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Medical Policy Manual

Topic: MRI-Guided Focused Ultrasound (MRgFUS)

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Magnetic resonance imaging (MRI)- guided focused ultrasound (MRgFUS), also known as high-intensity focused ultrasound, is proposed as a noninvasive approach to the ablation of uterine fibroids and for pain palliation of bone metastases, using an integrated imaging system that combines:

- Focused ultrasound waves
  High-frequency, high-energy sound waves are focused to heat and destroy tissue. The ultrasound causes a local increase in temperature in the target tissue, resulting in coagulation necrosis.

- Magnetic resonance imaging (MRI) and thermometry
  The MRI is used to visualize patient anatomy, finalize patient positioning, and map the volume and location of tissue to be treated, minimizing exposure of other organs to the ultrasound. MRI thermal measurements are used to confirm the correct area will receive treatment, begin the focused ultrasound heating of the target tissue, and monitor thermal destruction in real time.

Regulatory Status

Two devices have received U.S. Food and Drug Administration (FDA) approved via the Premarket Application (PMA) process:

- The ExAblate®2000 System (InSightec, Inc.) was approved for two indications: "ablation of uterine fibroid tissue in pre- or peri- menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure," and for palliation of pain associated with tumors metastatic to bone.[1]

  For uterine fibroids, the FDA approval letter states that patients must have a uterine gestational size of less than 24 weeks and those patients must have completed childbearing.

  In the initial safety and efficacy studies, the FDA limited MRI-guided focused ultrasound to 33% of fibroid volume with a maximum treatment time of 120 minutes. Guidelines were later modified to allow up to 50% treatment volume, 180-minute maximum treatment time, and a second treatment if within a 14-day period.

  The ExAblate 2000 treatment is contraindicated for use in women who have MRI-related issues, such as metallic implants, or sensitivity to MRI contrast agents; obstructions in the treatment beam path, such as a scar, skin fold, or irregularity, bowel, pubic bone, intrauterine device, surgical slips, or any hard implants; and fibroids that are close to sensitive organs such as the bowel or bladder, or are outside the image area.

- The ExAblate® 2100 System also received approval through the PMA process.[2] It includes several modifications to the previous system including enhanced sonication and a detachable cradle, and only certain cradle types can be used for palliation of pain associated with metastatic bone cancer. Approval remains limited to treatment of patients with metastatic bone cancer who failed or are not candidates for radiation therapy; or, in patient with symptomatic uterine fibroids with a uterine size of less than 24 weeks and those who have completed child bearing.

- In October 2012, the FDA approved the ExAblate® System, Model 2000/2100/2100 VI for pain palliation via the PMA process. For pain palliation, the intended use of the device is in adult patients with metastatic bone cancer who failed or are not candidates for radiation therapy. The device was evaluated through an expedited review process. The FDA required a post-approval study with 70 patients to evaluate the effectiveness of the system under actual clinical conditions.

  For treating pain associated with bone metastases, the aim of MRgFUS treatment is to destroy nerves in the bone surface surrounding the tumor. Metastatic bone disease is one of the most common causes of cancer pain. Existing treatments include conservative measures (e.g., massage, exercise), pharmacologic agents (e.g., analgesics, bisphosphates, corticosteroids) and radiotherapy, especially conventional external beam radiotherapy (EBRT) for tumors that do not involve the nervous system.

MRgFUS is also being studied for the treatment of other tumors, including breast, prostate, renal, and for brain tumors. However, the FDA has only approved MRI-guided ultrasound ablation devices for the treatment of uterine fibroids and for the treatment of tumors metastatic to bone for the palliation of pain.

MEDICAL POLICY CRITERIA

MRI-guided high intensity focused ultrasound ablation (MRgFUS) is considered **investigational** for all indications, including but not limited to treatment of the following:

1. Uterine fibroids
2. All tumors, including but not limited to brain, breast, prostate and renal
3. Bone metastases for palliation of pain

SCIENTIFIC BACKGROUND

Uterine Fibroids

There are several approaches that are currently available to treat symptomatic uterine fibroids: hysterectomy; abdominal myomectomy; laparoscopic and hysteroscopic myomectomy; hormone therapy; uterine artery embolization; and watchful waiting. Hysterectomy and various myomectomy procedures are considered the gold standard treatment. Comparisons to these procedures in well-designed prospective clinical trials are needed to determine whether MRI-guided high intensity focused ultrasound ablation (MRgFUS) results in the same or better health outcomes with respect to long-term treatment effects, recurrence rates and impact on future fertility and pregnancy. The focus of this review is therefore on randomized controlled trials.

Systematic Reviews/Technology Assessments

A 2007 technology assessment published by the Agency for Healthcare Research and Quality (AHRQ) concluded that the strength of the evidence for MRgFUS was weak (defined as evidence from a limited number of studies of weaker design; studies with strong design either have not been done or are inconclusive).[3] The literature included one industry-sponsored prospective case series (n = 109) that was ranked as poor for informing clinical decision-making.[4,5] This study was conducted to support the FDA approval application. The AHRQ report noted that while initial research demonstrated safety and preliminary efficacy, there is a need for comparative study and longer term follow-up.

The report also adds the following caution, now that the device is available outside a clinical research setting:

> Clinicians need to consider carefully the reality that, now that the systems are in use, care providers are using this new modality to treat fibroids more aggressively than had been allowed during the strict study protocol. The major change in how the systems are now being used is that a greater proportion of the total volume of the fibroid is treated. Therefore, no information exists at present that reflects *current* practice in terms of procedure-related risks and anticipated outcomes.

This report has now been archived by AHRQ, and there is a continued lack of publication of high-quality evidence from randomized controlled trials.

Randomized Controlled Trials

No published randomized controlled trials comparing MRgFUS to other treatments for uterine fibroids have been identified in the peer-reviewed literature.

Nonrandomized Trials

Several nonrandomized trials have been published, examples of which include:

- The "pivotal" study which led to FDA approval of the ExAblate® 2000 device was included in the AHRQ report discussed above.[4,5] Additional study outcomes have been subsequently reported from this same study, although interpretation of any such results is limited by the weak strength of the evidence from the original trial. For example, Taran and colleagues failed to report on the original primary outcome measure and instead reported findings on a different quality of life measure.[6] The different measures were subject to a multiple comparison bias; a large number of statistical comparisons were done for secondary outcomes, and p-values were not adjusted for increased risk of chance statistical findings.

- Another non-randomized comparative study compared two variations on the MRgFUS procedure.[7] Patients were either treated with the original protocol (33% of fibroid volume with a maximum treatment time of 120 minutes, n=96) or modified protocol (50% treatment volume, 180 minutes maximum treatment time, and a second treatment if within a 14-day period, n=64). Interpretation of these results was limited by 49% loss to follow-up; 55 patients (57%) from the original treatment protocol completed follow-up. Only 21 patients (33%) from the modified protocol group were evaluable at 12-month follow-up.

- A prospective registry of pregnancies after MRgFUS was maintained by the manufacturer of the ExAblate device. A 2008 article reported that there were 54 known pregnancies a mean of 8 months after treatment.[8] They included 8 pregnancies from clinical trials designed for women who did not desire pregnancy, 26 pregnancies after commercial treatment, and 20 pregnancies in 17 patients from an ongoing study of MRgFUS in women trying to conceive. Twenty-two of the 54 pregnancies (42%) resulted in deliveries, 11 were ongoing beyond 20 weeks at the time the article was written. There were 14 miscarriages (26%) and 7 elective terminations (13%). Among the 22 live births, the mean birth weight of live births was 3.3 kg, and the vaginal delivery rate was 64%. The article provides initial information on the impact of MRgFUS for uterine fibroids on pregnancy; findings suggest that fertility may be maintained but that the number of cases is too small to draw definitive conclusions. Moreover, the study does not address the possible impact of MRgFUS treatment on the ability to become pregnant.

- Other non-comparative, prospective and retrospective case series have been published; however, conclusions concerning health outcomes cannot be reached from these studies due to small study populations, and failure to control for bias which could impact treatment results.[9-14]

Although results from these trials contribute to the body of evidence on MRgFUS, interpretation of such results is limited by the lack of a comparative treatment group, the absence of which does not allow for the comparison of the relative treatment effect of MRgFUS with standard medical alternatives. In addition, there is insufficient evidence on the long-term treatment effects, recurrence rates, and impact on future fertility and pregnancy.

Palliative Treatment of Bone Metastases

Assessment of the safety and efficacy of MRgFUS treatment for bone metastases requires large, long-term, randomized controlled trials comparing this technique with the current standard of care for the condition being treated.

No controlled studies evaluating MRgFUS for palliative treatment of bone metastases have been published. Examples of nonrandomized trials include two small (n=11, 31, respectively), nonrandomized prospective studies evaluating MRgFUS for the treatment of bone metastases, both of which are industry-sponsored.[15,16] Although neither series reported any treatment-related adverse effects, and both reported improvements in pain and decreases in analgesic use, independent verification of treatment effects with larger groups of patients is needed. At present, results from these trials are not sufficient to reach conclusions regarding the impact of MRgFUs in palliation of pain related to bone metastases due to methodological limitations such as lack of an appropriate control group for comparison.

Other Tumors

MRgFUS is also being studied for several other clinical applications, including the treatment of benign and malignant tumors. As with MRgFUS treatment for uterine fibroids and bone metastases, randomized controlled trials comparing this technique with the current standard of care for the condition being treated are required in order to assess the efficacy of this treatment approach.

Breast Tumors

No controlled studies evaluating MRgFUS for treating breast cancer have been identified in the published literature. The published literature is limited to small case series, examples of which include six feasibility studies that describe preliminary results only.[17-22] Fibroadenoma, ductal carcinomas, adenocarcinomas, and lobular carcinomas were treated. The adverse effects profile includes a few second-degree skin burns, and protocols maintain a roughly 1-cm distance between the tumor margin and the skin or rib cage. Residual tumor in the treated area appears to be a problem, with authors recommending treatment of the entire tumor plus 1 cm of surrounding tissue, as is done in lumpectomy. No long-term outcome studies are available. As with uterine fibroids, interpretation of these results is limited by the lack of a comparative treatment group.

Brain Cancer

Evidence on MRgFUS in brain cancer is similarly restricted to case series, which include a report of initial findings in 3 patients.[23] The authors report that it was possible to focus an ultrasound beam into the brain transcranially, and they believe that thermal ablation without overheating the brain is possible; however, substantial technical barriers to using MRgFUS for treating brain tumors remain. Larger and longer comparative trials are needed to establish the use of MRgFUS for treating this indication.

Prostate Cancer

A single, small (n=5) feasibility study regarding the use of MRgFUS in patients with biopsy-proven prostate cancer demonstrated that the procedure may be performed in this patient population. An overlap of the ablated area and the devascularization of the target lesion were evaluated by MRI. Later, two patients were found to have residual bilateral tumors, which were not evident on the pretreatment MRI. Larger and longer comparative trials are needed to establish the use of MRgFUS for treating this indication.

Clinical Practice Guidelines

American Congress of Obstetrics and Gynecologists (ACOG)

A practice bulletin from ACOG considered MRgFUS as an alternative to hysterectomy as a treatment of uterine fibroids, but did not specifically recommend its use, stating:[24]

> Whereas short-term studies show safety and efficacy, long-term studies are needed to discern whether the minimally invasive advantage of MRI-guided focused ultrasound surgery will lead to durable results beyond 24 months. Protocols for treating larger leiomyoma volumes are being studied.

American College of Radiology (ACR)

The 2012 ACR Appropriateness Criteria guidelines regarding the treatment of uterine fibroids[25] mention the use of MRgFUS indicating that, "(t)o date, there is little long-term information on the efficacy of [MRgFUS] technology." However, the MRgFUS approach is not recommended as treatment for fibroids.

No other evidence-based clinical practice guidelines were identified that recommend MRgFUS as a treatment for any other condition.

Summary

Uterine Fibroids

To date, there are no published randomized controlled trials and only one industry-sponsored, non-randomized study of weak strength comparing magnetic resonance imaging (MRI)-guided focused ultrasound (MRgFUS) with a different treatment. The limited nature of this evidence-base raises concerns about the reliability and validity of reported findings. In particular, the durability of any early treatment effect with MRgFUS given the potential for regrowth of treated fibroids, is not clearly understood. Pending conclusive results from randomized controlled clinical trials, treatment of uterine fibroids with MRgFUS is considered investigational.

Palliative Treatment of Bone Metastases

To date, there are no published randomized controlled trials comparing magnetic resonance imaging (MRI)-guided focused ultrasound (MRgFUS) with a different treatment for pain palliation in patients with bone metastases. There are some preliminary reports of safety and efficacy in small numbers of patients; however, this evidence is insufficient, and the impact of MRgFUS on health outcomes remains unknown. Therefore, treatment of pain palliation with bone metastases with MRgFUS is considered investigational.

Other Tumors

(MRI)-guided focused ultrasound (MRgFUS) is being investigated for use in several applications that are not currently approved by the FDA. There are some preliminary reports of safety and efficacy in small numbers of patients; however, this evidence is insufficient, and the impact of MRgFUS on health outcomes remains unknown. Due to the lack of evidence from well-designed randomized controlled trials, the use of MRgFUS for the treatment of any condition is considered investigational.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	0071T	Focused ultrasound ablation of uterine leiomyomata, including MR guidance;

CODES	NUMBER	DESCRIPTION
		total leiomyomata volume of less than 200 cc of tissue.
	0072T	total leiomyomata volume greater or equal to 200 cc of tissue.
HCPCS	C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance