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**Medical Policy Manual** Surgery, Policy No. 139

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

**Effective**: December 1, 2024

**Next Review:** August 2025
**Last Review:** October 2024

**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. High-intensity focused ultrasound (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 either of the following indications:

A. Medicine-refractory essential tremors; or

B. Pain palliation in an adult (greater than or equal to 18 years) with metastatic bone cancer for whom radiotherapy has failed or who are not candidates for radiotherapy.

IV. Magnetic resonance (MR) guided focused ultrasound (MRgFUS) is considered **investigational** for all other indications not meeting Criterion III., including but not limited to treatment of the following:

A. Uterine fibroids; and

B. All tumors, including but not limited to brain, breast, prostate and renal; and

C. Tremor-dominant Parkinson's disease.

*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 4.2024)[1], in the presence of radiation therapy recurrence (see below), a candidate for local therapy includes:

- Biopsy positive
- Studies negative for distant metastatic disease
- Life expectancy greater than five years

### RADIATION RECURRENCE

NCCN guidelines for prostate cancer (version 4.2024) 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 PSA recurrence 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 External Beam Radiation Therapy (EBRT) with or without hormonal therapy; 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
- For pain palliation bone metastases, clinical documentation that radiotherapy has failed for the patient or the patient is not a candidate for radiotherapy

## 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 Outside of the Liver, 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, medicine-refractory tremor, 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:

High-Intensity Focused Ultrasound

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. In June 2018, EDAP received 510(k) clearance for its Focal-One® HIFU device designed for prostate tissue ablation procedures. This device fuses magnetic resonance and 3D biopsy data with real-time ultrasound imaging, allowing urologists to view detailed images of the prostate on a large monitor and direct high-intensity ultrasound waves to ablate the targeted area.

In 2020, the Sonalleve MR-HIFU received FDA approval through the Humanitarian Device Exemption PMA process for treatment of osteoid osteomas in the extremities.[2]

Magnetic Resonance-Guided Focused Ultrasound

The ExAblate® 2000 System (InSightec, Inc.) received premarket approval (PMA) from the FDA for the 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.[3]

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.[4] 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 childbearing.

In October 2012, the FDA granted PMA approval for ExAblate® System, for pain palliation due to metastatic bone cancer.[5] 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.

In July 2016, the FDA granted premarket approval (PMA) of the ExAblate® Neuro System for the treatment of essential tremor in patients who have not responded to medication (beta-blockers or anticonvulsant drugs).[6] This PMA outlined required pending studies for the device, including investigational treatment with the ExAblate Neuro in 75 patients to be evaluated at two-, three-, four- and five-years post-operative.

In December 2018, the FDA granted premarket approval (PMA) of the ExAblate Model 4000 (Neuro) for the treatment of tremor-dominant PD with medication-refractory tremor.[7] This PMA outlined required post-approval study, including a prospective, multi-center, new enrollment, long-term safety and effectiveness study in 50 patients. The study is designed to evaluate the long-term safety of the device when used to treat patients who have failed medication.

The ExAblate® Model 4000 Type 1.0 and 1.1 System ("Exablate Neuro") received PMA approval in 2021 for three indications: the unilateral thalamotomy treatment of idiopathic essential tremor patients with medication-refractory tremor; the unilateral thalamotomy treatment of tremor-dominant Parkinson's disease with medication-refractory tremor; and the unilateral pallidotomy of medication-refractory Parkinson's disease patients with moderate to severe motor complications as a supplement to medication treatment.[8] FDA product codes: NRZ, POH.

MRgFUS is also being investigated for the treatment of other tumors, including breast, prostate, brain, and desmoid tumors as well as nonspinal osteoid osteoma.

## 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 treatments,* include 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.

Maestroni (2021) published a systematic review (SR) of studies evaluating the safety and cancer control rates of HIFU following failure of External Beam Radiation Therapy (EBRT).[9] Data from 1241 patients across 13 publications were included in the analysis. The mean age of the patients was 68.6 years (range 53 to 83 years, SD ±6.11). Of those included in the analysis, 38.3% of the patients were on androgen-deprivation therapy at the time of salvage HIFU, and 24.71% continued the therapy after the treatment. PSA nadir was 1.1 ng/mL (SD ±3.39). The time to which PSA nadir was reached was not reported in all series. Limited to these series, PSA nadir was achieved in a mean time of 11.7 weeks (SD ±9.1). Mean follow-up was 24.3 months after salvage HIFU treatment, ranging from 3 to 168 months. Overall survival (OS) was 85.2% at five years. One study reported OS of 72% at seven years.

Valle (2021) published a SR comparing the efficacy and toxicity of salvage radical prostatectomy (RP), HIFU, cryotherapy, stereotactic body radiotherapy (SBRT), low-dose-rate (LDR) brachytherapy, and high-dose-rate (HDR) brachytherapy in the management of locally recurrent prostate cancer.[10] Two- and five-year recurrence-free survival (RFS) rates and crude incidences of severe genitourinary (GU) and gastrointestinal (GI) toxicity were endpoints of interest. A total of 150 studies were included for analysis. Significant heterogeneity between studies was found within each modality, and covariates differed between modalities, necessitating adjustment. Adjusted five-year RFS ranged from 50% after cryotherapy to 60% after HDR brachytherapy and SBRT, with no significant differences between any modality and RP.

Ingrosso (2020) published a SR with meta-analysis on nonsurgical therapeutic strategies in patients with radiorecurrent prostate cancer.[11] 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 to 68%). The prevalence of incontinence was highest among patients treated with HIFU (28%, 95% CI 19 to 38%; $I^2$ = 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.[12] 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 to 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.[13] Morbidity rate for grade III/IVa complications was 3.6%. Smaller studies with shorter-duration of follow-up are in general agreement[14-17], however, patient selection criteria is an important predictor of treatment outcomes[18-21]. 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).[1]

Primary Treatment of Prostate Cancer

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).[14, 17, 22]Guang (2024) published a SR of oncological and functional outcomes following whole-gland HIFU as the primary treatment for localized prostate cancer.[23] Primary review outcomes were biochemical disease-free survival rates, overall and prostate-specific survival rates, and

negative biopsy rates. Secondary outcomes were functional results and treatment complications. The review included 35 prospective and retrospective case series of 6,618 patients with follow-up at 10.9 to 94 months. Biochemical disease-free survival rate varied greatly across studies from 21.7% to 89.2%. 10-year prostate cancer-specific survival rate after HIFU was 90%, 99%, and 100% in three studies. Negative biopsy rates post-HIFU ranged from 20% to 92.7%. Common side effects of HIFU included urinary incontinence (grade 1: 0% to 22.7%), erectile dysfunction (11.6% to 77.1%), urinary tract infections (1.5% to 47.9%), and bladder outlet obstruction mainly as urethral strictures (7% to 41.2%). The reviewers concluded that oncological and functional outcomes varied greatly across studies and that additional prospective trials are needed to assess whole-gland HIFU as a treatment for localized prostate cancer.

Hopstaken (2022) conducted a SR to assess the effectiveness of focal therapy in localized prostate cancer on functional and oncological outcomes.[24] The review included 72 studies: 27 reported on HIFU, nine on irreversible electroporation, 11 on cryoablation, eight each on focal laser ablation and focal brachytherapy, seven on photodynamic therapy, two on RFA, and one on prostatic artery embolization. Results revealed photodynamic therapy and HIFU to have potentially promising results. HIFU studies reported a median of 95% pad-free (regarding continence) patients and a median of 85% of patients with no clinically significant cancer in the treated area. No changes in continence were noted, and a median of 90% of patients were without clinically significant cancer in the treated area among those receiving photodynamic therapy. Both treatments were well-tolerated. Despite these positive results, the authors noted that most studies concerning focal therapy are still in an early research stage and that definitive proof of oncological effectiveness of focal therapy against standard of care is still pending. More high-quality evaluations are needed, preferably via multicenter RCTs with long-term follow-up, predefined assessment of oncological and functional outcomes, and health-related quality-of-life measures.

Bakavicius (2022) published a SR of data from studies with at least 50 patients published 2010 to 2020 that evaluated focal HIFU therapy as a primary treatment for localized prostate cancer.[25] Data from 20 publications were included in the final analysis consisting of one randomized feasibility study (Hamdy 2018),[26] ten prospective development studies, and nine retrospective case series (total n=4209). Across all studies, clinically significant in-field recurrence and out-of-field progression were detected in 22% and 29% patients, respectively. The authors conclude intermediate- and long-term outcomes are needed from high-quality comparative trials evaluating the HIFU in comparison to standard of care.

Bates (2021) published a SR that evaluated studies published from January 2000 to June 2020 on focal therapy as a treatment for histologically proven, clinically localized prostate cancer compared to standard management.[27] Focal therapy interventions included HIFU, vascular targeted photodynamic therapy, laser ablation, thermal ablation, focal brachytherapy, radiofrequency waves, microwave ablation, focal external-beam radiotherapy, and irreversible electroporation. The comparator intervention included any standard management option such as radical prostatectomy, external beam radiotherapy, whole gland brachytherapy, and active surveillance/monitoring. Overall, five articles reporting on four primary comparative studies (one RCT and three retrospective nonrandomized comparative studies; n=3961) and 10 eligible systematic reviews were identified. One retrospective study comparing focal HIFU with robotic radical prostatectomy found no significant difference in treatment failure at three years, with better continence and erectile function recovery with HIFU. Regarding the included systematic reviews, virtually all concluded that there was insufficient high certainty evidence to

make definitive conclusions regarding the clinical effectiveness of focal therapy. The authors conclude that the "certainty of the evidence regarding the comparative effectiveness of focal therapy as a primary treatment for localized prostate cancer was low, with significant uncertainties" and that "until higher certainty evidence emerges...focal therapy should ideally be performed within clinical trials or well-designed prospective cohort studies."

### Uterine Fibroids

Ali (2024) published a SR and meta-analysis of the safety of HIFU for obstetric and gynecological diseases including adenomyosis, ectopic pregnancy, endometriosis, or gestational trophoblastic disease.[28] 56 studies of 11,740 participants were included; 42 were cohort studies, and 14 were case reports. The reviewers reported multiple mild to moderate adverse events including pain at the treatment site, estimated risk ratio (RR) with 95% CI: 0.61 (0.33 to 0.89), abnormal vaginal discharge 0.16 (0.073 to 0.24), low-grade fever (<38 °C) 0.005 (0.002 to 0.009). Regarding adverse events that required clinical treatment, 99 of 6,437 patients had small vesicles and superficial burns (RR and 95% CI: 0.012 [0.007 to 0.018]), groin or lower abdominal pain (RRs with 95% CIs were 0.1 (0.067 to 0.13) and 0.38 (0.25 to 0.51). The reviewers concluded that HIFU is a safe approach for multiple gynecological and obstetric diseases. The reviewers rated the risk of bias to be good to fair for the included case reports and fair for the included cohort studies. The review is limited by lack of comparative studies and heterogeneity of studies included in the meta-analysis.

Tsai (2021) published a SR with meta-analysis of studies comparing the outcome of HIFU and conventional surgery (myomectomy and hysterectomy) for the treatment of uterine myomas.[29] The review included 10 studies inclusive of one RCT, six prospective studies and three retrospective studies with sample sizes ranging from 39 to 1353 (total n=4217). HIFU improved uterine myoma symptoms compared with conventional surgery at six months (MD −1.61; 95% confidence interval [CI], −2.88 to −0.33) and 12 months (MD −2.44; 95% CI, −3.68 to −1.20) after treatment as well as quality-of-life score at six (MD 2.14; 95% CI, 0.86 to 3.42) and 12 (MD 2.34; 95% CI, 0.82 to 3.86) months after treatment compared to the surgery group. Overall, nine studies, including RCTs and non-RCTs had moderate risk of bias and one study had serious risk of bias. Three studies reported the incidence of skin burns in the HIFU group. Considerable heterogeneity was observed across the studies with respect to treatment techniques, outcomes, and timepoints of assessment of outcomes. Patients with more than three uterine myomas or larger myomas were not included in any of the studies and four studies recruited patients with only certain types of uterine myoma, which limits the generalizability of observations.

A 2017 SR published by the Agency for Healthcare Research and Quality (AHRQ) on the management of uterine fibroids included evaluation studies of HIFUS.[30] 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.

### Other Indications

HIFU has been investigated as a treatment for other indications, such as adenomyosis[31] and thyroid disorders,[32, 33] but these are generally small, noncomparative studies. Systematic reviews of HIFU in the treatment of malignant lesions of the hepatobiliary system,[34]

pancreas,[35] and benign thyroid nodules[36, 37] 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

Miller (2021) published a meta-analysis that evaluated the efficacy of MRgFUS for treating medication-refractory essential tremor (ET) with a focus on long-term trends and the durability of the response.[38] Data from patients with comorbid conditions such as Parkinson's disease, were not included. Twenty-one studies (n=395) were included; 17 were prospective studies, three were retrospective, and one was the RCT published by Elias (2016) discussed below. Hand tremor scores decreased from a weighted mean pre-operative value of 19.2±5.0 to 7.4±5.0 after three months. Over time, the hand tremor score values gradually increased: 8.3±5.3 after 12 months and 9.1±5.4 after 36 months. The pooled standardized mean difference of hand tremor scores compared to pre-treatment values was 2.68 (95% CI, 1.94 to 3.41) at three months (five studies), 2.44 (95% CI, 1.97 to 2.91) at the 12-month time point (seven studies), and 2.18 (95% CI, 1.50 to 2.86) at the 24-month time point (three studies). Clinical Rating Scale for Tremor scores were reported through 12 months. The pooled standardized mean difference in Clinical Rating Scale for Tremor (CRST) scores compared to pre-treatment values was 1.86 (95% CI, 1.51 to 1.21) at the three-month time point (eight studies) and 2.24 (95% CI, 1.55 to 2.94) at the 12-month time point (six studies). Six studies reported Quality of Life in Essential Tremor Questionnaire (QUEST) scores as a quality-of-life measure. The pooled pre-treatment QUEST score was 48.2±22.4, which improved to 24.9±18.2 at three months. Additionally, a single study detailed a mean 23.8±19.6 QUEST score at 36 months follow-up, an increase of 2.2 over 30 months.

A SR of 29 studies (n=617) on MRgFUS in the treatment of ET was published by Agrawal (2021).[39] Studies that reported outcomes in patients with tremors secondary to any other causes, such as drug-induced tremor, trauma, psychogenic tremor, or co-morbid Parkinson disease and dystonia were excluded. The ventral intermediate nucleus of the thalamus is the common target region. Of the 29 studies, only one (Elias 2016, below) was an RCT, the remaining were observational studies. Pre- and post- procedure changes in the CRST score, hand score, disability and quality of life scores were evaluated. A significant difference was observed in the pooled standard mean difference between pre- and post-operative total CRST score ($p<0.001$), hand score ($p<0.05$), and disability at 12 months ($p<0.01$), although the number of included studies ranged from five to nine for the assessed outcomes. Disability, assessed by the CRST Part C, at three months after MRgFUS, was reported by five studies in which the pooled standard mean difference was −2.66 with 95% CI: −3.53 to −1.79 ($p=0.08$). Disability at 12 months after MRgFUS was reported by eight cohorts and the pooled standard mean difference was −4.54 (95% CI: −8.95 to −0.12, $p<0.01$). More than one third of patients developed sonication related complications, amongst which head pain and dizziness were the most common. The pooled proportion of ataxia, which included gait disturbance and hand ataxia, was 50% at the short-term was found to be as high as 31% at three years post-treatment. No hemorrhage, seizure or trajectory related complications were reported.

Giordano (2020) conducted a systematic review with meta-analysis to compare unilateral MRgFUS to unilateral and bilateral deep brain stimulation (DBS) for medication-refractory ET.[40] Forty-five studies published between 1996 and 2019 were identified. Thirty-seven studies (n=1202) evaluated DBS and eight studies (n=477) evaluated MRgFUS. Fifteen studies had a retrospective study design, while 30 were prospectively designed. Means and standard deviations were calculated for each intervention and differences between groups were compared where appropriate. The average percentage improvement in tremor severity was significantly improved in the pooled DBS group (60.1%±9.7%) compared to the MRgFUS group (55.6%±8.2%, p<0.001). Subgroup analyses demonstrated that the improvement in tremor severity was significantly greater with the bilateral DBS (61.2%±5.2%) compared to both unilateral DBS (56.4%±9.7%) and MRgFUS; there was no significant difference between unilateral DBS and MRgFUS. MRgFUS was associated with significantly improved quality of life compared to DBS (61.9%±7.9% vs 52.5%±16.2%, p<0.001). There were 517 complications reported in the DBS group and 484 complications reported in the MRgFUS group. The most common adverse events reported with DBS were lead-related complications (11.4%) and speech disturbances (11.1%). For MRgFUS, adverse events of sensory nature (36.7%) and gait disturbances/muscle problems (34.4%) were most common. Limitations of the review included the different scales used in studies to measure tremor severity and quality of life. There was only one retrospective study that directly compared DBS and MRgFUS.

A technology assessment was published by Health Quality Ontario (2018).[41] 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 quality of life. 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.[42] 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

Cosgrove (2022) published an open-label, prospective study of the long-term safety and efficacy of MRgFUS unilateral thalamotomy for essential tremor, evaluating patients who had participated in a previous RCT.[43] 45 and 40 patients completed the four- and five-year follow-ups, respectively. Clinical Rating Scale for Tremor (CRST) scores for the treated hand continued to show significant improvement by 73.3% and 73.1% from baseline at years four and five (p<0.0001). Combined hand tremor and motor scores improved by 49.5% and 40.4% at years four and five (p<0.0001). Quality of Life in Essential Tremor Questionnaire (QUEST) scores also remained significantly improved at year four (p<0.0001) and year 5 p<0.0003). All

adverse events at four- and five-year follow-ups were mild (71%) or moderate (29%). No new types of adverse events, compared to earlier follow-ups, occurred at four or five years. Overall, at the five-year follow-up, remaining adverse events were paresthesia (n=8 patients), imbalance (n=6), unsteadiness (n=2), gait disturbances (n=2), limb weakness (n=2), dysmetria (n=2), dysgeusia (n=2), slow movements (n=1), and head pressure (n=1).

A high-quality double-blind, sham-controlled randomized trial by Elias (2016)[44] was identified by the systematic reviews above. Trial selection criteria included patients with moderate or severe postural or intention tremor of the hand (≥2 on the Clinical Rating Scale for Tremor) and refractory to at least two medical therapies. Patients were excluded if they had a neurodegenerative condition, unstable cardiac disease, coagulopathy, risk factors for deep-vein thrombosis, severe depression, or cognitive impairment or if they had undergone a previous brain procedure (transcranial magnetic stimulation, deep-brain stimulation, stereotactic lesioning, or electroconvulsive therapy). Patients were randomized to MRgFUS thalamotomy (n=56) or sham treatment (n=20). Outcomes were tremor severity, improvement, and quality of life 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 quality of life were maintained at 12 months in the MRgFUS group.

Chang (2018) published results from 76 patients who participated in the open-label extension of the RCT.[45] 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

Several 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.[46-49]

**Parkinson’s Disease**

Systematic Reviews

Ge (2021) published a SR of data from RCTs comparing MRgFUS to sham procedure in the treatment of Parkinson’s Disease (PD).[50] The available data from RCTs consisted of the trials by Bond (2017) and Martinez-Fernandez (2020) below, in which the blinded phase lasted for four months three months, respectively. The MRgFUS group showed significant improvement in limb tremor on the treated side (SMD: - 1.20; 95% CI: - 2.06 to - 0.34) and the ability to perform daily activities (SMD: - 0.86; 95% CI: - 1.41 to 0.32) compared to the sham group, however, no other treatment effects were found. Dizziness was more common in the treatment group (OR: 4.68; 95% CI: 1.20 to 18.23) and symptoms such as hemiparesis, ataxia, dysmetria, speech impairment, and anxiety were found only in the treatment group in both studies. Heterogeneity in patient selection (asymmetric motor symptoms vs. tremor-dominant

PD) surgical target site (dorsolateral subthalamic nucleus or ventral intermediate thalamus), and assessed outcomes, as well as small sample sizes, and limited follow-up times are limitations to the available data. Larger, longer-term trials are needed to determine the role of MRgFUS in the treatment of Parkinson's disease.

Randomized Controlled Trials

Krishna (2023) published results from a multi-center, prospective, double-blind, randomized, sham-controlled trial to evaluate the safety and efficacy of MRgFUS ablation of the globus pallidus internus for treatment of medication-refractory idiopathic Parkinson's disease.[51] 94 participants with Parkinson's disease, dyskinesias or motor fluctuations, motor impairment, and who were not taking medication, were randomized (3:1) to undergo either MRgFUS ablation opposite the most symptomatic side of the body (n=69 patients) or a sham procedure (n=25). 65 patients in the active treatment group and 22 patients in the control group were assessed at three months for the primary outcome: response defined by a decrease of at least three points from baseline either in the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) score for the treated side while off-medication, or in the score on the Unified Dyskinesia Rating Scale (UDysRS) in the on-medication state. After a three-month blinded phase, an open-label phase lasted 12 months. Within the active treatment group, 45 patients (69%) had a response, compared to 7 (32%) in the control group (difference, 37%, 95% CI, 15 to 60, p=0.003). Of patients in the active-treatment group who responded, 19 met the MDS-UPDRS III criterion only, 8 met the UDysRS criterion only, and 18 met both criteria. 30 of the 39 patients in the active-treatment group who had a response at three months continued to show a response at 12 months. Pallidotomy-related adverse events in the active-treatment group included dysarthria, gait disturbance, loss of taste, visual disturbance, and facial weakness. The authors note that longer and larger trials are required to determine the efficacy and safety of MRgFUS of the globus pallidus.

Martinez-Fernandez (2023) conducted a prospective, open-label, long-term follow-up study of 32 patients with Parkinson's disease who received unilateral MRgFUS subthalamotomy in a previous open-label pilot study and the RCT published by Martinez-Fernandez (2020).[52] Participants were evaluated three years after treatment. The MDS-UPDRS III score for the treated hemibody off-medication was improved by 52.3% from baseline to three years (score reduction from 19.0 to 8.9, 95% CI 8.7 to 11.6, p<0.001). The total MDS-UPDRS III off-medication score was 22.9% lower at three years than before treatment (36.8 versus 27.4, 95% CI 6.0 to 11.5, p<0.001). No disabling or delayed adverse events were reported.

Martinez-Fernandez (2020) published the results of a RCT of 40 patients with asymmetric Parkinson's disease with predominant motor features randomly assigned to focused ultrasound subthalamotomy (n=27, active treatment) or sham procedure (n=13, control).[53] The lesion site was targeted to the dorsolateral subthalamic nucleus and immediately dorsally to impinge on the pallidothalamic tract and adjusted according to clinical effects. The primary efficacy outcome was between-group difference in the change from baseline in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score and the primary safety outcome was procedure-related complications, both assessed at four months post-procedure. MDS-UPDRS III score for the more affected side decreased from 19.9 at baseline to 9.9 in the active-treatment group (least-squares mean difference, 9.8 points; 95% confidence interval [CI], 8.6 to 11.1) and from 18.7 to 17.1 in the control group (least-squares mean difference, 1.7 points; 95% CI, 0.0 to 3.5); between group difference = 8.1 (95% CI, 6.0 to 10.3; p<0.001). Adverse events in the active-treatment group were dyskinesia in the

off-medication state in six patients and in the on-medication state in six, which persisted in three and one, respectively, at four months; weakness on the treated side in five patients, which persisted in two patients at four months; speech disturbance in 15 patients, which persisted in three at four months; facial weakness in three patients, which persisted in one at four months; and gait disturbance in 13 patients, which persisted in two at four months. In six patients in the active-treatment group, some of these deficits were present at 12 months.

A double-blind, sham-controlled, randomized pilot trial by Bond (2017) assessed the safety and efficacy of unilateral MRgFUS thalamotomy in patients with tremor-dominant PD.[54] Adult patients over 30 years with idiopathic PD were included if their subtype was tremor-dominant that was deemed medication-refractory, severe, and disabling. A total of 27 patients were randomized (2:1) to MRgFUS thalamotomy (n=20) or a sham procedure (n=7) at two centers. The lesion target described in the study was the ventral intermediate thalamus. The primary efficacy outcome was change from baseline (on-medication state) to three months after post-procedure in the hand tremor subscore in the Clinical Rating Scale for Tremor (CRST). On-medication median tremor scores improved 62% (IQR, 22%-79%) from a baseline of 17 points (IQR, 10.5-27.5) following MRgFUS thalamotomy and 22% (IQR, -11% to 29%) from a baseline of 23 points (IQR, 14.0-27.0) after sham procedures (Wilcoxon p= 0.04). The most common thalamotomy-related adverse events reported for all 26 patients treated were finger paresthesia (39%), ataxia (35%), and orofacial paresthesia (27%). Paresthesia and ataxia persisted to one year in 19% and 4% of patients, respectively. Eight severe adverse events were reported in four patients, and three were thalamotomy-related (two patients with persistent mild hemiparesis and one patient had an associated persistent mild ataxia). After unblinding at three months, six of the seven patients who received sham procedures crossed over to undergo open-label treatment with MRgFUS. Limitations to the study include small sample size, comparison to a sham treatment instead of an alternative surgical procedure and lack of long-term follow-up.

Section Summary

There is insufficient evidence for the use of MRgFUS as a treatment for Parkinson’s disease compared to established procedures. While MRgFUS effects on tremor are promising, existing evidence among Parkinson’s disease patients is from small studies, most of which have included short term follow-ups (e.g., up to 12 months), and multiple adverse events have occurred. Randomized studies have compared MRgFUS to sham procedures rather than current surgical standard treatments. Additional larger, long-term follow-up studies are needed to assess the safety and efficacy of MRgFUS for the treatment of Parkinson’s disease.

**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 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

A SR with meta-analysis published by Xu (2021) assessed re-intervention rates of myomectomy, uterine artery embolization (UAE), and MRgFUS for the treatment of uterine fibroids across 31 studies (n=42,103).[55] Shorter-term (12-month) pooled re-intervention rate estimations of MRgFUS, UAE, and myomectomy were 0.12 (95%CI, 0.04 to 0.20; $I^2$=89.1%; p=0.000), 0.07 (95%CI, 0.06 to 0.09; $I^2$=14.2%; p=0.324), and 0.06 (95%CI, 0.01 to 0.11; $I^2$=95.1%; p=0.000), respectively. Twenty-four-month: 0.14 (95%CI, 0.07 to 0.21), 0.08 (95%CI, 0.01 to 0.17; $I^2$=75.7%; p=0.016), and 0.10 (95%CI, 0.04 to 0.16; $I^2$=76.0%; p=0.002), and 36-month: 0.22 (95%CI, 0.11 to 0.32; $I^2$=86.3%; p=0.002), 0.14 (95%CI, 0.05 to 0.23; $I^2$=94.7%; p=0.000), and 0.09 (95%CI, 0.05 to 0.13; $I^2$=0.0%; p=0.508), respectively. Longest-term (60-month) estimations of the pooled re-intervention rates for MRgFUS, UAE, and myomectomy were 0.49 (95%CI, 0.21 to 0.77; $I^2$=96.5%; p=0.000), 0.21 (95%CI, 0.17 to 0.25; $I^2$=84.1%; p=0.000), and 0.19 (95%CI, 0.15 to 0.24; $I^2$=53.7%; p=0.071), respectively. No evidence of publication bias was found. In sum, estimations of the pooled 12-month, 24-month, 36-month and 60-month re-intervention rates of MRgFUS were 12%, 14%, 22% and 49%, which were the highest rates across all interventions assessed. Myomectomy had the lowest re-intervention rate.

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.

Barnard (2017) published preliminary results from Fibroid Interventions: Reducing Symptoms Today and Tomorrow trial, a parallel RCT and cohort study comparing MRgFUS with fibroid embolization to treat uterine fibroids.[56] For the RCT, patients were randomized to uterine artery embolization (UAE; n=22) or to MRgFUS (n=27). Patients and investigators were not blinded. Women who did not want to be randomized were enrolled in the cohort study; 16 underwent UAE and 16 underwent MRgFUS. After six weeks of follow-up, there were no differences between groups in fatigue, hot flashes, discomfort urinating, vaginal discharge, or constipation. Recovery was significantly faster in the MRgFUS group, as measured by the first day back to work and the first day back to normal. Medication use (ie, opioids, nonsteroidal anti-inflammatory drugs, acetaminophen or aspirin, nausea medication, bowel medication) was also significantly lower in the MRgFUS group. Analyses combining the RCT and cohort patients showed similar results. The MRgFUS procedure took significantly longer than the UAE procedure. A trial limitation was the inability to recruit more patients. Long-term follow-up results were reported by Laughlin-Tommaso (2019).[57] Patients in both the RCT and cohort studies had follow-up for up to three years. The primary outcome assessed was reintervention for uterine fibroids within three years; secondary outcomes included change in anti-Mullerian hormone levels and standardized measures of quality of life, pain, sexual function, and fibroid symptoms. Among the women in the MRgFUS arm (n=43), 13 (30%) had a second fibroid procedure compared to 5 (13%) women in the UAE arm (hazard ratio [HR], 2.81; 95% confidence interval [CI], 1.01 to 7.79). Both quality of life and pain scores improved in both arms, however there was a larger improvement in the UAE arm. There was a significantly greater absolute decrease in anti-Mullerian hormone levels at 24 months in the UAE arm compared to the MRgFUS arm.

A SR 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.[58] 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.[59] 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.

Randomized Controlled Trials

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.[60] 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.

Quality of life 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

A prospective cohort study by Otonkoski (2023) evaluated if there was any adverse impact of MRgFUS treatment on ovarian reserve.[61] 74 premenopausal women were included who had either symptomatic uterine fibroids or adenomyosis. Ovarian reserve was estimated using serum Anti-Mullerian hormone (AMH) levels before and three months after treatment. The median baseline AMH level prior to treatment was 1.20 (range, 0.1 to 7.75 µg/L) and 1.23 (range, 0.1 to 8.51 µg/L) after treatment, and no statistically significant change was detected ($p=0.90$). No patients reported any symptoms that would indicate a loss of ovarian function.

The “pivotal” study which led to FDA approval of the ExAblate® 2000 device was included in the AHRQ report discussed above.[62, 63] 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.[64] 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.[65] 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.[66] 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.[67-74]

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. Systematic review of long-term follow-up results indicate that there is a lower reintervention rate and greater improvement in symptoms after uterine artery embolization compared to MRgFUS. 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

Baal (2021) conducted a systematic review (SR) of studies published between 2007 and 2019 evaluating MRgFUS treatment for painful bone metastases.[75] A total of 33 studies were reviewed, inclusive of three noted as randomized control trials, six retrospective studies, and 24 prospective studies (n=1082). The 2014 RCT by Hurwitz discussed below appears to be the only RCT reporting clinical outcomes in a full publication; one randomized trial evaluated molecular outcomes and one RCT was published only as a conference abstract. Overall, thirteen studies were available in abstract form only. The median study sample size was 21 patients (range 5 to 140) with a median follow-up period of three months (range, 1 to 12 months). The median age of patients was 60 years (22 studies including one study on a pediatric study population, range 4.3–69). Efficacy was assessed by treatment response (complete response or partial response [≥ 2-point improvement in pain score]) and the mean difference in pain scores (10-point VAS [visual analog scale] or NRS [numeric rating scale]) from baseline to month one/month three. The pooled proportion of patients with a treatment response to MRgFUS was 79% (95% confidence interval [CI], 73% to 83%; based on 20 studies [n=636]). The pooled one-month and three-month mean difference from baseline in pain scores were -3.8 (95% CI, -4.3 to -3.3) and -4.4 (95% CI, -5.0 to - 3.7), respectively (based on 20 studies [N=543]). Across 26 studies (n=799), seven high-grade adverse events were observed (one deep vein thrombosis, two cases of grade 3 skin burn, and four fractures). Approximately 11.8% of patients experienced sonication-related pain during MRgFUS treatment. The analysis was limited by a lack of a pooled comparator and heterogeneity of data with respect to populations (e.g., type of primary cancer), reported data, and treatment details. Most studies had follow-up periods that were limited to three months.

A SR with meta-analysis by Han (2021) included 15 studies (n=362) inclusive of the 2014 RCT by Hurwitz and a matched-pair study by Lee (2017) described below and.[76] The studies were conducted in China (n=112), the United States (n=112), Israel (n=38), Italy (n=23), France (n=17), Netherlands (n=15), Canada (n=21), Japan (n=10), South Korea (n=5), and the United Kingdom (n=9). Most of the included studies were single-arm clinical studies. The quality of studies was assessed by the MINORS score, a validated instrument for assessment of quality in non-randomized surgical studies ranging from 0-24. The mean MINORS score was 14.6 (range: 9–24). Lack of blinding and control groups were found in most of the studies, which contributed to risk of bias in study quality evaluations, however no evidence of publication bias was found. All but one paper included in the study used 10-point scales to assess pain and the data of the one paper using a 100-point scale was transformed into a 10-point scale for comparison purposes. Compared with baseline, pain was significantly improved at 0 to 1 week (mean reduced pain scores = 2.54 [95% CI: 1.92 to 3.16, p<0.01] and at 1 to 5 weeks (3.56

[95% CI: 3.11 to 4.02, p<0.01]), and at 5 to 14 weeks (4.22 [95% CI: 3.68 to 4.76, p<0.01]). Pain outcomes were not assessed at all timepoints across trials and heterogeneity was high in all timeframes; nine studies (n=268) assessed pain at 0 to 1 week ($I^2$ = 98.7%), 10 trials (n=291) assessed at 1 to 5 weeks ($I^2$ = 98.2%), and nine trials (n=289) assessed pain at 5 to14 weeks ($I^2$ = 99.7%). The overall complete response rate, defined as a pain score of 0 with no medication increase was 0.36 (95% CI: 0.24 to 0.48) and the partial response rate, defined as a drop of 2 on a 10-point scale without an increase in pain medications or a drop of 25% in pain medication without increase in the reported pain score, was 0.47 (95% CI: 0.36 to 0.58), and no response (no drop of score and no changes in medication use) rate was 0.23 (95% CI: 0.13 to 0.34). Among the 14 studies (n=352) reporting complications, 93 (26.4%) patients had minor complications and five (1.42%) had major complications.

A SR 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.[77] 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. All techniques achieved pain relief at one and three months in up to 91% and 95% of patients respectively. Across all modalities, the number of minor complications ranged from 0 to 59 (complication ratio 0–1.17), and the number of significant adverse effects ranged from 0 to 4 (complication ratio 0–0.04). Specific to MRgFUS, only the RCT by Hurwitz (2014, below) reported complications, which are summarized below.

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.[78] The study was included in the SRs discussed above and included patients age 18 years and older 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. Patient-rated tumor pain on a numeric rating scale (NRS) at four or higher on a 10-point scale and up to five painful lesions were inclusion criteria, however, only one lesion was treated and it had to cause at least two 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 two 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 seven (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

Lee (2017) published the results of a matched-pair study of MRgFUS or conventional radiation therapy (RT) as a treatment for patients with painful bone metastasis.[79] A total of 63 patients (21 MRgFUS and 42 RT-treated) were matched 1:2 by age, sex, primary cancer, pretreatment pain score, and treated site. All patients were followed for at least three months post-treatment. Mean numerical rating scale (NRS) for the MRgFUS-treated group was significantly lower at one-week post-treatment (2.5 versus 4.8, p<0.0001), two weeks (2.1 versus 3.6, p<0.05) and three months (1.0 versus 2.3, p<0.05) post-treatment compared to the RT-treated group, however, no significant difference was found at one- or two-month timepoints. Mean morphine-equivalent daily dose change from baseline did not differ between groups. At one-week post-treatment, 71% of the MRgFUS and 26% of the RT- treated patients had experienced a treatment response (successful pain palliation), a statistically significant difference (p<0.001). No statistically significant group difference in response rate were found at subsequent timepoints. No adverse events above grade 2 were observed for either group. This study was limited by small sample size and short-term follow-up.

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.[80-83] 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[84-89] 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 one 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 one 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. A 2016 case series by Merckel[90] included ten patients with early-stage invasive breast cancer who underwent MRgFUS prior to surgical resection. Ablation was confirmed histopathologically in six of these patients. The investigators concluded that MRgFUS is safe and feasible. A noted limitation is the long procedure time (average, 145 minutes), due to waiting time after contrast injection and time to find a proper magnetic resonance navigator signal.

### 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.[91] 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*

Ghai (2021) conducted a phase II trial to evaluate the safety and efficacy of transrectal MRgFUS treatment for intermediate-risk prostate cancer in 44 men, 36 with grade group (GG) 2 and eight with GG 3 disease.[92] The primary efficacy endpoint was the presence of residual disease at the treatment site at five months post- procedure. The International Prostate Symptom Score (IPSS) and International Index of Erectile Function-15 (IIEF-15) score were assessed at six weeks and five months, and multiparametric MRI and targeted biopsy of the treated area was obtained at five months post-procedure. Ninety-three percent of patients (95% CI: 82 to 98) were free of clinically significant prostate cancer, defined as (≥6 mm GG 1 disease or any volume ≥GG 2 disease) at the five-month biopsy. Median IIEF-15 and IPSS scores were not significantly different at baseline compared to five months (IIEF-15 score at

baseline, 61 [IQR, 34–67] and at five months, 53 [IQR, 24–65.5], p=0.18; IPSS score at baseline, 3.5 [IQR, 1.8–7] and at five months, 6 [IQR, 2–7.3], p=0.43). Seven percent (95% CI, 2.4 to 18.2) had residual disease at five months after ablation. No major treatment-related adverse events were reported, however, 16 patients reported dysuria; five patients required antispasmodics for bladder spasm in the first week; two patients had urinary retention; and one patient had severe pelvic pain. Study limitations include the short follow-up time to assess efficacy; however, a biopsy at a 24-month follow-up is planned, which will address persistence and recurrent prostate cancer.

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.[93-95] 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.

Other tumors

Several studies have investigated the use of MRgFUS for nonspinal osteoid osteoma.[96-98] Arrigoni (2021) conducted a propensity score-matched retrospective study to compare treatment with radiofrequency ablation and MRgFUS.[97] A total of 116 patients were treated (61 with radiofrequency ablation and 55 with MRgFUS). After propensity score matching, both radiofrequency ablation and MRgFUS treatment resulted in a significant reduction in pain from baseline as measured by VAS (8.9 to 0.02 and 8.8 to 0.54, respectively). There was no statistically significant difference between the mean values of both groups after the treatment. Four cases of relapse (one with radiofrequency ablation and three with MRgFUS) were observed. Arrigoni (2019) prospectively enrolled children into a study to evaluate MRgFUS treatment for osteoid osteoma.[96] The primary clinical endpoint was defined as the absence of pain (evaluated on the Faces Pain Scale-Revised) at the first follow-up study one week after the procedure. A total of 33 children were included in the study and treated with MRgFUS. The mean pain score at baseline was 7.6; the score at week one after the procedure significantly improved in all children (mean score, 0.21). Complete absence of pain was reported in 32 of 33 (97%; 95% CI, 84 to 100) of patients at week one. At the 24-month follow-up visit, imaging results confirmed the complete disappearance of bone edema around all lesions. Geiger (2014) prospectively enrolled patients into a study to evaluate MRgFUS treatment for osteoid osteoma.[98] Clinical success was evaluated based on pain reduction (evaluated on a VAS) through 12 months. At the 12-month follow-up, complete clinical success was achieved in 90% of the 29 patients enrolled (mean VAS, 0±0 points); partial success was achieved in the remaining patients (mean VAS, 5±0 points).

## 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:[99]

> 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 2023 American College of Radiology (ACR) Appropriateness Criteria regarding the management of uterine fibroids state, “Laparoscopic or open myomectomy, medical management, MRgFUS, or UAE is usually appropriate for the initial therapy of a reproductive age patient with uterine fibroids, symptomatic with heavy uterine bleeding or bulk symptoms (eg, pressure, pain, fullness, bladder, or bowel symptoms).”[100] This recommendation is independent of the patient’s desire to preserve fertility. The ACR literature review summarized a clinical trial which compared MRgFUS to placebo and demonstrated greater decreases in fibroid diameter, improvements in quality of life, and a reintervention rate of 33% at two years and an RCT which showed a higher reintervention rate (30% vs. 13%) and decreased symptom control with MRgFUS compared to UAE.

## AMERICAN UROLOGICAL ASSOCIATION

In 2022, the American Urological Association (AUA) published a joint guideline (with the American Society for Radiation Oncology [ASTRO], endorsed by the Society of Urologic Oncology [SUO], regarding clinically localized prostate cancer[101]. 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 inform patients with intermediate-risk prostate cancer considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance.Clinicians should not recommend whole gland or focal ablation for patients with high-risk prostate cancer outside of a clinical trial.

## NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 4.2024) 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.[1] (Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate).

The NCCN Guideline on adult cancer pain (version 2.2024)[102] does not include ultrasound ablation specifically in pain management algorithms, however, the guideline states:

> Image-guided ablation of bone lesions has proven successful in pain management, especially for those failing to achieve adequate analgesia without intolerable effects. Several small studies also have demonstrated the palliative effects of HIFU treatment of bone lesions.

## 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.”[103] 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

Medicine-Refractory Essential Tremor

It appears that Magnetic Resonance-guided focused ultrasound (MRgFUS) may help those with medicine-refractory essential tremor. At least one high quality randomized study and several large systematic reviews of MRgFUS used specifically in the treatment of essential tremor have demonstrated improvement in symptoms with MRgFUS treatment and improved overall quality of life. Therefore, MRgFUS may be considered medically necessary for medicine-refractory essential tremors when policy criteria are met.

Parkinson's Disease

There is not enough research to know if or how well Magnetic Resonance-guided focused ultrasound (MRgFUS) works to treat people with Parkinson's Disease. There is evidence that the use of MRgFUS in the treatment of Parkinson's Disease is associated with high rates of adverse events. No evidence-based clinical practice guidelines recommend MRgFUS for the treatment of Parkinson's Disease. Therefore, treatment of Parkinson's Disease with MRgFUS is considered investigational.

### Palliative Treatment of Bone Metastases

It appears that Magnetic Resonance-guided focused ultrasound (MRgFUS) may provide effective palliation of pain due to bone metastases in adults. Evidence-based clinical practice guidelines note the success of image-guided ablation in pain management, especially for those failing to achieve adequate analgesia without intolerable effects Therefore, pain palliation of bone metastases with MRgFUS may be considered medically necessary 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) 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.

**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 when policy criteria are not met.

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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 |

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