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Horizon Scanning Technology Prioritising Summary Update

Breast cancer diagnosis using ultrasound elasticity imaging

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UPDATE PRIORITISING SUMMARY 2008

REGISTER ID: **000339**

NAME OF TECHNOLOGY: **BREAST CANCER DIAGNOSIS USING ULTRASOUND ELASTICITY IMAGING**

PURPOSE AND TARGET GROUP: **BREAST CANCER**

2008 EFFECTIVENESS AND SAFETY ISSUES

Since the initial prioritising summary was produced, five studies have been identified by this update, investigating the value of ultrasound elasticity imaging (USEI) in the diagnosis of breast cancer.

Tan et al (2008) conducted a prospective study to evaluate the diagnostic utility of real-time USEI and B mode ultrasound (US) in differentiating breast lesions. A total of 415 consecutive women with 550 breast lesions diagnosed by B mode US were assessed with USEI. The B mode images were categorised according to Breast Imaging Reporting and Data System (BI-RADS) lexicon of the American College of Radiology (American College of Radiology 2003). BI-RADS categories 2 and 3 are classified as benign lesions; while categories 4 and 5 are malignant lesions. USEI was scored in line with elasticity as follows: score 1: even strain over the entire low echo area; score 2: strain over most of the low echo area; score 3: strain at the periphery, the low echo area spared; score 4: no strain over the entire low echo area; and score 5: no strain over the entire low echo area or surrounding area (Itoh et al 2006).

Of the 550 breast lesions, 119 were breast cancers confirmed by fine needle aspiration cytology (FNAC), core biopsy, or excision biopsy; and 431 were benign. The histological results were used as the reference standard. There was a good correlation between elasticity scores and histological results, with the elasticity scores lowest (median score: 2) in benign lesions and highest (median score: 5) in cancers. The percentage of lesions with an elasticity score of 1 or 2 that were benign was 98.6 (95% CI: 96.8-99.4). Around 83 per cent of lesions with a score of 4 or 5 were malignant (95% CI: 74.0%-88.9%). Using a threshold of 3 for USEI[1], the overall accuracy for USEI was 93.8 per cent, with a sensitivity of 78.0 per cent, and a specificity of 98.5 per cent. There was no significant difference in either sensitivity or specificity for USEI between palpable and non-palpable lesions (77.8% vs. 78.2% and 98.6% vs. 98.3%). Both the sensitivity (86.6%) and the specificity (98.8%) of B mode US were higher than those of USEI. There also existed a good correlation between BI-RADS category and elasticity score: lesions classified as falling into BI-RADS categories 2 and 3 had lower overall median elasticity scores than those of categories 4 and 5.

[1] A threshold of 3 can be interpreted as being negative for cancer if the score is 3 or below and as positive if the score is 4 or 5.

In a 2007 study, the effectiveness of differentiating breast malignancies from benign lesions was compared using USEI, mammography, and B mode US (Zhi et al 2007). The diagnostic results from USEI were scored according to the system proposed by Itoh et al as described above. Histological results from FNACs, core biopsies or excision biopsies, which were performed after imaging examinations, were used as the reference standard. Of a total of 296 lesions, 87 were histologically confirmed malignancies; the other 209 were benign lesions. The diagnostic results of USEI, mammography, and B mode US are summarised in Table 1. Of the three diagnostic modalities, USEI had the highest specificity (95.7%, correctly identifying those who *do not* have the disease), a good positive predictive value (PPV) (87.1%), and lowest false-positive rate (4.3%). The diagnostic accuracy for USEI (88.2%) was significantly higher than that for B mode US. Mammography had higher specificity (87.1%), accuracy (82.7%), and PPV (70.0%) than B mode US. There were no significant differences in sensitivity, negative predictive value (NPV), or false negative rates among the three diagnostic imaging examinations. A joint use of USEI and B mode US yielded higher sensitivity, (89.7%), higher accuracy (93.9%), and lower false negative rate (9.2%) than any of the three stand-alone examinations. Although the 95.5 per cent specificity and the 89.7 per cent PPV for USEI+B mode US were not significantly different from those for USEI alone, they were significantly higher than the specificities and PPVs for mammography and B mode US alone. The authors concluded that USEI was superior to US or mammography alone and that USEI in combination with US may be a promising technique for evaluating breast lesions and avoiding unnecessary biopsies (level II diagnostic evidence).

Table 1 Diagnostic results of USEI, mammography, and B mode US

	Sensitivity (n)	Specificity (n)	Accuracy (n)	PPV (n)	NPV (n)
USEI	70.1 (61/87)	95.7% (200/209)[2,3]	88.2% (261/296)[3]	87.1% (61/70)[2,3]	88.5% (200/226)
Mammography	72.4 (63/87)	87.1% (182/209)[3]	82.7% (245/296)[3]	70.0% (63/90) [3]	88.3% (182/206)
B mode US	71.2 (62/87)	73.2% (153/209)	72.6% (215/296)	52.5% (62/118)	86.0% (153/178)
USEI+B mode US	89.7 (78/87)[1,2,3]	95.7% (200/209)[2,3]	93.9% (278/296)[1,2,3]	89.7% (78/87)[2,3]	95.7% (200/209)[3]

1: $p<0.05$ versus USEI, 2: $p<0.05$ versus mammography, 3: $p<0.05$ versus B mode US

There were two studies investigating the value of USEI in diagnosing *non-palpable* breast lesions. Scaperrotta et al (2008) carried out a prospective study comparing the diagnostic performances of USEI and B mode US for the differentiation of 293 non-palpable breast lesions with BI-RADS categories 3-5. Of the 293 lesions, 110 were biopsy-confirmed malignancies; the remaining 183 lesions were benign. Using a threshold of 3 for both USEI and US, US was superior to USEI in both sensitivity (95.4%vs 80%) and specificity (87.4% vs 80.9%), suggesting USEI is an inferior diagnostic examination to US in differentiating non-palpable malignancies from benign breast lesions. This study also indicated that a combination of USEI and US did not offer a substantial improvement over US alone in the diagnostic setting, with an area under the receiver operating characteristic curve (AUC-ROC) of 0.925 for

USEI+US and 0.926 for US alone (level III-1 diagnostic evidence). In the second study, Cho et al (2008) reported that although the AUC-ROC for real-time USEI was slightly higher than that for US (0.916 vs. 0.901), the difference was not significant (p=0.808) (level III-2 diagnostic evidence).

Booi and colleagues evaluated the use of differential correlation coefficients (DCCs)[1], obtained from 2-dimension breast elastography, in distinguishing non-simple cysts from solid breast masses in a small group of 18 patients (Booi et al 2007; Booi, 2008). It was observed that the DCCs for non-simple cysts (13%-36%) were significantly higher than those for solid breast lesions. The results indicated that USEI might improve the diagnosis of non-simple cysts by showing lower correlation coefficient values in cysts than those in surrounding tissues in 2-dimension elastography (level III-2 diagnostic evidence).

2008 Cost Impact

No cost information was found during the preparation of this update.

2008 Summary of findings:

Most studies identified by this update demonstrated that USEI is not a superior imaging examination to conventional US in the diagnosis of breast cancers. In addition, there is conflicting evidence on the diagnostic value of using a combination of USEI and conventional US.

2008 HealthPACT Action:

HealthPACT noted that although elastography appears to be a viable imaging tool for liver fibrosis, the use of elastography for breast imaging is limited. Therefore HealthPACT has recommended that further assessment of this technology is no longer warranted.

2008 References:

American College of Radiology (2003). *Breast imaging reporting and data system (BI-RADS), Ultrasound*, ACR, Reston, VA. Available at: http://www.acr.org (accessed on 15 September 2008).

Booi, R. C., Carson, P. L., et al. (2007). 'Diagnosing Cysts with correlation coefficient images from 2-dimensional freehand elastography'. *J Ultrasound Med*, 26 (9)**,** 1201-1207.

Booi, R. C., Carson, P. L., et al. (2008). 'Characterization of cysts using differential correlation coefficient values from two dimensional breast elastography: preliminary study'. *Ultrasound in Medicine and Biology*, 34 (1)**,** 12-21.

Cho, N., Moon, W. K., et al. (2008). 'Nonpalpable breast masses: evaluation by US elastography'. *Korean J Radiol*, 9 (2)**,** 111-8.

[1] Differential correlation coefficient is defined as the difference between the correlation coefficient of a breast lesion and the correlation coefficient of surrounding tissues.

Itoh, A., Ueno, E., et al. (2006). 'Breast disease: clinical application of US elastography for diagnosis '. *Radiology*, 239 (2)**,** 341-350.

Scaperrotta, G., Ferranti, C., et al. (2008). 'Role of sonoelastography in non-palpable breast lesions'. *Eur Radiol*.

Tan, S. M., Teh, H. S., et al. (2008). 'Improving B mode ultrasound evaluation of breast lesions with real-time ultrasound elastography-A clinical approach'. *Breast*, 17 (3)**,** 252-7.

Zhi, H., Ou, B., et al. (2007). 'Comparison of ultrasound elastography, mammography, and sonography in the diagnosis of solid breast lesions'. *J Ultrasound Med*, 26 (6)**,** 807-15.

LIST OF STUDIES INCLUDED

Total number of studies	
Level II diagnostic evidence	2
Level III-1 diagnostic evidence	1
Level III-2 diagnostic evidence	2

PRIORITISING SUMMARY 2007

REGISTER ID: **000339**

NAME OF TECHNOLOGY: **BREAST CANCER DIAGNOSIS USING ULTRASOUND ELASTICITY IMAGING**

PURPOSE AND TARGET GROUP: **BREAST CANCER**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☒	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☒	No	
☐	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
USA	✓		
Australia	✓		
Europe	✓		

IMPACT SUMMARY:

This prioritising summary investigates the emerging use of ultrasound elasticity imaging (USEI) for the diagnosis of breast cancer. This service could be provided by clinics and hospitals, which currently have the facilities to perform ultrasound (US) breast examinations. Siemens Medical Solutions markets the eSie Touch™ elasticity imaging system for select models in its US system range. Hitachi Medical Systems GmbH offers USEI capability in its Hitachi EUB-8500 model.**BACKGROUND**

X-ray mammography is widely used in the diagnosis of breast cancer, and is safe and effective, many lesions found using this technique are of an indeterminate nature, and thus require biopsy for definitive status determination. The fact that the majority of biopsies are performed on what eventuate to be benign lesions, means that many unnecessary and costly procedures are performed on healthy women (Sehgal et al 2006).

Ultrasound (US) is used as an adjunct to X-ray mammography and has several useful advantages including: the ability to be used for women with dense breast tissue, guiding interventions such as biopsy, and in women for whom exposure to X-ray radiation is contraindicated. US is also useful to determine whether a lesion is malignant or benign (Sehgal et al 2006).

USEI is a modification of standard US to incorporate tissue compression and elasticity measurements to the scan result. Data are collected using the US device both before and after tissue compression. The manner in which the various components of the tissue respond to compression results in slightly different US echogenicity, which can be visualised in real time in a similar way to conventional US. Malignant masses are stiffer and therefore deform less than benign masses. Malignant masses appear darker than benign masses on the elasticity image. In addition, benign masses have better delineated boundaries between the mass and the surrounding tissue. Malignant masses are believed to have a less defined boundary due to the infiltration of the malignancy into the surrounding tissue. These properties are exploited in USEI. When the breast tissue is subjected to compression, benign masses appear to remain the same size due to their definite boundaries, while malignant masses appear larger as the indefinite boundaries are enhanced visually under compression increasing the apparent size of the mass. Thus this technique allows the US device to distinguish between benign and malignant masses (Sehgal et al 2006).

CLINICAL NEED AND BURDEN OF DISEASE

The age-standardised incidence of breast cancer has steadily been rising in Australia reaching 117 per 100,000 women in 2002, which is 80 per cent above the 1983 level. The overall numbers of breast cancer diagnoses is also rising, estimated to be 13,261 in 2006 and predicted to rise to 14,800 in 2011. Despite this, the age-standardised death-rate has decreased from 31.0 deaths per 100,000 women in 1990 to 23.4 per 100,000 in 2004. The total number of female deaths due to breast cancer in 2004 was 2,641. Additionally between 2000-04 there were 601 cases where breast cancer was an associated but not the underlying, cause of death (AIHW & NBCC 2006).

According to Medicare data, which records the use of diagnostic rather than screening mammography, there were 337,918 claims for this procedure in the 2004-05 period. Conventional US may be used as a breast cancer diagnostic tool in young or breastfeeding women, as an adjunct to mammography in women with dense breast tissue, for image guided intervention, and for pre-operative assessment of women with breast cancer. Currently the specificity of mammography and US, with regard to determining whether a lesion is benign or malignant, is quite low. This may result in suspect lesions being biopsied to determine their status. Up to 80 per cent of such lesions are benign and therefore biopsy was unnecessary (Mitka 2007). There is therefore a need to reduce the number of benign lesions biopsied, both in terms of reducing patient risk and for economic savings.

DIFFUSION

Conventional US is widely available in Australia in clinics and in public and private hospitals. The uptake of USEI would depend on the number of manufacturers offering the technology to current users. Currently Siemens Medical Solutions market an US system capable of imaging using USEI. It is unclear whether current users of Siemens models could upgrade to USEI on their conventional US systems or would have to purchase a new system to obtain the capability. Hitachi Medical Systems GmbH markets the Hitachi EUB-8500 which was used in Thomas et al (2006a).

COMPARATORS

X-ray mammography followed by biopsy is the gold standard for breast cancer diagnosis in Australia. Other comparable techniques used for diagnosing breast cancer are conventional US and magnetic resonance imaging.

The current standard, X-ray mammography, lacks specificity due to its qualitative nature. Many variations can occur in the interpretation of mammograms due to operator variations, image quality, patient factors including the presence of implants or high density breast tissue. Hence the final categorisation of the lesion must be performed by biopsy (Sehgal et al 2006).

SAFETY AND EFFECTIVENESS ISSUES

Several issues have been addressed in the patient studies identified for this summary, including the effectiveness of USEI versus X-ray mammography and conventional US; computer aided analysis of USEI; and inter-operator variability of USEI.

The ability of USEI to distinguish between benign and malignant lesions was reported in a prospective study of 101 consecutive patients referred for biopsy (Regner et al 2006)(level II diagnostic evidence). The lesions were originally detected by conventional US. From this patient group 23 women were excluded either due to indeterminate biopsy pathology, or for technical or assessor training reasons. The majority of lesions were biopsied on the day of the USEI analysis. The USEI assessors were blinded to the results of any patients who had biopsies prior to the USEI scan. The analysis in this study was not performed in real-time. The conventional US and USEI data were collected and further processed off-line to obtain the final US and USEI images. Five assessors were used to analyse the resulting images. The best parameters to distinguish benign lesions from malignant lesions were found to be area ratio or width ratio, that is, either the width or area of the lesion in the US image compared with the width or area of the lesion in the USEI image. The area and width ratios were not significantly different in their ability to distinguish benign or malignant lesions. Overall the sensitivity and specificity of USEI was 96 and 24 per cent, respectively, for the area ratio; and 96 and 21 per cent, respectively, for the width ratio. Using the area ratio parameter, one assessor obtained a sensitivity of 96 per cent and a specificity of 61 per cent. Better performance was

observed when the assessors were able to spend more time on the analysis of the images. Distinguishing benign from malignant lesions was performed poorly when the assessors were in a busy clinical setting. Combined parameters did not have any additive effect to the ability to correctly categorise lesions.

A study using continuous processing of US images to give USEI data showed that the method yielded a sensitivity and specificity of 85 (34/40) and 88 per cent (53/60), respectively (Moon et al 2005)(level III-2 diagnostic evidence). The patient group consisted of 86 consecutive patients who had a total of 100 solid breast tumours. Of these, 60 were benign and 40 were malignant by pathology. The following four parameters were used to analyse the lesions; contour difference, shift distance, area difference; and one shape parameter, solidity. All four of these variables were found to be significantly different for benign and malignant lesions. The continuous method uses several frames obtained during a compression of the breast tissue with the US probe. This was found to be more accurate than the standard comparison of a non-compressed US image to a single image obtained by US during compression. In contrast to the previous study the data analysis was computer aided.

USEI, US and X-ray mammography were compared in a 2007 study using fifty patients with either benign (n=25) or malignant (n=25) lesions (Thomas et al 2007) (level III-2 diagnostic evidence). The analysis of the USEI was performed offline using either maximum strain factor, or area quotient, determined by comparing the US and USEI data. Both these factors were found to be significantly different in benign and malignant lesions, allowing them to be discriminated (Table 1). USEI was as sensitive (96%), and was substantially more specific (80% vs 68%) than US alone. The use of combined US and X-ray mammography greatly increased the sensitivity (ie the ability to correctly identify those who have the disease), but resulted in a much reduced specificity (ie the ability to correctly identify those who do not have the disease).

Table 2 Sensitivity and specificity for detection of malignant lesions

	Sensitivity	Specificity
US	96%	68%
US+ X-ray mammography	100%	40%
USEI	96%	80%

Adapted from (Thomas et al 2007)

Two studies identified used real-time analysis of the USEI data in contrast to the previous studies which used offline analysis performed after the scan was complete. Real-time analysis, if equal or better than offline processing, would be an improvement to the USEI technique. In the initial study histology was the reference standard against which USEI was compared and two independent assessors were used to evaluate the lesions (Thomas et al 2006a)(level III-2 diagnostic evidence). Of 108 patients with lesions that were of known status by cytology or histology, 59 had

benign and 49 had malignant lesions. The results of US and USEI compared to the reference standard are presented in Table 2. Specificity of USEI was significantly increased when compared to US alone. One noted weakness in this study was that USEI was not able to evaluate lesions deeper than 1cm. In addition, markedly reducing the sensitivity may be unacceptable.

Table 3 Comparison of US and USEI vs the reference standard, histology (n=108)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
US	91.8	78	77.6	92
USEI observer 1	77.6	91.5	88.4	83.1
USEI observer 2	79.6	84.7	81.3	83.3

Adapted from (Thomas et al 2006a)

In a subsequent study involving 300 patients, the ability of USEI to discriminate between malignant and benign lesions was compared to US and X-ray mammography (Thomas et al 2006b) (level III-2 diagnostic evidence). The subject group consisted of 168 patients with benign and 132 patients with malignant lesions. The results of this study indicate that USEI only slightly increases the specificity of detecting malignant breast lesions at the expense of a small decrease in sensitivity (Table 3).

Table 4 Comparison of the discriminative ability of three diagnostic tests on lesions of known status

	Sensitivity (%)	Specificity (%)
US	94	83
X-ray mammography	87	85
USEI	82	87

Adapted from (Thomas et al 2006b)

No safety issues were addressed in the studies analysed in the preparation of this summary.

Most studies demonstrate that USEI gives an increase in specificity compared to US alone, at the expense of a reduction in sensitivity, although there is a wide disparity in the results of studies. The increase in specificity when using USEI is important due the fact that the main weakness of US is its false positive rate, leading to unnecessary biopsies. There appears to be progress from the earlier to the more recent studies which incorporate real time processing and display of the USEI data. In addition, different research groups have used different lesion parameters, cut offs and reference standards to establish the status of a lesion. Further improvements in USEI may be expected as the technology matures and standards and guidelines for which parameters and cut offs are used to determine whether a lesion is malignant or benign.

COST IMPACT

No cost information was found during the preparation of this summary.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

An international, multicentre trial is currently underway to assess USEI.

SUMMARY OF FINDINGS

When diagnosing whether a lesion is malignant or benign the majority of studies reported an increase in the specificity and a decrease in sensitivity compared to US or X-ray. As yet there is no consensus as to which lesion parameters and cut offs are appropriate to use. Recently, real-time USEI has become available and will likely be the method of choice. The increased specificity of USEI may result in a reduced number of unnecessary biopsies being performed, which would benefit the patient and also save on health care costs. However the trade-off with reduced sensitivity is unlikely to be acceptable.

HEALTHPACT ACTION:

The field of USEI is rapidly evolving and shows promise in the deliverance of patient and economic benefits, however, the reduced sensitivity of USEI is of concern. The loss of sensitivity may be addressed by combining both mammography and USEI. In addition, this technology is diffusing rapidly with some centres in Australia currently utilising this technology. Therefore HealthPACT have recommended that this technology be monitored for further information in 12-months time.

NUMBER OF INCLUDED STUDIES

Total number of studies	
Level II diagnostic evidence	1
Level III-2 diagnostic evidence	4

REFERENCES:

AIHW & NBCC (2006). *Breast cancer in Australia: an overview, 2006,* Australian Institute of Health and Welfare & National Breast Cancer Centre 2006.http://www.nbcc.org.au/bestpractice/resources/BCR_breastcancerinaustra.pdf

Mitka, M. (2007). 'New ultrasound "elasticity" technique may reduce need for breast biopsies', *Jama,* 297 (5), 455.

Moon, W. K., Chang, R. F. et al (2005). 'Solid breast masses: classification with computer-aided analysis of continuous US images obtained with probe compression', *Radiology,* 236 (2), 458-464.

Regner, D. M., Hesley, G. K. et al (2006). 'Breast lesions: evaluation with US strain imaging--clinical experience of multiple observers', *Radiology,* 238 (2), 425-437.

Sehgal, C. M., Weinstein, S. P. et al (2006). 'A review of breast ultrasound', *J Mammary Gland Biol Neoplasia,* 11 (2), 113-123.

Thomas, A., Fischer, T. et al (2006a). 'Real-time elastography--an advanced method of ultrasound: First results in 108 patients with breast lesions', *Ultrasound Obstet Gynecol*, 28 (3), 335-340.

Thomas, A., Kummel, S. et al (2006b). 'Real-time sonoelastography performed in addition to B-mode ultrasound and mammography: improved differentiation of breast lesions?' *Acad Radiol*, 13 (12), 1496-1504.

Thomas, A., Warm, M. et al (2007). 'Tissue Doppler and strain imaging for evaluating tissue elasticity of breast lesions', *Acad Radiol*, 14 (5), 522-529.

SEARCH CRITERIA TO BE USED:

Breast Neoplasms/pathology/radiography/ ultrasonography
Elasticity
Female
Humans
Image Processing, Computer-Assisted
Mammography
Image Interpretation, Computer-Assisted