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Magnetic resonance spectroscopy for the diagnosis of suspected breast cancer malignancies

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PRIORITISING SUMMARY

REGISTER ID: **000225**

NAME OF TECHNOLOGY: **MAGNETIC RESONANCE SPECTROSCOPY**

PURPOSE AND TARGET GROUP: **DIAGNOSIS OF MALIGNANCY IN SUSPICIOUS LESIONS OF THE BREAST**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

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

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
Australia	✓		
United States	✓		

IMPACT SUMMARY:

This prioritising summary investigates the use of magnetic resonance spectroscopy (MRS) as an adjunct to magnetic resonance imaging (MRI) for the diagnosis of malignancy in suspicious lesions of the breast.

BACKGROUND

In Australia, X-ray mammography is the conventional imaging modality used in the early diagnosis of breast cancer. Free mammographic screening is offered on a biennial basis to all asymptomatic women aged 50 to 69 years as part of the BreastScreen Australia program. Although mammography is cost-effective, accurate and well accepted, the technique has decreased efficiency in women who have had breast surgery or silicone augmentation, or with dense breast tissue (Friedrich 1998). For these women, magnetic resonance imaging (MRI) may offer a more reliable method for diagnosing breast cancer. Other benefits of MRI include its safety (it does not use ionising radiation) and ability to define, where applicable, morphologic features of lesion architecture (Nunes et al 1997).

Following the discovery of a suspicious mass on an MRI scan of the breast, a patient may be required to undergo a biopsy in order to accurately determine whether the mass is benign or

malignant. A biopsy is an invasive procedure in which tissues and cells are removed and analysed. Using biopsy results as a gold standard, MRI has been reported to have excellent sensitivity (88 to 100%) and variable specificity (37 to 97 %) for detecting breast malignancy (see for example Kaiser & Zeitler 1989; Nunes et al 1999; Yen et al 2000). The positive predictive value of MRI (and also for mammography) is poor, however, meaning that a large percentage of lesions referred for biopsy are ultimately found to be benign. Given the financial, medical and emotional costs associated with biopsy referrals, any method to improve the positive predictive value of MRI in this regard is likely to improve both patient acceptability and the overall cost-effectiveness of the imaging technique (Bartella et al 2006).

Magnetic resonance spectroscopy (MRS) is an application of MRI that provides biochemical information about tissue metabolism. Unlike MRI, which detects the resonance spectra of water in tissues, MRS detects the resonance spectra of a variety of chemical compounds, thereby allowing for a description of *in situ* chemistry (Shah et al 2006). Historically MRS has been used in the detection and evaluation of brain cancer, but more recently has also been used to diagnose cancer in other regions of the body. Proton ^{1}H (hydrogen one) MRS is increasingly being studied as a potential adjunct to MRI in the classification of suspicious lesions of the breast. The diagnostic value of proton ^{1}H MRS is based on the detection of choline-containing compounds, which are markers of cancerous tissue (Negendank 1992). Studies have found that malignant lesions (and not benign lesions) contain choline-containing compounds, particularly phosphocholine, that resonate at a chemical shift of 3.2ppm (Roebuck et al 1998).

Recent evidence suggests that MRS, if incorporated into a standard MRI examination, may be effective in increasing the specificity and positive predictive value of lesion evaluation. For benign lesions where MRI is inconclusive, MRS may eliminate the need for biopsy by demonstrating the lack of a choline resonance at a chemical shift of 3.2ppm. The incorporation of MRS into a breast MRI examination takes less than 10 minutes (Cecil et al 2001), and therefore should be readily accepted by patients and radiologists if shown to be effective.

CLINICAL NEED AND BURDEN OF DISEASE

In estimating the clinical demand for MRS, it is necessary to first quantify the potential usage of MRI for the purpose of breast cancer diagnosis. In Australia, MRI may be used for a more definitive diagnosis of breast cancer following the discovery of a suspicious mass or lesion by X-ray mammography. In 2002-2003, more than 1.6 million Australian women aged between 50 and 69 years were screened as part of the BreastScreen Australia program. In total, 9.3 per cent of women attending their first round of breast screening and 4 per cent of women attending a subsequent round of screening were recalled for further testing based on suspicious or abnormal mammography results (AIHW, 2006).

MRI may also be useful as a diagnostic tool in women for whom X-ray mammography has reduced accuracy. In addition to women who have had breast surgery or silicone augmentation, MRI may be of particular use in women considered to be at a high age-adjusted risk of developing breast cancer (Liberman 2004; Morris et al 2003). These women tend to develop the disease at a significantly younger age and are usually pre-menopausal.

Due to their age, these women are likely to have high-density breast tissue, making them difficult to assess using conventional X-ray mammography. Women considered to be at high-risk of developing breast cancer include those with a familial or personal history of breast or ovarian cancer, or those with a demonstrated germ-line mutation in a breast-cancer associated gene such as BRCA1, BRCA2 or Tp53 (NHMRC 1999). The number of women considered to be at high-risk of developing breast cancer has been estimated to be less than one per cent of the total female population of Australia. Using a crude population estimate of 6.3 million females over the age of 25 years (ABS 2002), approximately 63,000 women could benefit from MRI assessment. Despite their higher risk, the majority of women likely to benefit from MRI assessment will not go on to develop breast cancer (NHMRC 1999). Given that MRS would only be used as an adjunct to MRI for the evaluation of malignancy in lesions found to be suspicious according to MRI, a relatively small percentage of the 63,000 high-risk women would likely benefit from additional MRS.

DIFFUSION

MRS can be performed on MRI equipment using specialised software packages. A number of software packages have been approved by the FDA for the evaluation of suspected tumours in the brain and the prostate, but none have been approved for the purpose of diagnosing breast cancer. In addition to regulatory approval, potential uptake of MRS for the evaluation of breast malignancy depends to a large degree on the availability of MRI equipment. MRI is available in a number of public and private hospitals in Australia; however the use of MRI for breast cancer diagnosis is not common. Further, at present, MRI for breast cancer diagnosis is not reimbursed through the MBS and is only regarded as a complementary imaging modality to conventional X-ray mammography and ultrasound.

COMPARATORS

The most relevant comparator for MRS as an adjunct to MRI is MRI alone. In Australia however, MRI for breast cancer diagnosis is not currently listed on the MBS. Mammography could be proposed as an alternative comparator; however X-ray mammography has reduced effectiveness in those women for which a program of MRS and MRI might be recommended (i.e. women with dense breast tissue).

EFFECTIVENESS AND SAFETY ISSUES

The use of MRS as an adjunct to MRI in the evaluation of breast lesions was first investigated by Cecil et al (2001). In the study (level III-1 diagnostic evidence), MRS was acquired as part of an MRI examination of 38 women, all who presented with a suspicious mass in the breast of 1cm in diameter or larger (as revealed by a palpable mass or abnormal mammographic finding). Using biopsy results as the gold standard, the authors found that blinded review of MRI results predicted tumour malignancy with a sensitivity and specificity of 95 and 86 per cent respectively. Blinded review of spectroscopy results alone was also found to be fairly accurate, with sensitivity and specificity reported to be 83 and 87 per cent respectively. The authors noted that if tubular adenomas, a well-known source of false positive readings on MRS, had been excluded by the MRI, the specificity and positive predictive value of MRS would have improved to 93 and 95 per cent respectively.

In a more recent study, Meisamy et al (2005) retrospectively investigated the diagnostic properties of MRS and MRI in 55 patients who had previously undergone biopsy (level III-2 diagnostic evidence). In the study, four radiologists were required to individually estimate the probability of breast malignancy based on MRI results, and make a hypothetical recommendation based on these results as to whether a patient should undergo confirmatory biopsy. The radiologists were then required to re-examine their decisions following the disclosure of MRS results. For all four radiologists, the addition of MRS to the breast examination resulted in higher sensitivity, specificity and accuracy (as indicated by the area under the ROC curve) regarding the malignancy of the lesion. Two of the four radiologists recorded significant improvements in sensitivity over the two conditions, while all four radiologists demonstrated significant improvements in diagnostic accuracy. The weighted mean sensitivity and specificity for the initial interpretations was 87 and 51 per cent respectively, whereas in the second interpretation, the weighted mean sensitivity and specificity improved to 94 and 57 per cent respectively.

In perhaps the most relevant study into the clinical utility of MRS, Bartella et al (2006) investigated the diagnostic performance of MRS and MRI in 56 patients with 57 distinct lesions (level III-2 diagnostic evidence). Of the 57 lesions examined in the study, 40 had been classified as suspicious by MRI and had been referred for further biopsy, while 17 of the lesions had already proven to be cancerous by biopsy. Using biopsy as a gold standard, 31 and 26 of the 57 lesions were found to be malignant and benign respectively. A choline peak was found in all 31 biopsy-proven malignant lesions (100 % sensitivity), while peaks were absent in 23 of 26 benign lesions (88% specificity). To determine the effect the introduction of MRS would have had on biopsy referrals, the authors investigated the 40 lesions initially classified as suspicious by MRI. In these lesions, the use of MRS as an adjunct to MRI would have significantly improved the positive predictive value of biopsy referrals from 35 to 82 per cent ($p < 0.01$). If biopsy had only been performed on those lesions with a choline peak, biopsy recommendations would have been spared in 23 of 40 lesions (58 %) and not a single malignant lesion would have been missed (i.e. a negative predictive value of 100%).

COST IMPACT

The cost impact of a program of breast MRS and MRI for the diagnosis of breast cancer is currently unknown. At this stage, MRS for breast cancer diagnosis has not received marketing approval from the TGA, and so the cost of the relevant software has not been established. It is also unclear whether the uptake of MRS technology for breast cancer diagnosis would require the purchase of additional MRI units. These additional costs would need to be compared to the cost savings associated with a reduced number of biopsy referrals.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

MRI and therefore MRS is contraindicated in patients with cardiac pacemakers, automatic cardiac defibrillators, intracranial ferromagnetic aneurysm clips, implanted neurostimulators or bone growth stimulators, intraocular ferromagnetic foreign bodies, cochlear implants, who are pregnant or have allergies to gadolinium (ICSI 2003).

CONCLUSION:

Proton MRS is a complementary technique to MRI capable of improving patient management by reducing the number of unnecessary biopsy referrals. Given appropriate infrastructure, the incorporation of MRS into a breast MRI examination could be achieved in less than 10 minutes. At present however, there is only limited evidence demonstrating the effectiveness of MRS for improving the diagnostic qualities of MRI breast examinations.

HEALTHPACT ACTION:

Although it is unclear how easily MRS could be incorporated into an MRI examination of the breast in Australia, the technology may offer benefits to a select group of patients. At present an MSAC report into the use of MRI for diagnosing breast cancer in high risk women is pending completion. It is recommended that MRS for breast cancer examination be monitored until the results of the MSAC assessment are finalised.

SOURCES OF FURTHER INFORMATION:

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Meisamy, S., Bolan, P. J. et al (2005). 'Adding in vivo quantitative 1H MR spectroscopy to improve diagnostic accuracy of breast MR imaging: preliminary results of observer performance study at 4.0 T', *Radiology,* 236 (2), 465-475.

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Nunes, L. W., Schnall, M. D. et al (1999). 'Correlation of lesion appearance and histologic findings for the nodes of a breast MR imaging interpretation model', *Radiographics,* 19 (1), 79-92.

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Roebuck, J. R., Cecil, K. M. et al (1998). 'Human breast lesions: characterization with proton MR spectroscopy', *Radiology,* 209 (1), 269-275.

Shah, N., Sattar, A. et al (2006). 'Magnetic resonance spectroscopy as an imaging tool for cancer: a review of the literature', *J Am Osteopath Assoc,* 106 (1), 23-27.
Yen, Y. F., Han, K. F. et al (2000). 'Dynamic breast MRI with spiral trajectories: 3D versus 2D', *J Magn Reson Imaging,* 11 (4), 351-359.

LIST OF STUDIES INCLUDED

Total number of studies	
Level III-1 Diagnostic evidence	1
Level III-2 Diagnostic evidence	2

SEARCH CRITERIA TO BE USED:

Breast Neoplasms/*diagnosis/pathology

Magnetic Resonance Imaging

Biopsy

Magnetic Resonance Spectroscopy/*diagnostic use/methods/statistics & numerical data