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Horizon Scanning Technology Prioritising Summaries

Magnetic resonance image (MRI) guided cryotherapy for the treatment of uterine fibroids

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ASERNIP-S
Australian Safety and Efficacy Register of New Interventional Procedures - Surgical

Royal Australasian College of Surgeons

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This Horizon scanning prioritising summary was prepared by staff from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

Name of Technology:

Magnetic resonance image (MRI) guided cryotherapy for the treatment of uterine fibroids.

Purpose and Target Group:

Women suffering from symptomatic uterine fibroids.

Stage of Development (in Australia):

- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established but changed indication or modification of technique
- ☐ Should be taken out of use
- ☑ Not yet emerged

This procedure utilises a combination of existing devices. As there are numerous cryoprobes and MRI machines available in Australia, ARTG numbers were not retrieved.

International Utilisation:

COUNTRY	LEVEL OF USE		
	Trials underway	Limited use	Widely diffused
United States	✓		
Japan	✓		

Impact Summary:

Background

Uterine fibroids, otherwise known as leiomyomas, arise due to the overgrowth of smooth muscle and connective tissue in the uterus. The pathology of uterine fibroids is not well understood, however, there is some evidence that ovarian steroid hormones (estrogen and progesterone) contribute to the development of uterine fibroids. Progesterone in particular is capable of increasing the mitotic rate of tumours *in vitro* and thus may have an effect on growth factors or their receptors during the luteal phase (Cowan 2004). Other evidence that points towards the role of hormones includes the discovery of estrogen and progestin receptors on fibroids as well as the observation that fibroids usually shrink after menopause but regrowth may occur with hormonal therapy (Thomason *et al.* 2005).

Approximately 50% of women with uterine fibroids will suffer from clinical symptoms (Sakuhara *et al.* 2006). Abdominal uterine bleeding, pelvic pain, pelvic pressure, abdominal distension, genitourinary dysfunction, infertility, lower extremity oedema, constipation and intestinal obstruction are common clinical symptoms of uterine fibroids which require treatment (Siskin *et al.* 2005). In addition to this, the presence of uterine fibroids can lead to

complications during pregnancy; this includes spontaneous abortion, intrauterine growth retardation, preterm labor, uterine dyskinesia, obstruction of the birth canal, postpartum haemorrhage and hydonephrosis (Thomason *et al.* 2005).

In mild cases, medical treatment utilising gonadotrophin-releasing hormone agonists can provide limited relief of symptoms. In severe cases of symptomatic uterine fibroids, surgical intervention may be warranted. At the time of writing, hysterectomy is the most effective treatment as it completely removes all fibroids as well as any chance of regrowth. However, hysterectomy is often unfavourable in women of childbearing age and can have various undesirable physiological and psychological effects. An alternative to hysterectomy is myomectomy, a surgical procedure where the fibroid is surgically removed without the removal of the uterus. Uterine fibroid embolisation (UFE) is a relatively new treatment that essentially restricts blood flow to the fibroids by blocking the main uterine artery, thus 'starving' the fibroid from nutrients (Sewell *et al.* 2001). However, this technique is associated with significant pelvic pain and cramping as well as nausea and vomiting during the recovery period (Siskin 2005).

Recently, a new technique known as MRI-guided cryotherapy has been proposed as an alternative to existing treatments. Cryotherapy is the process of freezing the tumour, which results in destruction of the tissue via intracellular freezing, extracellular crystallisation of interstitial water followed by lethal cell dehydration, thrombosis of blood vessels and mechanical damage to cellular integrity due to expansion of ice (Dohi *et al.* 2004). This technique has been purportedly more accurate than other treatments due to the capability of magnetic resonance to provide clear real-time imaging of cryoprobe insertion. In addition to this, MRI enables clear contrast depiction of frozen and non-frozen areas and therefore allows the operator to accurately adjust the freezing diameter to the size of the fibroid, avoiding unnecessary damage to surrounding healthy tissue (Sakuhara *et al.* 2006).

Clinical Need and Burden of Disease

Uterine fibroids are the most common gynaecological benign tumours. In the United States, 20-50% of women aged over 30 years have been diagnosed with uterine fibroids (Thomason *et al.* 2005). Approximately 200,000 to 300,000 hysterectomies in the Untied States are performed each year to treat uterine fibroids (Cowan *et al.* 2002).

The incidence of symptomatic uterine fibroids in Australia is not known but is presumably similar to international estimates.

Estimated Speed, Geographic and Practitioner Use, Patterns of Diffusion in the Health System

Due to the high prevalence of uterine fibroids, MRI-guided cryotherapy may offer a new treatment alternative to hysterectomy or myomectomy. If proven safe and effective, this minimally invasive procedure may gain widespread use. Coupled with the fact that the

devices required (MRI machine and cryoprobe) are already available in the Australian market, it may be an attractive alternative to current treatments.

Existing Comparators

- Myomectomy
- Hysterectomy
- MRI guided laser ablation
- Ultrasound guided radiofrequency ablation
- Uterine fibroid embolisation

Estimated Cost Impact

This procedure utilises equipments that are currently available in the Australian healthcare system, however the exact cost of the procedure is unknown. The Medicare Benefits Schedule reimbursement fees for procedures related to the treatment of uterine fibroids are listed below (Table 1) (Medicare Australia 2006):

Table 1: Medical Benefits Schedule of Fees for procedures related to uterine fibroids

Category	Item Number	Benefit (AU$)	Number of Claims (July 2004 to June 2005)
Magnetic resonance imaging (contrast) – scan of person under the age of 16 for pelvic or abdominal mass.	63440	403.20	157
Modifying items for use with magnetic resonance imaging or magnetic resonance. Scan performed: involves the use of contrast agent.	63491	44.80	0
Hysteroscopic resection of myoma, or myoma and uterine septum resection, followed by endometrial ablation by laser or diathermy.	35623	709.00	627
Endoscopic examination of and ablation of the endometrium by microwave or thermal balloon or radiofrequency electrosurgery, for chronic refractory menorrhagia.	35616	389.10	1339
Endoscopic ablation of the endometrium by laser or diathermy, for chronic refractory menorrhagia.	35622	521.40	1786
Abdominal hysterectomy or uterine myomectomy.	35649	463.90	768
Hysterectomy, Abdominal, Subtotal or Total, with or without removal of uterine adnexae.	35653	583.90	4891
Vaginal hysterectomy with or without uterine curettage.	35657	583.90	5547

Efficacy and Safety Issues

List of Studies Found

Total number of studies	4
Case series studies	3
Case reports	1

The studies included in this summary are highlighted in bold in the reference list.

Safety and efficacy data from three case series studies and one case report have been selected for inclusion in this summary.

Sakuhara *et al.* (2006) utilised MRI-guided percutaneous cryoablation to treat 6 patients suffering from symptomatic uterine fibroids. All treated fibroids (7 fibroids in total) reduced in size during follow-up examination with MRI, mean volume reduction rate was 40.3% (range 20.9 to 80.1%) 6 weeks post-treatment and 79.4% (range: 60.8 to 99.6%) at 9 to 12 months post-treatment. Residual tumours were discovered in the circumference of the treated areas in 5 of the 7 tumours (71%); however no regrowth was identified throughout the follow-up period. Five patients (83%) experienced improvement of symptoms; the one patient that did not experience improvement had multiple fibroids. Cryoablation was conducted on two large fibroids in this patient while the other small fibroids were not treated. Unfortunately, despite that the two treated fibroids shrank, monorrhalgia and menorrhagia persisted. This patient underwent uterine fibroid embolisation 4 months after cryoablation (Sakuhara *et al.* 2006).

Nine women with large symptomatic uterine fibroid tumours were treated in the case series study by Cowan *et al.* (2002). Of these, eight patients were available for subsequent follow-up (range 48 to 334 days) and mean volume reduction in all treated fibroid tumours was 65.0% ± 7%. All patients reported improvement of their symptoms (Cowan *et al.* 2002).

Dohi *et al.* (2004) treated eight women with symptomatic uterine fibroids using MRI guided cryotherapy. However, the procedure was conducted transvaginally instead of percutaneously as described in Cowan *et al.* (2002) and Sakuhara *et al.* (2006). Follow-up assessments at 2 to 3 weeks and 6 to 7 weeks post-treatment revealed mean fibroid volume reductions of 72.6% (range: 57.0% to 94.1%) and 58.9% (range: 17.0% to 77.4%) respectively. Follow-up magnetic resonance examinations were conducted at 9 to 12 months post-procedure in 5 patients and a mean fibroid volume reduction of 67.7% (range: 0% to 75%) was recorded. Six (75%) patients achieved improvement in menstrual scores, one patient remained the same while another had a slightly worse score (Dohi *et al.* 2004).

The case report by Sewell *et al.* (2001) recorded 65% and 57% reduction in fibroid volume 8 weeks after MRI-guided cryotherapy in two patients. Both patients experienced minimal pain which lasted less than two days after the treatment. Symptoms relating to the fibroid were eliminated and all patients experienced an improvement in their quality of life (Sewell *et al.* 2001).

With regards to the safety of this procedure, Sakuhara and colleagues (2006) stated that no serious complications occurred during the procedure; however patients experienced mild pain intraoperatively. Overall, patients were hospitalised for a mean of 14.7 ± 14.3 days (range 3 to 45 days), much longer than conventional myomectomy (1 to 3 days). However, the authors attributed this long duration of hopitalisation to the fact this technique is relatively new and therefore warranted longer observation. All patients experienced postoperative fever, but one patient suffered from persistent high fever accompanied with abdominal pain. Clinical examination revealed the existence of an abcess in the probe channel between the abdominal wall and uterus. Antibiotic treatment failed to provide resolution of symptoms and the patient underwent surgical drainage. Another patient had increased lactate dehydrogenase (LDH) levels one day post-treatment. At four days post-treatment, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ –GPT) and alkaline phosphatase (ALP) levels increased. Six days post-treatment, concentrations of LDH, AST, ALT and γ-GPT were at their highest. Meanwhile peak ALP concentration was achieved 6 days post-treatment, this gradually decreased and normalised 6 weeks post-treatment. The cause of these fluctuations has been attributed to transient liver damage possibly due to the large frozen area for this patient (249.2 cm^2, largest compared to other patients in the cohort), but the reason for this is unclear (Sakuhara *et al.* 2006).

One patient from the study conducted by Cowan *et al.* (2002) suffered laceration of a blood vessel that coursed over the serosa of a fibroid tumour which resulted in continuous bleeding after the procedure, this was resolved with laparatomy and myomectomy but the patient was not available for follow-up evaluation. Another patient suffered a mild peritoneal nerve defect which was associated with a mild footdrop but was resolved within 4 months of diagnosis. A third patient experienced nausea and was admitted for 24 hour observation. Three other patients had mild abdominal discomfort which was treated with nonsteroidal anti-inflammatory drugs (Cowan *et al.* 2002). Uterine bleeding (menorrhagia) occurred in two patients with primary pelvic mass after the treatment, one patient underwent submucous pedunculated myoma while the second patient ceased bleeding 3 months after the procedure. One patient underwent hysterectomy 10 months post-treatment due to continuous growth of a second large fibroid tumour which was not treated with cryotherapy (Cowan *et al.* 2002).

Dohi *et al.* (2004) reported that 4/8 (50%) patients experienced pain during needle puncture while 3/8 (38%) patients had lower abdominal pain after the procedure. Two patients experienced mild fever the day after the procedure and were treated with oral antibiotics and non-steroidal anti-inflammatory drugs. A minor increase in serum LDH from 316 IU/L to 600 IU/L was detected (normal range 130 < 235 IU/L) and transient occult hematuria was detected in all patients. However, these values returned to normal values 6 to 7 weeks after the procedure. Two cases of anaemia and abdominal pain were reported but were resolved after treatment; no cases of dysfunctional uterine bleeding were observed (Dohi *et al.* 2004).

In all included studies, the authors did not conduct tests to determine any reduction in uterine wall integrity post-treatment. Therefore, the extent which MRI-guided cryotherapy compromises uterine wall integrity is not known. Compared to UFE and myomectomy, MRI-guided cryoablation appears to cause little pain with comparable ratios of symptom improvement to UFE (UFE ~ 90%, MRI-guided cryotherapy ~ 97.5%) as well as similar ratios of fibroid volume reduction (UFE: 23% to 57% at 2 to 4 months; MRI-guided cryotherapy: 35% to 65% at 1.5 to 11 months) (Dohi *et al.* 2004).

Ethical Issues

No issues were identified from the retrieved material.

Cultural or Religious Considerations

No issues were identified from the retrieved material.

Other Issues

In all the included studies, the Cryohit cryotherapy system (Galil Medical Ltd., Yoknaem, Israel) was the system of choice due to its compatibility with MRI.

In 3/4 studies, the treated fibroids were subjected to one freeze-thaw cycle (Cowan *et al.* 2002, Sewell *et al.* 2001, Dohi *et al.* 2004) while one study utilised two freeze-thaw cycles (Sakuhara *et al.* 2006).

Recommendation

The evidence available on MRI-guided cryotherapy is scarce and limited to small patient numbers. Despite the promising results of the studies, the long-term safety and efficacy of the procedure is not known. At the time of writing, none of the identified studies reported whether MRI-guided cryotherapy weakens the uterine wall, a complication that is potentially

fatal during pregnancy. Previous studies have determined that surgical excision of fibroids have < 1% risk of rupture (Dubuisson *et al.* 2000), while myolysis techniques (electromyolysis) has a rupture risk greater than 1% (Vilos *et al.* 1998). In addition to this, tumour recurrence rates for MRI-guided cryotherapy are unknown and the evidence of residual tumours in 71% of cases by Sakuhara *et al.* (2006) is disconcerting. Based on the evidence and the alternative treatments available, we recommend that this procedure should be archived.

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Search Criteria:

A search of MEDLINE, PubMed and Cochrane Library, Current Controlled Trials metaRegister, UK National Research Register, International Network for Agencies for Health Technology Assessments, relevant online journals and the Internet was conducted in April 2006.

Search terms used were: 'fibroid cryotherapy', 'fibroid cryoablation', 'MRI cryoablation', 'MRI cryotherapy'.

This Horizon Scanning Prioritising Summary was prepared by Mr. Irving Lee from the NET-S Project, ASERNIP-S for the Health Policy Advisory Committee on Technology (Health PACT), on behalf of the Medical Services Advisory Committee (MSAC) and the Australian Health Ministers' Advisory Council (AHMAC).