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MR and transient elastography for the non-invasive assessment of liver fibrosis

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PRIORITISING SUMMARY

REGISTER ID: **000228**

NAME OF TECHNOLOGY: **MAGNETIC RESONANCE AND TRANSIENT ELASTOGRAPHY**

PURPOSE AND TARGET GROUP: **NON-INVASIVE ASSESSMENT OF LIVER FIBROSIS IN PATIENTS AT RISK OF LIVER DISEASE**

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
United States	✓		
Europe	✓		
Japan	✓		

IMPACT SUMMARY:

Elastography is an emerging technique in which the elasticity or stiffness of soft tissue is measured. This prioritising summary investigates the application of elastography to the assessment of liver fibrosis.

BACKGROUND

Liver fibrosis refers to the accumulation of connective scar tissue in the liver. As opposed to a healthy liver in which the production and breakdown of scar tissue are in balance, a fibrotic liver is unable to decompose scar tissue at the same rate it is being produced (Highleyman & Franciscus 2004). As liver fibrosis progresses in severity, the liver gradually becomes stiffer and blood flow is reduced. Often this can lead to the development of cirrhosis, a condition in which liver transplantation is the only treatment option available for preventing death. Risk factors for liver fibrosis include viral-associated hepatitis (B and C), excessive alcohol consumption, autoimmune disease and metabolic disorders (Kawamoto et al 2006).

Tests for diagnosing and assessing the extent of liver fibrosis are particularly important to the treatment of the condition and the prevention of cirrhosis. Given the asymptomatic nature of

early stage fibrosis, diagnostic testing is usually reserved for individuals at a high risk of developing the condition (for example individuals with hepatitis C). Currently the 'gold standard' for diagnosing and grading liver fibrosis in these individuals is liver biopsy. Unfortunately, patient acceptability of liver biopsy is relatively low due to the invasive nature of the procedure and the possibility for developing potentially life-threatening complications (Bravo 2001). The performance of liver biopsy, in terms of accuracy and reproducibility, is also questionable due to sampling errors and the presence of inter- and intra-observer variability (Regev et al 2002). Due to its invasive nature, liver biopsy may not be acceptable when there is a need for repeated assessments of fibrosis over short periods of time. These shortcomings highlight the need for alternative non-invasive measures of liver fibrosis.

Elastography is an emerging technique capable of non-invasively assessing the extent of liver fibrosis. To date, two distinct techniques of elastography have been developed; transient elastography and magnetic resonance (MR) elastography. Transient elastography can be performed using the commercially available Fibroscan® device manufactured by Echosens (Paris). Briefly, the device emits a low-frequency vibration that induces an elastic shear wave in the liver tissue. Meanwhile a pulse-echo ultrasound is used to follow the propagation of the shear wave through the tissue and record its velocity. The speed of the shear wave is directly related to the degree of fibrosis in the liver. The harder or more fibrotic the tissue, the faster the shear wave propagates (Sandrin 2003). For each patient, the final measurement of fibrosis severity is typically obtained as the median value of several measurements (expressed in kilopascals).

Similar to transient elastography, MR elastography allows for the assessment of liver fibrosis through the measurement of liver elasticity. The technique involves measuring the wavelength of vibrations passing through the liver using MR imaging equipment (as opposed to ultrasound equipment). By pulsing the magnetic field of the MRI scanner in tune with the mechanical vibrations, snapshots of the mechanical waves are obtained (similar to a stroboscope). The snapshots are then processed to generate a quantitative image of tissue elasticity known as an elastogram (from which wavelengths can be measured). Although the frame rate of MR elastography is substantially slower than in transient elastography, the technique may offer superior sensitivity and resolution in the assessment of fibrosis (McCracken et al 2005).

CLINICAL NEED AND BURDEN OF DISEASE

The largest risk factor for liver fibrosis and cirrhosis, at least in absolute terms, is the hepatitis C virus. In 2004, it was estimated that 260,000 Australians were living with hepatitis C, including 195,000 cases of chronic infection. Of those with chronic hepatitis C, an estimated 153,000 had early stage liver disease, 33,000 had moderate liver disease, and 8,000 were living with hepatitis C related cirrhosis (DoHA 2006). It has been estimated that approximately 10 to 20 per cent of patients with chronic hepatitis C have cirrhosis at the time of their first clinical presentation, and as many as 30 per cent of those who do not have cirrhosis will develop the condition within 10 years (Niedarau 1998).

Progression from early stage liver fibrosis through to end stage cirrhosis does not occur at the same rate in all individuals with hepatitis C. Indeed, fibrosis may remain stable or even regress over time (Highleyman & Franciscus 2004). Several factors that affect the rate of liver

fibrosis and progression to cirrhosis have been identified. Fibrosis occurs more rapidly (and therefore the risk of cirrhosis is higher) in men than in women and in individuals who consume excessive amounts of alcohol. The risk of cirrhosis is also higher in older adults, particularly those over the age of 50 (Highleyman & Franciscus 2004). In 1998, cirrhosis of the liver was the underlying cause of 1,018 deaths and the contributing factor in a further 876 deaths. Death rates were higher among males than females, especially males between the ages of 55 and 79 years (AIHW 2000).

In 2004, 2,390 public hospital separations for chronic and acute viral hepatitis C were recorded in Australia, with an average length of stay of 1.5 days. During that same year, a total of 1,657 public hospital separations for unspecified cirrhosis were reported, with an average length of stay of 4.8 days (AIHW 2006).

DIFFUSION

The Fibroscan® is distributed in Europe by Echosens (Paris). At this stage however, the device has not been approved for use in the United States or Australia. It is unclear when the device will be available for purchase in Australia.

Magnetic resonance elastography is a relatively new technique that is still being trialled in early clinical studies. The technique has not been approved for use in the United States or Australia.

COMPARATORS

Liver biopsy is considered to be the gold standard of liver fibrosis assessment. The stage of fibrosis following histopathological analysis is usually quantified according to the METAVIR scoring system. Using the system, fibrosis is given a score between F0 and F4. F0 refers to no fibrosis; F1, mild fibrosis; F2, moderate fibrosis; F3, severe fibrosis; and F4, cirrhosis. The invasiveness and risk of complications associated with liver biopsy have led to poor patient and doctor acceptance of the technique. It is also a costly and painful procedure, and so its use in repeatedly assessing asymptomatic patients or monitoring the effectiveness of treatment programs is limited. In terms of accuracy, liver biopsy suffers from poor inter- and intra-observer reliability, and is prone to sampling error due to the small size of samples taken for histopathological assessment (Regev et al 2002).

EFFECTIVENESS AND SAFETY ISSUES

A number of studies have investigated the diagnostic properties of transient elastography in assessing the degree of liver fibrosis. In a recent study, Gomez-Dominguez et al (2006) assessed the performance of transient elastography (Fibroscan®) in 103 patients who had previously undergone liver biopsy in order to confirm suspected liver disease (level III-2 diagnostic evidence). The authors divided the patients into two groups according to their METAVIR scores. Patients with a METAVIR score of F1 or F2 formed a mild fibrosis group, while patients with a score of F3 or F4 formed a severe fibrosis group. The median elasticity value as measured by transient elastography was 7.4 ± 5.0 kPa in the mild fibrosis group and 16.4 ± 10.0 kPa in the severe fibrosis group ($p < 0.05$). The area under the receiver operating characteristic curve (AUC) for discriminating between these two fibrosis groups using transient elastography was calculated to be 0.72, with sensitivity and specificity values of 58

and 89 per cent respectively. When the authors reclassified the patients according to the presence of cirrhosis (i.e. F4 vs. F1, F2, F3), the sensitivity and specificity of elasticity values improved to 89 and 96 per cent respectively (AUC = 0.94). Although the sensitivity and specificity of transient elastography was not particularly high in the study, this could conceivably be a reflection of the inaccuracy of liver biopsy rather than a limitation of the technique.

In a similar study, Foucher et al (2006) assessed the diagnostic properties of transient elastography in 711 patients with chronic liver disease (level III-2 diagnostic evidence). Aetiologies of liver disease in the patient group included hepatitis B and C, non-alcoholic steatohepatitis and alcoholic related liver disease. In the study, liver biopsy was again employed as the gold standard of measurement (using the METAVIR scoring system). In discriminating between patients with mild or moderate fibrosis (F0, F1, F2) and patients with severe fibrosis or cirrhosis (F3, F4), transient elastography reported a sensitivity and specificity of 65 and 95 per cent respectively (AUC = 0.90). When patients were reclassified according to a liver biopsy diagnosis of cirrhosis (F4), the sensitivity and specificity of transient elastography improved to 77 and 97 per cent respectively (AUC = 0.96).

To date, only a handful of small-scale studies have investigated the performance of MR elastography in the assessment of liver fibrosis. Rouvière et al (2006) compared elasticity measurements using MR elastography to liver biopsy results in a group of 12 healthy volunteers and 12 patients with chronic liver disease (level III-2 diagnostic evidence). The mean liver elasticity was found to be significantly lower in the healthy volunteers (2.0 ± 0.3 kPa) than in patients with chronic liver disease (5.6 ± 5.0 kPa). Unfortunately, the sample size employed in the study was too small to assess differences in elasticity according to METAVIR scores, or to provide an assessment of the diagnostic properties of MR elastography using receiver operating characteristic curves. In a similar study by Huwart et al (2006), liver biopsy and MR elastography results were obtained in 25 consecutive patients suspected of chronic liver disease (level III-2 diagnostic evidence). The mean elasticity was found to be 2.24 ± 0.23 kPa in patients with mild fibrosis (F0 – F1). Patients with moderate to severe fibrosis reported a mean elasticity value of 2.56 ± 0.24 kPa, while patients with cirrhosis (F4) reported a mean elasticity value of 4.68 ± 1.61 kPa. Although the authors demonstrated a significant difference in mean elasticity values according to METAVIR groups, again the sample size was too small to allow for a meaningful assessment of sensitivity and specificity values.

COST IMPACT

The current Medicare Benefits Schedule fee for percutaneous liver biopsy is $151.50 (item number 30409). In addition, there may be associated costs involved in the performance of a liver biopsy such as the cost of an inpatient stay in hospital.

The investment cost for a Fibroscan® in Europe translates to an Australian cost of $121,000, together with an annual maintenance and insurance cost of $9,100 (CEDIT 2004). The usage costs of the device are minimal, and as a result, the overall cost effectiveness of Fibroscan® depends largely on the number of examinations likely to be performed each year.

At present the cost of MR elastography is unknown, although Huwart et al (2005) have noted that the technique is likely to be more expensive than transient elastography.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

Transient elastography cannot be used in patients who are obese as the shear waves used by the technique have relatively poor tissue penetration (Sandrin 2003). The compressional waves used in MR elastography have good penetration throughout the liver, and so the technique is reliable in obese patients (Huwart et al 2006).

CONCLUSION:

The shortcomings of liver biopsy highlight the need for a reliable and non-invasive measure of liver fibrosis. Although elastography appears to be a promising technique for assessing the extent of liver fibrosis, the technique, particularly in the case of MR elastography, is in an early stage of development. Questions still remain regarding the diagnostic effectiveness of elastography, the cost implications of its introduction and the length of time before the technology is available for use in Australia.

HEALTHPACT ACTION:

Elastography appears to be a reliable technique for diagnosing severe liver fibrosis. For conditions such as viral hepatitis however, antiviral therapy should ideally begin in the early stages of fibrosis. Given the low quality of evidence outlining the ability of elastography to detect mild or moderate fibrosis, it is recommended that the technology be archived.

SOURCES OF FURTHER INFORMATION:

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Rouviere, O., Yin, M. et al (2006). 'MR elastography of the liver: preliminary results', *Radiology*, 240 (2), 440-448.

Sandrin, L., Fourquet, B. et al (2003). 'Transient elastography: a new noninvasive method for assessment of hepatic fibrosis', *Ultrasound Med Biol*, 29 (12), 1705-1713.

LIST OF STUDIES INCLUDED

Total number of studies
Level III-2 Diagnostic evidence 4

SEARCH CRITERIA TO BE USED:

Fibrosis/pathology

Liver/anatomy & histology/pathology

Magnetic Resonance Imaging/*methods

Liver Cirrhosis/classification/*diagnosis/*physiopathology