

## ***Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS) and High Intensity Focused Ultrasound (HIFU) Ablation***

**Effective:** January 1, 2021

**Next Review:** August 2021

**Last Review:** December 2020

### **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 (MR) guided focused ultrasound (MRgFUS) and high-intensity focused ultrasound (HIFU) concentrate high-energy ultrasound waves via probe on a single location to cause coagulative necrosis.

### **MEDICAL POLICY CRITERIA**

- I. High-intensity focused ultrasound (HIFU) may be considered **medically necessary** as a local treatment for prostate cancer when all of the following (A.-D.) criteria are met:
  - A. For the treatment of radiation recurrence (see Policy Guidelines); and
  - B. The patient is a candidate for local therapy (see Policy Guidelines); and
  - C. Transrectal ultrasound guided (TRUS) biopsy positive; and
  - D. In the absence of metastatic disease.
- II. HIFU is considered **investigational** for all other indications not meeting Criterion I.

- III. Magnetic resonance (MR) guided focused ultrasound (MRgFUS) may be considered **medically necessary** for medicine-refractory essential tremors.
- IV. Magnetic resonance (MR) guided focused ultrasound (MRgFUS) is considered **investigational** for all indications, including but not limited to treatment of the following:
  - A. Uterine fibroids
  - B. All tumors, including but not limited to brain, breast, prostate and renal
  - C. Bone metastases for palliation of pain

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

### CANDIDATE FOR LOCAL THERAPY

According to National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 2. 2020), in the presence of radiation therapy recurrence (see below), a candidate for local therapy includes:

- Original clinical stage T1-T2, NX or N0
- Life expectancy > 10y
- PSA now < 10 ng/mL

### RADIATION RECURRENCE

NCCN guidelines for prostate cancer (version 3.2018) cite radiation therapy recurrence as either 1) a positive digital rectal exam (DRE), or 2) Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology (RTOG-ASTRO) Phoenix Consensus biochemical failure.

RTOG-ASTRO Phoenix Consensus biochemical failure is further defined as:

- 1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; and
- 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy.

Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

## LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical
- Treatment plan including treatment area

- For essential tremors, clinical documentation must demonstrate medicine-refractory symptoms
- For prostate cancer treatment, clinical documentation must also demonstrate results from transrectal ultrasound guided (TRUS) biopsy

## CROSS REFERENCES

1. [Radioembolization, Transarterial Embolization \(TAE\), and Transarterial Chemoembolization \(TACE\)](#), Medicine, Policy No. 140
2. [Radiofrequency Ablation \(RFA\) of Tumors Other than Liver](#), Surgery, Policy No. 92
3. [Cryosurgical Ablation of Miscellaneous Solid Tumors](#), Surgery, Policy No. 132
4. [Microwave Tumor Ablation](#), Surgery, Policy No. 189
5. [Ablation of Primary and Metastatic Liver Tumors](#), Surgery, Policy No. 204
6. [Focal Laser Ablation of Prostate Cancer](#), Surgery, Policy No. 222

## BACKGROUND

Magnetic resonance (MR) guided focused ultrasound (MRgFUS) and high-intensity focused ultrasound (HIFU) are proposed as less invasive approaches than surgery for treatment of localized prostate cancer, uterine fibroids, and pain palliation of bone metastases. Broadly, these devices use an integrated imaging system to take measurements, confirm the treatment area, and monitor thermal destruction in real time.

MRgFUS is a noninvasive treatment that combines focused ultrasound and magnetic resonance imaging (MRI). The ultrasound beam penetrates through the soft tissues and, using MRI for guidance and monitoring, the beam can be focused on targeted sites. Ultrasound causes a local increase in temperature in the target tissue, resulting in coagulation necrosis while sparing the surrounding normal structures. Ultrasound waves from each sonication are focused at a focal point that has a maximum focal volume of 20 nm in diameter and 15 nm in height/length. This causes a rapid rise in temperature (to approximately 65°C-85°C), which is sufficient to achieve tissue ablation at the focal point. In addition to providing guidance, the associated MRI can provide online thermometric imaging that provides a temperature “map” to confirm the therapeutic effect of the ablation treatment and allow for real-time adjustment of the treatment parameters.

HIFU focuses high-energy ultrasound waves on a single location, which increase the local tissue temperature to over 80°C. This causes a discrete locus of coagulative necrosis of approximately 3×3×10 mm. In the treatment of prostate cancer, HIFU is a minimally invasive localized option. The surgeon uses a transrectal probe to plan, carry out, and monitor ablative treatment in a real-time sequence with a combination of ultrasound and MRI imaging.

## REGULATORY STATUS

Devices have received U.S. Food and Drug Administration (FDA) approval via the De Novo and Premarket Application (PMA) processes:

### HIFU

The Sonablate® 450 (SonaCare Medical) is the first high-intensity ultrasound system for prostate tissue ablation to receive FDA approval, and therefore underwent the *de novo* application process, obtaining clearance in 2015. Shortly thereafter, Ablatherm Integrated Imaging® (EDAP TMS) received PMA approval.

## MRgFUS

MRgFUS systems may also be referred to as “high-intensity” ultrasound.

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.<sup>[1]</sup>

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.<sup>[2]</sup> 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.<sup>[1]</sup> 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.

## EVIDENCE SUMMARY

## HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU)

### Prostate Cancer

Given significant uncertainty in predicting the behavior of individual localized prostate cancers, and the substantial adverse effects associated with definitive treatments, investigators have sought a therapeutic middle ground. The latter seeks to minimize morbidity associated with radical treatment in those who may not actually require surgery while reducing tumor burden to an extent that reduces the chances for rapid progression to incurability. Locally directed therapies, also termed *focal treatment* includes several ablative methods, one of which is high-intensity focused ultrasound (HIFU). The overall goal of any focal treatment is to minimize the risk of tumor progression and preserve erectile, urinary, and rectal functions by reducing damage to the neurovascular bundles, external sphincter, bladder neck, and rectum.

Ingrosso (2020) published a systematic review (SR) with meta-analysis on nonsurgical therapeutic strategies in patients with radiorecurrent prostate cancer.<sup>[3]</sup> The review addressed the clinical outcomes and toxicity profiles of treatments including HIFUS, brachytherapy, external beam radiotherapy, and cryotherapy. Thirteen of the 64 case-series studies were publications reporting HIFUS as the salvage treatment. Among the treatments studied, biochemical control rates were lowest for patients treated with HIFU (58%, 95% confidence interval [CI] 47–68%). The prevalence of incontinence was highest among patients treated with HIFU (28%, 95% CI 19–38%; I<sup>2</sup> = 89.7%). The authors concluded that good efficacy and tolerability was found after local treatment of radiorecurrent prostate cancer, but that high-quality data from prospective trials are needed to validate the long-term outcomes of these strategies for the treatment of intraprostatic recurrence after previous radiotherapy.

A 2020 SR by Khoo also evaluated 15 studies (14 case series and one comparative study) reporting outcomes after focal salvage brachytherapy (five studies), cryotherapy (seven studies) and HIFU (three studies) in the treatment of localized non-metastatic radiorecurrent prostate cancer.<sup>[4]</sup> Rates of biochemical disease-free survival (BDFS), metastasis, conversion to second-line therapies, and adverse events were assessed and median follow-up ranged from 10 to 56 months. At three years, BDFS ranged from 61% to 71.4% after brachytherapy, 48.1–72.4% after cryotherapy and 48% after HIFU. The authors note high heterogeneity in patient selection, individual treatment protocols and outcome reporting. Additional studies comparing the treatment modalities is recommended.

As a salvage treatment, that is, for recurrent disease following initial therapy, Crouzet (2017) reported that HIFU is associated with cancer-specific (CSS) and metastasis-free survival (MFS) of at least 80% at seven years in a study of over 400 men.<sup>[5]</sup> Morbidity rate for grade III/IVa complications was 3.6%. Smaller studies with shorter-duration of follow-up are in general agreement<sup>[6-9]</sup>, however, patient selection criteria is an important predictor of treatment outcomes<sup>[10-13]</sup>. While this is still an area of investigation, there may be limited treatment for this population of men with recurrent disease. Current practice guidelines based on research recommend HIFU in the presence of radiation recurrence for carefully selected patients (e.g., no metastases, and good candidate for local therapy).<sup>[7]</sup>

As a primary treatment, evidence for HIFU is still accumulating. Data in the published literature are available for shorter follow-up times than in salvage treatment studies (e.g., two years)<sup>[6, 14]</sup>. Treatment free survival rate has been reported as 89% at two years, with acceptable morbidity – a grade III complication rate of 13%. Larger, longer-term comparative studies are needed.

## Other Indications

A 2017 systematic review (SR) published by the Agency for Healthcare Research and Quality (AHRQ) on the management of uterine fibroids included evaluation studies of HIFUS.<sup>[15]</sup> Outcomes following HIFUS were symptoms (two studies, N=53), sexual function (one study, n=50), and fibroid characteristics (five studies, N=216). The duration of follow-up studied ranged from less than one to 24 months. The conclusion of the review was that HIFU reduced fibroid size, but strength of evidence is low because of short followup and poor quality of overall study design. Evidence related to patient reported outcomes is insufficient.

HIFU has been investigated as a treatment for other indications, such as adenomyosis<sup>[16]</sup> and thyroid disorders,<sup>[17, 18]</sup> but these are generally small, noncomparative studies. Systematic reviews of HIFU in the treatment of malignant lesions of the hepatobiliary system<sup>[19]</sup> and benign thyroid nodules<sup>[20, 21]</sup> have concluded that although volumetric reduction or complete ablation was achieved with HIFU, additional studies are needed to determine the added benefit and long-term outcomes of the technology either alone or as a combination therapy on net health outcomes in these patient populations.

## MAGNETIC RESONANCE (MR) GUIDED FOCUSED ULTRASOUND (MRGFUS)

### Essential Tremors

#### Systematic Reviews

A technology assessment was published by Health Quality Ontario (2018).<sup>[22]</sup> The literature search, conducted through April 2017, identified nine studies for inclusion: four single cohort studies, two retrospective chart reviews, two uncontrolled prospective studies, and an RCT. The RCT compared MRgFUS with sham treatment, the chart reviews compared MRgFUS with deep brain stimulation and radiofrequency thalamotomy. Study quality was evaluated using the GRADE system. The RCT was rated high quality, the uncontrolled comparative studies were rated very low quality, and the remaining studies were rated low quality. All studies reported tremor severity as an outcome. Pooling of results was not conducted due to heterogeneity in study designs, analyses, and outcomes across the studies. Reviewers determined that, overall, MRgFUS decreased tremor severity and improved QOL. The high-quality RCT by Elias (2016) is discussed below.

Mohammed (2018) conducted a meta-analysis evaluating the use of MRgFUS to treat medicine-refractory essential tremors.<sup>[23]</sup> The literature search, conducted through August 2017 identified 9 studies (total n=160 patients) for inclusion, eight of which were also evaluated in the Ontario technology assessment. Pooled analyses found significant improvements in the mean percentage change in Clinical Rating Scale for Tremor scores (62.2%) and Quality of Life in Essential Tremor scores (46.5%). Complications included nausea, vomiting, and ataxia, which decreased during the 12-month follow-up.

#### Randomized Controlled Trials

A single high-quality study, a double-blind, sham-controlled randomized trial by Elias (2016),<sup>[24]</sup> was identified by the two systematic reviews above. Trial selection criteria included patients with moderate or severe postural or intention tremor of the hand ( $\geq 2$  on the Clinical Rating Scale for Tremor) and refractory to at least two medical therapies. Patients were randomized to MRgFUS thalamotomy (n=56) or sham treatment (n=20). Outcomes were tremor severity, improvement, and QOL, measured at three months postprocedure. Patients in the treatment

group were followed for an additional 12 months. Mean score for hand tremor improved significantly from baseline in the treatment group (47%) compared with the sham group (0.1%) at three months. Change in mean functional improvement score from baseline differed significantly in the MRgFUS group (62%) compared with the sham group (3%) at three months. Change in Quality of Life in Essential Tremor Questionnaire scores also differed significantly in the treatment group compared with the sham group, with the largest improvements experienced in the psychosocial domain. The improvements in hand tremor score, functional improvement, and QOL were maintained at 12 months in the MRgFUS group.

Chang (2018) published results from 67 patients who participated in the open-label extension of the RCT.<sup>[25]</sup> Because nine patients from the original trial received additional treatment during the two-year follow-up, they were excluded from the analysis. Improvements in tremor and disability scores were maintained at the two-year follow-up (tremor, 19.8±4.9 [baseline] to 8.8±5.0 [at two years]; disability, 16.4±4.5 [baseline] to 6.5±5.0 [at two years]).

### Nonrandomized Studies

A number of nonrandomized studies (n=11 to 15) reported results from trials implementing MRgFUS as a treatment for essential tremor and many were included in the systematic reviews discussed above.<sup>[26-29]</sup>

### **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 randomized 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

In the 2017 AHRQ review of management of uterine fibroids summarized above, of the six studies assessing HIFU for fibroid ablation, only one fair quality pilot study (n=20) used magnetic resonance imaging (MRI) guidance.

A systematic review, published by Gizzo (2013) identified 38 uncontrolled studies with a total of 2,500 patients (mean age 43.67 years) who underwent MRgFUS for treatment of uterine fibroids.<sup>[30]</sup> All of the published studies included women older than age 18 years with symptomatic uterine fibroids, and most excluded patients who desired future pregnancies. The authors of the systematic review did not pool study findings, noting there was no uniform consensus regarding the parameters for evaluating treatment results and considerable variety in the inclusion criteria and follow-up periods. The review confirms the continued absence of published randomized controlled trials on MRgFUS for uterine fibroids.

Clark (2014) published a review of the evidence regarding the role of MRgFUS in the treatment of fibroids and its impact upon future fertility and reproductive outcomes.<sup>[31]</sup> The authors identified 35 reports of pregnancy after MRgFUS in the available literature; however, additional

studies are needed to evaluate the impact of MRgFUS upon future fertility and reproductive outcomes.

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).<sup>[32]</sup> The literature included one industry-sponsored prospective case series (n=109) that was ranked as poor for informing clinical decision-making.<sup>[33, 34]</sup> 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. This report has since been archived by AHRQ.

The report also added 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.

### Randomized Controlled Trials (RCTs)

A pilot sham-controlled RCT with 20 patients was published by Jacoby (2015). The study was designed to determine the feasibility of a full scale randomized study evaluating MRgFUS for treatment of uterine fibroids.<sup>[35]</sup> The study included premenopausal women with symptomatic uterine fibroids. Women who were pregnant or had a desire for future fertility were excluded. Patients were randomized to MRgFUS with the ExAblate 2000 system (n=13) or a sham treatment in which no thermal energy was delivered (n=7). The investigators did not specify primary outcomes. The sample size of 20 was selected, not to have sufficient statistical power, but to assess the feasibility of a larger trial. All patients assigned to the MRgFUS group and six of seven in the placebo group received their allocated treatment and all treated patients completed three months of follow-up. Patients were unblinded at three months and given the sham group was given the option of active treatment.

QOL outcomes included the Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire (UFS-QOL), which has subscales including the Symptom Severity Score (SSS) and Health Related Quality of Life (HRQL) score. Other measure was the Medical Outcomes Study (MOS), which has a Mental Component Summary (MCS) and Physical Component Summary (PCS). At both the 4- and 12-week follow-ups, there were no statistically significant differences (at the  $p<0.05$  level) between the MRgFUS and sham groups in the SSS, HRQL, PCS, or MCS. Change in uterine and fibroid volume, however, differed significantly between groups at 12 weeks. Uterine volume decreased by 17% in the MRgFUS group and by 3% in the sham group ( $p=0.04$ ). Total fibroid volume decreased 18% in the MRgFUS group and did not change in the sham group ( $p=0.03$ ). The authors concluded that women are willing to participate in a sham-controlled RCT of MRgFUS and that larger trials are feasible.

### Nonrandomized Studies



The “pivotal” study which led to FDA approval of the ExAblate® 2000 device was included in the AHRQ report discussed above.<sup>[33, 34]</sup> 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 (2009) failed to report on the original primary outcome measure and instead reported findings on a different quality of life measure.<sup>[36]</sup> 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 nonrandomized study compared two variations on the MRgFUS procedure.<sup>[37]</sup> 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 eight months after treatment.<sup>[38]</sup> 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 seven 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, high rate of loss to follow-up, and failure to control for bias which could impact treatment results.<sup>[39-46]</sup>

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.

### Section Summary

There is insufficient evidence regarding the use of MRgFUS as a treatment of uterine fibroids compared to other established procedures. Evidence from randomized controlled trials is lacking and conclusions concerning the safety and efficacy of MRgFUS cannot be drawn from nonrandomized studies due to methodological limitations such as an inability to isolate treatment effects. Questions remain regarding the durability of MRgFUS treatment or the impact of this treatment upon future fertility.

## **Palliative Treatment of Bone Metastases**

The principal outcomes for treatment of pain are symptom relief and improved functional level. Relief of pain is a subjective outcome and can be influenced by nonspecific effects, placebo response, the natural history of the disease, and regression to the mean. Therefore, RCTs are important to control for nonspecific effects and to determine whether any treatment effect provides a significant advantage over the placebo/sham treatment or other treatments. Appropriate comparison groups depend on the condition being treated and may include placebo/sham stimulation, or medical or surgical management.

Therefore, the 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.

### Systematic Reviews

A systematic review by Gennaro (2019) evaluated multiple thermal ablation techniques for relief of bone pain due to metastatic disease, including MRgFUS, radiofrequency ablation, microwave ablation and cryoablation.<sup>[47]</sup> The review included 11 papers and reported a mean reduction in pain scores of 26% to 91% at four weeks and 16% to 95% at 12 weeks. The authors noted that MRgFUS was associated with a higher rate of adverse events than the other modalities.

### Randomized Controlled Trials

Hurwitz (2014) published results from a randomized trial that evaluated the safety and efficacy of MRgFUS on palliation of pain due to bone metastases.<sup>[48]</sup> The study included patients with at least three months of life expectancy who had bone metastases that were painful, despite radiotherapy treatment, or who were unsuitable for or declined radiotherapy. Patients included had to rate tumor pain on a numeric rating scale (NRS) at 4 or higher on a 10-point scale. They could have up to five painful lesions; however, only one lesion was treated and it had to cause at least 2 points greater pain on the NRS than any other lesion. In addition, targeted tumors needed to be device accessible.

Study participants were randomized in a 3:1 ratio to active (n=122) or sham (n=39) MRgFUS treatment. Ten patients in the treatment group and four in the sham group did not receive the allocated treatment. An additional 26 patients in the treatment group and 23 in the sham group did not complete the three-month follow-up. A much larger proportion of the placebo group dropped out; 17 (49%) of 35 who were treated decided to have rescue MRgFUS treatment after lack of response to placebo. A modified intention-to-treat analysis was used that included patients who had at least one MRgFUS or placebo sonication. Missing values were imputed using the last observation carried forward method.

The primary efficacy end point, assessed at three months, was a composite outcome comprised of change in baseline in worst NRS score and morphine equivalent daily dose (MEDD) intake. Patients were considered responders if their worst NRS score decreased by at least 2 points and if their MEDD intake did not increase more than 25% from baseline to three months. NRS score and MEDD intake separately were reported as secondary outcomes.

Seventy-two (64%) of 112 patients in the MRgFUS group and 7 (20%) of 35 patients in the control group were considered responders, as previously defined. The difference between groups was statistically significant (p=0.01), favoring active treatment. When the two measures

comprising the primary end point were analyzed separately, there was a statistically significant difference between groups in change in worst NRS score and a nonsignificant difference in change from baseline in pain medication. The NRS score decreased by a mean (SD) of 3.6 (3.1) points in the MRgFUS group and by a mean of 0.7 (2.4) in the placebo group ( $p < 0.01$ ). Change in MEDD was only reported in a figure. Fifty-one (46%) patients in the MRgFUS group and one (3%) in the placebo group experienced at least one adverse event (AE). Most AEs were transient, and the most common was sonication pain, experienced by 36 (32%) patients in the MRgFUS group. In 17 (15%) patients, sonication pain was severe; three patients did not complete treatment due to pain. The most clinically significant AEs that lasted more than a week were third-degree skin burns in one patient (associated with noncompliance with the treatment protocol) and fracture in two patients (one of which was outside the treatment location). Potential limitations of the trial included a nonconventional primary outcome measure and the small initial size of the sham group. Moreover, a large number of sham patients (66%) did not complete the three-month follow-up; the authors did state that this low completion rate was due to lack of response to placebo treatment. Additional randomized studies are required to isolate the treatment effect of MRgFUS upon pain and better characterize the benefit and length of symptom relief with MRgFUS in patients with bone metastases.

### Nonrandomized Studies

Examples of nonrandomized trials include four small ( $n = 11$  to  $31$ ), nonrandomized prospective studies evaluating MRgFUS for the treatment of bone metastases, the majority of which are industry-sponsored.<sup>[49-52]</sup> Although none reported any treatment-related adverse effects, and all reported improvements in pain and two reported 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.

In addition, there have been several small case series published on the use of MRgFUS for treatment of bone metastases. However, these series did not compare the safety and efficacy of this treatment to other treatment options.

### **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

#### *Nonrandomized Studies*

No controlled studies evaluating MRgFUS for treating breast cancer have been identified in the published literature. Evidence is limited to small case series, examples of which include six feasibility studies that describe preliminary results only.<sup>[53-58]</sup> 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

### *Nonrandomized Studies*

Evidence on MRgFUS in brain cancer is similarly restricted to case series, which include a report of initial findings in three patients.<sup>[59]</sup> The authors reported 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

### *Nonrandomized Studies*

Small (n=1 to 5) feasibility studies regarding the use of MRgFUS in patients with biopsy-proven prostate cancer have demonstrated that the procedure may be performed in this patient population.<sup>[60-62]</sup> At least one study was conducted using the ExAblate® 2100 System, which is not FDA approved for this indication. Larger and longer comparative trials are needed to establish the use of MRgFUS for treating prostate cancer.

## PRACTICE GUIDELINE SUMMARY

### **AMERICAN CONGRESS OF OBSTETRICS AND GYNECOLOGISTS**

A practice bulletin from American Congress of Obstetrics and Gynecologists (ACOG) considered MRgFUS as an alternative to hysterectomy as a treatment of uterine fibroids, but did not specifically recommend its use, stating:<sup>[63]</sup>

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**

The 2017 American College of Radiology (ACR) Appropriateness Criteria guidelines regarding the treatment of uterine fibroids mention the use of MRgFUS indicating that, “(t)o date, there is little long-term information on the efficacy of [MRgFUS] technology.”<sup>[64]</sup> However, the MRgFUS approach is not recommended as treatment for fibroids.

### **AMERICAN UROLOGICAL ASSOCIATION**

In 2017, the American Urological Association (AUA) published a joint guideline (with the American Society for Radiation Oncology [ASTRO], and the Society of Urologic Oncology [SUO] regarding clinically localized prostate cancer.<sup>[65]</sup> Nearly all recommendations regarding HIFU as a treatment for prostate cancer were Expert Opinion, that is, the committee did not

have sufficient evidence to grade the strength of the evidence. Additionally, the following recommendation was made:

*Clinicians should advise localized prostate cancer patients considering HIFU that tumor location may influence oncologic outcome. Limiting apical treatment to minimize morbidity increases the risk of cancer persistence. (Moderate Recommendation; Evidence Level: Grade C)*

Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data).

## **NATIONAL COMPREHENSIVE CANCER NETWORK**

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 2.2020) include high-intensity focused ultrasound ablation as a recommended treatment option in the presence of radiation recurrence in a manner that is consistent with the policy criteria.<sup>[7]</sup>

## **SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA**

In 2015, the Society of Obstetricians and Gynaecologists of Canada published a clinical practice guideline entitled “Management of Uterine Fibroids in Women with Otherwise Unexplained Fertility.”<sup>[66]</sup> The guideline states that there are no studies comparing MRgFUS with myomectomy or in women with fibroids who have infertility as their primary complaint, and thus additional data are needed before the treatment is offered to this patient population.

## **SUMMARY**

### **HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) ABLATION**

It appears that high-intensity focused ultrasound (HIFU) ablation may improve overall health outcomes for select men with localized recurrent prostate cancer. Clinical guidelines based on research recommend HIFU for specific patient populations. Therefore, high-intensity focused ultrasound may be considered medically necessary to treat localized prostate cancer when policy criteria are met. Due to a lack of research and clinical practice guidelines, HIFU is considered investigational for all other indications that do not meet the policy criteria.

### **MAGNETIC RESONANCE (MR) GUIDED FOCUSED ULTRASOUND (MRGFUS)**

#### **Movement Disorders**

It appears that (MRI)-guided focused ultrasound (MRgFUS) may help those with medicine-refractory essential tremor. At least one high quality randomized study has demonstrated improvement in symptoms with MRgFUS treatment and may improve overall quality of life. Therefore, MRgFUS may be considered medically necessary for medicine-refractory essential tremors when policy criteria are met.

#### **Uterine Fibroids**

The evidence for MRgFUS in individuals who have uterine fibroids includes a pilot RCT, nonrandomized comparative studies, and case series. The pilot RCT (N=20 patients)

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reported some health outcomes, but its primary purpose was to determine the feasibility of a larger trial. It did not find statistically significant differences in quality of life outcomes between active and sham treatment groups, but did find lower fibroid volumes after active treatment. The pivotal Food and Drug Administration trial was not randomized, the clinical significance of the primary outcome was unclear, and there were no follow-up data beyond one year. 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. Therefore, 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 is a single randomized trial comparing MRgFUS to placebo as well as 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 and other Indications**

(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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## CODES

**NOTE:** There are no specific CPT codes for the use of magnetic resonance–guided high-intensity ultrasound ablation in certain cancers. In these situations an unlisted code would be used based on the anatomic location of the metastasis being treated (eg, 23929 for the clavicle) or perhaps one of the radiation oncology unlisted codes (eg, 77299 or 77499).

Codes	Number	Description
CPT	0071T	Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume of less than 200 cc of tissue
	0072T	;total leiomyomata volume greater or equal to 200 cc of tissue
	0398T	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed
	23929	Unlisted procedure, shoulder
	55880	Ablation of malignant prostate tissue, transrectal, with high intensity-focused ultrasound (HIFU), including ultrasound guidance
	58578	Unlisted laparoscopy procedure, uterus
	58579	Unlisted hysteroscopy procedure, uterus
HCPCS	C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance
	<del>C9747</del>	<del>Ablation of prostate, transrectal, high intensity focused ultrasound (HIFU), including imaging guidance (Deleted 01/01/2021)</del>

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