOM

- NHS Quality Improvement Scotland

  http://www.nhshealthquality.org

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for health Technology Assessment (NCCHTA)

  http://www.hta.nhsweb.nhs.uk/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD)

  http://www.your.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE)

  http://www.nice.org.uk/

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)

  http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry

  http://www.tufts-nemc.org/cearegistry/index.html

- U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (TEC)

  http://www.bcbs.com/tec/index.html

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