MRI-Guided High-Intensity Focused Ultrasound (MRgFUS) Ablation

Medical Policy #: 04.01.09
Original Effective Date: August 2007
Reviewed: January 2022
Revised: January 2019

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DESCRIPTION

An integrated system providing magnetic resonance imaging (MRI)-guided focused ultrasound (MRgFUS) treatment is proposed as a noninvasive therapy for uterine fibroids and for pain palliation of bone metastases. MRgFUS is also being investigated for the treatment of other benign and malignant tumors (breast, prostate, brain and desmoid tumors as well as nonspinal osteoid osteoma), essential tremor and chronic neuropathic pain.

Magnetic resonance-guided focused ultrasound (MRgFUS) is a non-invasive treatment that combines 2 technologies: 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. The ultrasound causes a local increase in temperature in the target tissue, resulting in coagulation necrosis while sparing the surrounding normal structures. The ultrasound waves from each sonication are directed at a focal point which has a maximum focal volume of 20 nm in diameter and 15 nm in height/length. This causes a rapid rise in temperature (i.e., to approximately 65°C to 85°C), which is sufficient to ablate tissue at the focal point. In addition to providing guidance, the associated MRI can provide on-line 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.

Clinical Context and Procedure Purpose
The clinical purpose of magnetic resonance – guided focused ultrasound (MRgFUS) in patients with uterine fibroids, pain palliation of bone metastases, other tumors (breast, prostate, brain and desmoid tumors), or essential tremors is to provide a treatment option that is an alternative to or an improvement of existing therapies.

Populations
The relevant populations of interest are patients with:

- Uterine fibroids
- Pain palliation of bone metastases who have failed radiotherapy or who are not candidates for radiotherapy
- Other tumors (breast, prostate, brain and desmoid tumors as well as nonspinal osteoid osteoma)
- Essential tremors who are medication-refractory

Interventions
The therapy being considered is magnetic resonance-guided focused ultrasound (MRgFUS), which is a thermoablative procedure to heat targeted tissue in small volume increments, under constant magnetic resonance imaging guidance.

Comparators
Comparators of interest, by indication, include:

- For uterine fibroids, alternatives nonsurgical treatments or surgery
- For pain palliation of bone metastases, supportive care
- For other tumors (breast, prostate, brain and desmoid tumors as well as nonspinal osteoid osteoma), standard of care
- For essential tremor, neurosurgery or standard of care. Surgical procedures include deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus and stereotactic thalamotomy

Outcomes
The following therapies and practices are currently being used, by indication:

- For uterine fibroids, the goal is to reduce or eliminate fibroid-related symptoms by reducing fibroid size. Measures to assess the effect of treatment include

quality of life (QOL), change in uterine and fibroid volume, pain levels, and pain medication use.
- For pain palliation of bone metastases, the goal is to alleviate pain. Measures to assess the effect of treatment include pain levels and pain medication use.
- For other tumors (breast, prostate, brain and desmoid tumors as well as nonspinal osteoid osteoma), the goal is tumor ablation. Outcomes include reduction in tumor size.
- For essential tumors, the goal is to decrease the frequency of tremors and improve quality of life (QOL).

Outcome measures can be assessed at several months to several years post-procedure.

Uterine Fibroids
To date, the primary clinical application of magnetic resonance-guided focused ultrasound (MRgFUS) has been for treatment of uterine fibroids (leiomyomata) which is one of the most common conditions affecting women in the reproductive years. Symptoms of uterine fibroids include menorrhagia, pelvic pressure, or pain. There are several approaches currently available to treat symptomatic uterine fibroids to include: hysterectomy; abdominal myomectomy; laparoscopic and hysteroscopic myomectomy; hormone therapy; uterine artery embolization; and watchful waiting. Hysterectomy and various myomectomy procedures are considered the criterion standard treatment.

In 2017, Agency for Healthcare Research and Quality issued a comparative effectiveness review on management of uterine fibroids which concluded: Six studies (reported in 7 publications) assessed high intensity focused ultrasound (HIFU) for fibroid ablation, but only one fair quality pilot study (n=20) used magnetic resonance imaging (MRI) guidance, which is used in the United States. The other studies were rated as poor quality primarily due to lack of masking participants and outcome assessors to the intervention received. In four studies reporting effects on fibroid size, the magnitude of fibroid volume reduction was greater at 12 months after ultrasound destruction than at 1 month post treatment. One year after treatment fibroid volume decreased by averages of 90 and 170 cm^3 in two studies. Studies did not report on bleeding, pain, or pregnancy outcomes. One study addressed quality of life but did not report baseline data, and one reported improvement in sexual function. One study reported no transfusions among 48 participants. No study reported major complications. HIFU reduced fibroid and uterine size, but strength of evidence is low because of short follow-up and poor quality of overall study design. Evidence related to patient reported outcomes is insufficient.

Randomized Controlled Trials
In 2016, Jacoby et. al. published a pilot, randomized, placebo-controlled trial (PROMISe trial), evaluating magnetic resonance guided focused ultrasound (MRgFUS) for the treatment of symptomatic uterine fibroids in premenopausal women. The participants were randomized in a 2:1 ratio to receive MRgFUS or placebo procedure. Outcome measures included change in fibroid symptoms from baseline to 4 and 12 weeks after treatment assessed by the Uterine Fibroid Symptom Quality of Life Questionnaire (UFS-

QOL); secondary outcome: incidence of surgery or procedures for recurrent symptoms at 12 and 24 months. Twenty women with a mean age of 44 years (±standard deviation 5.4 years) were enrolled, and 13 were randomly assigned to MRgFUS and 7 to placebo. Four weeks after treatment, all participants reported improvement in the UFS-QOL: a mean of 10 points in the MRgFUS group and 9 points in the placebo group (for difference in change between groups). By 12 weeks, the MRgFUS group had improved more than the placebo group (mean 31 points and 13 points, respectively). The mean fibroid volume decreased 18% in the MRgFUS group with no decrease in the placebo group at 12 weeks. Two years after MRgFUS, 4 of 12 women who had a follow-up evaluation (30%) had undergone another fibroid surgery or procedure. The authors concluded, women with fibroids were willing to enroll in a randomized, placebo-controlled trial of MRgFUS. A placebo effect may explain some of the improvement in fibroid-related symptoms observed in the first 12 weeks after MRgFUS. Larger sham-controlled randomized trial of MRgFUS was feasible.

Bernard et. al. (2017) published preliminary results from Fibroid Interventions: Reducing Symptoms Today and Tomorrow study, a parallel randomized controlled trial (RCT) and cohort study comparing MRgFUS with fibroid embolization to treat uterine fibroids. Premenopausal women with symptomatic uterine fibroids seen at 3 U.S. academic medical centers were enrolled in the randomized controlled trial (n = 57). Women meeting identical criteria who declined randomization but agreed to study participation were enrolled in a nonrandomized parallel cohort (n = 34). The 2 treatment groups were analyzed by using a comprehensive cohort design. All women undergoing focused ultrasound and uterine artery embolization received the same post-procedure prescriptions, instructions, and symptom diaries for comparison of recovery in the first 6 weeks. Return to work and normal activities, medication use, symptoms, and adverse events were captured with post-procedure diaries. Data were analyzed using the Wilcoxon rank sum test or χ^2 test. Multivariable regression was used to adjust for baseline pain levels and fibroid load when comparing opioid medication, adverse events, and recovery time between treatment groups because these factors varied at baseline between groups and could affect outcomes. Adverse events were also collected. Of 83 women in the comprehensive cohort design who underwent treatment, 75 completed post-procedure diaries. Focused ultrasound surgery was a longer procedure than embolization (mean [SD], 405 [146] vs 139 [44] min; P <.001). Of women undergoing focused ultrasound (n = 43), 23 (53%) underwent 2 treatment days. Immediate self-rated post-procedure pain was higher after uterine artery embolization than focused ultrasound (median [interquartile range], 5 [1-7] vs 1 [1-4]; P = .002). Compared with those having focused ultrasound (n = 39), women undergoing embolization (n = 36) were more likely to use outpatient opioid (75% vs 21%; P < .001) and nonsteroidal anti-inflammatory medications (97% vs 67%; P < .001) and to have a longer median (interquartile range) recovery time (days off work, 8 [6-14] vs 4 [2-7]; P < .001; days until return to normal, 15 [10-29] vs 10 [10-15]; P = .02). There were no significant differences in the incidence or severity of adverse events between treatment arms; 86% of adverse events (42 of 49) required only observation or nominal treatment, and no events caused permanent sequelae or death. After adjustment for baseline pain and uterine fibroid load, uterine

artery embolization was still significantly associated with higher opioid use and longer time to return to work and normal activities ($P < .001$ for each). Results were similar when restricted to the randomized controlled trial. The authors concluded, women undergoing uterine artery embolization have longer recovery times and use more prescription medications, but women undergoing focused ultrasound have longer treatment times. These findings were independent of baseline pain levels and fibroid load. A trial limitation was the inability to recruit more patients. Long-term follow-up results will be forthcoming.

Systematic Reviews

Yu et al. (2021) conducted a comparative meta-analysis on the efficacy and safety of magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) and ultrasound-guided HIFU. Forty-eight studies were included for review; twenty eight addressed the MR-HIFU and 20 focused on US-HIFU. Uterine fibroids with of a volume of <300 cm3 3 were part of the inclusion criteria. Non-perfused volume rate (NPVR) is considered a significant parameter that is positively connected with clinical success rate. A NPVR for the MR-HIFU was 58.92% which was lower than that of the US-HIFU group which was 81.07%. A NPVR of greater than 80% is considered successful. The average treatment time for MR-HIFU was almost double that of USHIFU which had a mean of 96.9 minutes. For treatment of symptomatic uterine fibroids, the author conclusions revealed the US procedure had greater safety and efficacy than the MR procedure. Limitations included a loss of follow-up in the majority of the studies, poor documentation for number and location of fibroids, and lack of long-term outcomes.
A systematic review published by Gizzo et. al. (2014) conducted a systematic review about studies reporting data of myomectomy performed by magnetic resonance-guided focused ultrasound (MRgFUS) technique in order to define its safety, feasibility, indications, complications, and impact on uterine fibroid symptoms and health related quality of life (UFS-QOL) and fertility. Outcomes were considered according to fibroids shrinkage, nonperfused volume (NPV), NPV ratio, and uterine fibroid symptoms assessed with UFS-QOL questionnaire (baseline 3, 4, 6, and 12 months). They analyzed 38 eligible studies reporting outcomes about 2500 patients (mean age 43.67 years). Most excluded patients who desired future pregnancies. Reviewers did not pool study finding due to the heterogeneity of outcomes but concluded that, overall, MRgFUS appeared to be safe, noninvasive option for treating uterine fibroids. Future research, particularly randomized controlled trials (RCTs) were recommended to compare MRgFUS with other invasive procedures and to explore the fertility-sparing potential further.

Nonrandomized Studies

Froeling et. al. (2013) compared the long-term outcome after uterine artery embolization (UAE) versus magnetic resonance-guided high intensity focused ultrasound (MRgFUS) for symptomatic uterine fibroids. Seventy-seven women (median age, 39.3 years; range, 29.2-52.2 years) with symptomatic uterine fibroids, equally eligible for UAE and MR-g HIFU based on our exclusion criteria underwent treatment (UAE, N = 41; MR-g HIFU, N = 36) from 2002 to 2009 at our institution. Symptom severity (SS) and total health-related quality of life (Total HRQoL) scores were assessed by the uterine fibroid

symptom and quality of life (UFS-QoL) questionnaire before treatment and at long-term follow-up after UAE (median 61.9 months) and after MR-g HIFU (median: 60.7 months). Re-intervention rates were assessed for each therapy and compared. Re-intervention was significantly lower after UAE (12.2%) than after MR-g HIFU (66.7%) at long-term follow-up ($p<0.001$). After UAE changes in SS (50 pre-treatment vs. 6.3 post-treatment) and Total HRQoL (57.8 pre-treatment vs. 100 post-treatment) were significantly better than changes in SS (42.2 pre-treatment vs. 26.6 post-treatment) and Total HRQoL score (66.4 pre-treatment vs. 87.9 post-treatment) after MR-g HIFU ($p = 0.019$ and 0.049 respectively). The authors concluded, improvement of SS and Total HRQoL scores was significantly better after UAE resulting in a significant lower re-intervention rate compared to MR-g HIFU.

In 2016, Chen et. al. evaluated the safety and effectiveness of magnetic resonance-guided high intensity focused ultrasound (MRgFUS) therapy using a volumetric ablation technique in the treatment of symptomatic uterine fibroids. One hundred and seven patients (107) were enrolled and treated with MRgFUS in this study. Clinical efficacy was based on the proportion of patients with fibroid shrinkage (10 % volume reduction or more compared to baseline) at 6 months post treatment as measured with magnetic resonance imaging. The quality of life (QOL) and symptom outcome was assessed using the uterine fibroid symptom and quality of life questionnaire with symptom severity scoring. Safety was primarily assessed by evaluating the reported adverse events. Ninety nine of the 107 treated patients had fibroid shrinkage at 6 months post treatment. Resulting in an overall 93 % (95 % confidence interval 86-97 %) treatment success rate, p value <0.001; the symptom severity scoring and health-related quality of life at 6 months was statistically different from the screening symptom severity scoring at 0.05 level. Of 366 adverse events reported, there were no study procedure-related or device-related serious adverse events were in the study. The authors concluded, this study demonstrated that the volumetric magnetic resonance-guided high-intensity focused ultrasound device is safe and technically effective and can be utilized in clinically efficient treatments of symptomatic uterine fibroids.

Fertility Following Magnetic Resonance-Guided Focused Ultrasound

Rabinovici et. al. (2010) reported on a prospective registry of all known pregnancies occurring after magnetic resonance-guided focused ultrasound (MRgFUS) for the conservative treatment of clinically significant uterine fibroids maintained by the device manufacturer and reported to the Food and Drug Administration (FDA). Fifty-four pregnancies in 51 women have occurred after MRgFUS treatment of uterine leiomyomas (fibroids). The mean time to conception was 8 months after treatment. Live births occurred in 41% of pregnancies, with a 28% spontaneous abortion rate, an 11% rate of elective pregnancy termination, and 11 (20%) ongoing pregnancies beyond 20 gestational weeks. The mean birth weight was 3.3 kg, and the vaginal delivery rate was 64%. This study provided initial information on the impact of MRgFUS on uterine fibroids in pregnancy; findings suggested that fertility may be maintained but that the number of cases was too small to draw definitive conclusion. The study also did not address the possible impact of MRgFUS treatment on the future ability to become pregnant.

Summary Of Evidence
For individuals who have uterine fibroids who receive magnetic resonance-guided focused ultrasound (MRgFUS), the evidence includes systematic reviews, small randomized controlled trials (RCTs), nonrandomized comparative studies, and case series. While evidence may suggest that MRgFUS may be safe and effective minimally invasive option for the treatment of uterine fibroids the overall quality of the evidence is low due to the lack of well-designed controlled studies. Substantial uncertainty remains regarding the effect of magnetic resonance–guided focused ultrasound ablation of uterine fibroids on symptoms and the comparative effectiveness with other treatment alternatives. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Treatment of Other Tumors
Magnetic resonance-guided high-intensity focused ultrasound (MRgFUS) ablation is also being studied as a treatment of other tumors including breast, prostate, brain, and desmoid tumors as well as nonspinal osteoid osteoma.

The most recent case series on the use of magnetic resonance-guided high intensity focused ultrasound for breast cancer ablation was published by Merckel et. al. (2016). Patients with early-stage invasive breast cancer underwent partial tumor ablation prior to surgical resection. MR-HIFU (magnetic resonance high intensity focused ultrasound) ablation was performed using proton resonance frequency shift MR thermometry and an MR-HIFU system specifically designed for breast tumor ablation. The presence and extent of tumor necrosis was assessed by histopathological analysis of the surgical specimen. Pearson correlation coefficients were calculated to assess the relationship between sonication parameters, temperature increase and size of tumor necrosis at histopathology. Ten female patients underwent MR-HIFU treatment. No skin redness or burns were observed in any of the patients. No correlation was found between the applied energy and the temperature increase. In six patients, tumour necrosis was observed with a maximum diameter of 3-11 mm. In these patients, the number of targeted locations was equal to the number of areas with tumor necrosis. A good correlation was found between the applied energy and the size of tumor necrosis at histopathology (Pearson = 0.76, $p = 0.002$). The authors concluded, our results show that MR-HIFU ablation with the dedicated breast system is safe and results in histopathologically proven tumor necrosis. A noted limitation is the long duration of the procedure, average of 145 minutes due to the waiting time after the contrast injection and time for find a proper magnetic resonance navigator signal.

In 2010, McDannold et. al., evaluated the clinical feasibility of transcranial magnetic resonance imaging focused ultrasound (MRgFUS) of brain tumors (glioblastoma). Transcranial magnetic resonance imaging-guided focused ultrasound surgery offers a potential noninvasive alternative to surgical resection. The method combines a hemispherical phased-array transducer and patient-specific treatment planning based on acoustic models with feedback control based on magnetic resonance temperature imaging

to overcome the effects of the cranium and allow for controlled and precise thermal ablation in the brain. In initial trials in 3 glioblastoma patients, multiple focused ultrasound exposures were applied up to the maximum acoustic power available. Offline analysis of the magnetic resonance temperature images evaluated the temperature changes at the focus and brain surface. The authors found that it was possible to focus an ultrasound beam transcranially into the brain and to visualize the heating with magnetic resonance temperature imaging. Although limited by the device power available at the time and thus seemed to not achieve thermal coagulation, extrapolation of the temperature measurements at the focus and on the brain, surface suggests that thermal ablation will be possible with this device without overheating the brain surface, with some possible limitation on the treatment envelope. The authors concluded, although significant hurdles remain, these findings are a major step forward in producing a completely noninvasive alternative to surgical resection for brain disorders.

Napoli et. al. (2012) evaluated real time magnetic resonance-guided high intensity focused ultrasound (MRgFUS) therapy for localized prostate cancer. Five patients with unifocal, biopsy-proven prostate cancer (PCa) evident on multiparametric magnetic resonance imaging (MRI) were treated with magnetic resonance-guided focused ultrasound (MRgFUS) ablation before radical prostatectomy (RP). An endorectal probe featuring a phased-array focused ultrasound transducer was positioned for lesion ablation under MRI guidance. The tissue temperature and accumulation of thermal damage in the target zone was monitored during the procedure by MRI thermometry. Overlap between the ablation area and the devascularization of the target lesion was evaluated by contrast-enhanced MRI performed immediately after treatment. The procedure was uneventful, and no adverse events were observed. RP was safely performed without significant surgical difficulties in relation to the previous MRgFUS treatment. The histopathology report showed extensive coagulative necrosis, with no residual tumor in the ablated area. Significant bilateral residual tumor, not evident on pretreatment MRI, was observed outside the treated area in two patients. MRgFUS ablation of focal localized prostate cancer (Pca) is feasible and, if confirmed in appropriate studies, could represent a valid option for the focal treatment of localized prostate cancer (PCa).

In addition, several case series have investigated the use of magnetic resonance-guided high intensity focused ultrasound (MRgFUS) ablation for desmoid tumors. Avedian et. al. (2016) used MRgFUS to treat 9 patients with desmoid tumors. Five patients were available for MRI follow-up at 12 months or longer (mean, 18.2 months; range, 12-23 months). The radiographic and clinical outcomes of the five patients who had desmoid tumors treated with focused ultrasound were prospectively recorded. Patients were assessed preoperatively with MRI and followed at routine intervals after treatment with MRI scans and clinical examination. Four patients' tumors became smaller after treatment and one patient has slight progression at the time of last follow-up. The mean decrease in tumor size determined by MRI measurements was 36% (95% confidence interval, 7%-66%). No patient has received additional adjuvant systemic or local treatment. Treatment-related adverse events included first- and second-degree skin burns occurring in four patients, which were managed successfully without further surgery. The authors

concluded; this preliminary investigation provides some evidence that magnetic resonance-guided high-intensity focused ultrasound (MRgFUS) may be a feasible treatment for desmoid tumors. It may also be of use for other soft tissue neoplasms in situations in which there are limited traditional treatment options such as recurrent sarcomas. Further investigation is necessary to better define the indications, efficacy, role, and long-term oncologic outcomes of focused ultrasound treatment.

In 2017, Bucknor et. al. described the use of magnetic resonance-guided high intensity focused ultrasound (MRgFUS) ablation in 3 patients with large aggressive desmoid tumors within the posterior thigh. Each patient received multiple MRgFUS treatments. In this case series, use of MRgFUS for desmoid tumors required different treatment parameters than those used for fibroids or bone lesions, due to differences in vascularity of the target tissue and the need for effective skin protection when using MRgFUS on extremities.

Ghanouni et. al. (2017) assessed the feasibility, safety and preliminary efficacy of magnetic resonance-guided focused ultrasound (MRgFUS) ablation in a retrospective multicenter study for the treatment of extra-abdominal desmoid tumors. Fifteen patients with desmoid fibromatosis (six males, nine females; age range, 7-66 years) were treated with MRgFUS, with seven patients requiring multiple treatments (25 total treatments). Changes in viable and total tumor volumes were measured after treatment. Efficacy was evaluated using an exact one-sided Wilcoxon test to determine if the median reduction in viable tumor measured immediately after initial treatment exceeded a threshold of 50 % of the targeted volume. Median decrease after treatment of at least two points in numerical rating scale (NRS) worst and average pain scores was tested with an exact one-sided Wilcoxon test. Adverse events were recorded. After initial MRgFUS treatment, median viable targeted tumor volume decreased 63 %, significantly beyond our efficacy threshold ($P = 0.0013$). Median viable total tumor volume decreased (105 mL [interquartile range {IQR}, 217 mL] to 54 mL [IQR, 92 mL]) and pain improved (worst scores, 7.5 ± 1.9 vs 2.7 ± 2.6, $P = 0.027$; average scores, 6 ± 2.3 vs 1.3 ± 2, $P = 0.021$). Skin burn was the most common complication. This study was limited by sample size and the length of follow-up in some patients. The authors concluded, MRgFUS may safely and effectively treat extra-abdominal desmoid tumors. This non-invasive procedure can be used to eradicate viable tumor, or to provide durable control of tumor growth through repeated treatments. Compared to traditional treatment modalities, MRgFUS may have advantages including no cumulative dose limit, and relatively mild side effects, while preserving the ability to be used as an adjunct to other treatment methods. Given the promising outcomes seen in this study, further clinical trials are needed to confirm the safety of MRgFUS for the treatment of soft tissue tumors and to assess more definitively the rate of durable disease control.

Ghai et. al. (2021) conducted a phase II trial to evaluate the safety and efficacy of transrectal MRgFUS treatment for intermediate-risk prostate cancer. The primary efficacy endpoint was the presence of residual disease at the treatment site at 5 months after the procedure. Study characteristics and results are presented in Tables 1 and 2.

Ninety-three percent of patients were free of clinically significant prostate cancer at the 5-month biopsy. No major treatment-related adverse events occurred. 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.

Several case series have investigated the use of MRgFUS for nonspinal osteoid osteoma. Arrigoni et. al. (2021) conducted a propensity score-matched retrospective study to compare treatment with radiofrequency ablation and MRgFUS. 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 (1 with radiofrequency ablation and 3 with MRgFUS) were observed. Arrigoni et. al. (2019) prospectively enrolled children into a study to evaluate MRgFUS treatment for osteoid osteoma. The primary clinical endpoint was defined as the absence of pain (evaluated on the Faces Pain Scale-Revised) at the first follow-up study 1 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 1 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 1. At the 24-month follow-up visit, imaging results confirmed the complete disappearance of bone edema around all lesions.

Summary of Evidence
Evidence on the use of magnetic resonance-guided high intensity focused ultrasound (MRgFUS) for the treatment of prostate cancer consists of a nonrandomized, uncontrolled phase II trial, which reported a 93% success rate at 5 months. Evidence on the use of MRgFUS for the treatment of nonspinal osteoid osteoma consists of several case series, including a propensity score-matched retrospective study that reported similar reductions in pain with radiofrequency ablation and MRgFUS. Currently, evidence on the use of MRgFUS for the treatment of other tumors consists of small case series, which is insufficiently robust to draw conclusions about efficacy. RCTs comparing MRgFUS with other noninvasive procedures would be informative and are needed. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Palliative Treatment of Bone Metastases
Interest in minimally invasive local treatment options that target pain from bone metastases has increased because patient longevity and advances in cancer management have led to more people living with bone metastases. Magnetic resonance guided focused ultrasound (MRgFUS) may be used for palliating pain from bone metastases.

Bones are a common place for metastatic cancer cells to colonize and establish secondary tumor sites. Higher grade tumors and late diagnosis are also associated with the presence of bone metastasis. Metastases can develop in any bone, but certain cancers such as solid

tumors (breast, prostate, lung, thyroid, and kidney cancers) are more likely than others to spread to bone, and bone metastases occur in late stages of most solid tumor cancers.

Bone metastases are common cause of significant morbidity or mortality, metastatic lesions can predispose the bone to fractures. When metastases form in bone, the cancer cells release substances that can activate nearby bone cells, called osteoclasts and osteoblasts. Osteoclast's dissolve and weaken surrounding bone, which can lead to formation of osteolytic lesions. Osteoblasts stimulate bone formation, causing sclerotic, osteoblastic lesions. Both types of bone metastases can cause pain, but osteolytic lesions usually lead to fracture more often than osteoblastic lesions.

Clinical condition, life expectancy, and impact on quality of life (QOL) guide pain palliation treatment decisions. First line treatment is pain medication with nonsteroidal anti-inflammatory drugs progressing to opioids. Increasing opioid doses can result in nausea, sedation, constipation, somnolence, and dependence, which negatively affects a patient's QOL. External beam radiation therapy (EBRT) is the standard second line treatment for pain from bone metastases; however, radiation is effective in only 60% to 65% of patients, and pain relief may not occur in those patients for two to four weeks after treatment. EBRT is also limited by is cumulative radiation effects to healthy organs, bone and surrounding tissue. Patients who have previously had EBRT may be unable to tolerate additional EBRT. Furthermore, for patients who experience some relief from EBRT, the relief is only temporary for about 30% because of disease progression. Retreatment of patients who can be re-irradiated is effective only one about 30% of patients. Its effectiveness may be diminished by having to deliver a smaller dose because of concerns about cumulative radiation dose to normal tissues. Other systemic palliative therapies (e.g., chemotherapy, hormonal therapy, radioisotopes, bisphosphonates) are available; however, many patients experience inadequate pain control or unwanted side effects with these options. Thus, new options are needed, particularly for patients who are ineligible for EBRT.

More recent options involve methods to ablate the pain-transmitting cells at the boundary of bone tumors, which is believed to inhibit the patient's ability to feel pain. One such option is magnetic resonance imaging (MRI) – guided focused ultrasound (MRgFUS). Unlike diagnostic ultrasound, which exposes tissue to biologically insignificant acoustic energy levels, MRgFUS energy acts on bone primarily through thermal effects. MRgFUS energy can rapidly heat tissue to the point at which irreversible thermal ablation and coagulative necrosis occurs. The outer covering of the bone is the target for MRgFUS energy as the bone tumor itself may be more or less absorptive depending on whether it is osteolytic or osteoblastic (or mixed). Bone is particularly conducive to MRgFUS ablation because of its higher ultrasound energy absorption, lower thermal conductance, and less susceptibility to penetration of ultrasound waves than soft tissue. As a result, the absorption pattern by bones allows wider surface areas of the bone to be treated with each energy pulse.

MRgFUS to palliate bone metastases typically requires locoregional anesthesia or a combination of local anesthesia and deep sedation. Clinicians typically perform MRgFUS in the outpatient setting. Treatment typically requires about 1.5 hours per lesion but may vary depending on tumor size and location. Immediately after the procedure, a technologist performs contract enhanced MRI scan to verify ablation and assess potential damage to tissues adjacent to the target bone sites.

The reported benefits of MRgFUS for palliation of bone metastases are as follows:

- A noninvasive procedure
- Single session treatment usually performed on an outpatient basis
- Return to activity possible the next day; procedure discomfort dissipates in two to three days
- No ionizing radiation exposure
- No toxic effects on bone marrow
- Rapid (24 to 72 hours) pain relief lasting up to 3 months
- Both osteoblastic and osteolytic tumors can be treated
- Low reported occurrences of complications and side effects
- Retreatment for symptom recurrence or new tumors possible
- Provider option for patients who cannot receive further EBRT for bone metastases
- May reduce or obviate need for opioids and non-narcotic analgesics, thus eliminating side effects from these medications

Randomized Controlled Trials

In a randomized controlled trial (RCT) evaluating the ExAblative system for the treatment of painful bone metastases, Hurwitz et al. (2014) evaluated patients with painful bone metastases that were randomly assigned 3:1 to receive magnetic resonance-guided high intensity focused ultrasound (MRgFUS) ablation or placebo. The primary endpoint was improvement in self-reported pain score without increase of pain medication 3 months after treatment and was analyzed by Fisher's exact test. Components of the response composite, Numerical Rating Scale for pain (NRS) and morphine equivalent daily dose intake, were analyzed by t test and Wilcoxon rank-sum test, respectively. Brief Pain Inventory (BPI-QoL), a measure of functional interference of pain on quality of life, was compared between MRgFUS and placebo by t test. Statistical tests were two-sided. One hundred forty-seven subjects were enrolled, with 112 and 35 randomly assigned to MRgFUS and placebo treatments, respectively. Response rate for the primary endpoint was 64.3% in the MRgFUS arm and 20.0% in the placebo arm ($P < .001$). MRgFUS was also superior to placebo at 3 months on the secondary endpoints assessing worst score NRS ($P < .001$) and the BPI-QoL ($P < .001$). The most common treatment-related adverse event (AE) was sonication pain, which occurred in 32.1% of MRgFUS patients. Two patients had pathological fractures, one patient had third-degree skin burn, and one patient suffered from neuropathy. Overall, 60.3% of all AEs resolved on the treatment day. The authors concluded this multicenter phase III trial demonstrated that MRgFUS is a safe and effective, noninvasive treatment for alleviating pain result from bone metastases in patients that have failed standard treatments.

Observational Studies
In 2017, Arrigoni et. al. evaluated the use of magnetic resonance-guided focused ultrasound (MRgFUS) for treatment of intra-articular benign bone lesions as an alternative to surgery, and to monitor the success of the treatment on CT and MRI images. From March 2011 to August 2013, 14 intra-articular benign bone lesions were treated with MRgFUS. All patients were studied by CT and MRI imaging. Pain was measured using the visual analogue scale (VAS) before and after treatment (6 and 12 months). All patients in our series demonstrated regression in painful symptomatology during screening. A significant drop in the mean VAS pain score (from 7.8 to 0.6) was observed at 12-month follow-up, and pain medication was no longer needed after treatment. No complications were observed. Three diagnostic imaging signs were found suggesting absence of biological activity and confirming the clinical findings: calcification of the treated lesion, lack of contrast enhancement and disappearance of bone of edema around the lesions. The authors concluded the employment of MRgFUS is safe and effective in the treatment of intra-articular benign bone lesions. The clinical outcome is satisfactory, and the success of the treatment is confirmed by diagnostic imaging.

Systematic Reviews
Baal et. al. (2021) conducted a systematic review of studies published between 2007 and 2019 evaluating MRgFUS treatment for painful bone metastases. A total of 33 studies were identified, comprised of 3 RCTs, 6 retrospective studies, and 24 prospective studies, representing 1082 patients. 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 3 months (range, 1 to 12 months). 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 1/month 3. 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 1-month and 3-month mean difference from baseline in pain score 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), 7 high-grade adverse events were observed (1 deep vein thrombosis, 2 cases of grade 3 skin burn, and 4 fractures). Approximately 11.8% of patients experienced sonication-related pain during MRgFUS treatment. The analysis was limited by a lack of a pooled comparator. Additionally, there was substantial heterogeneity of the included studies due to variable study populations (e.g., type of primary cancer), reported data, and treatment details. The majority of the included studies had follow-up periods that were limited to 3 months.

Summary of Evidence
For individuals with painful metastatic bone cancer who have failed or are not candidates for radiotherapy who receive MRgFUS, the evidence consists of a systematic review of RCTs and observational studies, a single industry-sponsored RCT, and case series. The RCT found statistically significant improvement after MRgFUS in a composite outcome comprised of reduction in pain and morphine use, and in pain reduction as a stand-alone

outcome. This trial was appropriately sham controlled. A substantial proportion of patients in the treatment group experienced adverse events, but most of these were not severe and were transient. The observational studies also reported reductions in pain following MRgFUS treatment. Pooled efficacy data from a systematic review reported a treatment response to MRgFUS of 79%. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.

Essential Tremors

Essential tremor (ET) is one of the most common movement disorders. The cause of the disease and it pathomechanism are still unknown. The main symptoms include tremor of the hands, arms and head. The clinical course is frequently benign, however disability due to ET is common. Pharmacotherapy is usually the first line treatment and patients who do not respond to medications may be considered for surgical treatment (radiofrequency identification (RFID), stereotactic radiosurgery, gamma knife thalamotomy or deep brain stimulation). An alternative treatment being investigated for the treatment of essential tremor is the use of magnetic resonance-guided high intensity focused ultrasound (MRgFUS) to produce thermal ablation of the thalamic ventral intermediate nucleus (i.e., MRI-guided focused ultrasound thalamotomy).

Systematic Reviews

Miller et. al. (2021) published a meta-analysis that evaluated the efficacy of magnetic resonance-guided focused ultrasound (MRgFUS) for treating medication-refractory ET with a focus on long-term trends and the durability of the response. Twenty-one studies (N=395) were included; 17 were prospective studies, 3 were retrospective, and only 1 was an RCT. Hand tremor scores decreased from a weighted mean pre-operative value of 19.2±5.0 to 7.4±5.0 after 3 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 3 months (5 studies), 2.44 (95% CI, 1.97 to 2.91) at the 12-month time point (7 studies), and 2.18 (95% CI, 1.50 to 2.86) at the 24-month time point (3 studies). Clinical Rating Scale for Tremor scores were only reported through 12 months. The pooled standardized mean difference in Clinical Rating Scale for Tremor scores compared to pre-treatment values was 1.86 (95% CI, 1.51 to 1.21) at the 3-month time point (8 studies) and 2.24 (95% CI, 1.55 to 2.94) at the 12-month time point (6 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 3 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.

Giordano et al (2020) conducted a meta-analysis to compare unilateral magnetic resonance-guided focused ultrasound (MRgFUS) to unilateral and bilateral DBS for medication-refractory ET. Forty-five studies published between 1996 and 2019 were identified. Thirty-seven studies (n=1202) evaluated DBS and 8 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%) as compared to the MRgFUS group (55.6%±8.2%, p<.001). Subgroup analyses demonstrated that the improvement in tremor severity was significantly greater with the bilateral DBS (61.2%±5.2%) as compared to both unilateral DBS (56.4%±9.7%) and MRgFUS; there was no significant difference between unilateral DBS and MRgFUS. For average percentage improvement in quality of life, MRgFUS was associated with significantly improved measures as compared to DBS (61.9%±7.9% vs 52.5%±16.2%, p<.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 1 retrospective study that directly compared DBS and MRgFUS.

The technology assessment was published by Health Quality Ontario (2018). The assessment aimed to determine the effectiveness and safety of magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery for the treatment of moderate to severe, medication-refractory essential tremor in Ontario. A systematic review of the clinical literature published up to April 11, 2017, that examined MRgFUS neurosurgery alone or compared with other interventions (deep brain stimulation and radiofrequency thalamotomy) for the treatment of moderate to severe, medication-refractory essential tremor. They assessed the risk of bias of each study and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. Nine studies met inclusion criteria for the clinical evidence review. In non-comparative studies, MRgFUS neurosurgery was found to significantly improve tremor severity and quality of life and to significantly reduce functional disability (GRADE: very low). In the randomized controlled trial (RCT) it was also found to be significantly more effective than a sham procedure (GRADE: high). Found no significant difference in improvements in tremor severity, functional disability, or quality of life between MRgFUS neurosurgery and deep brain stimulation (GRADE: very low). Found no significant difference in improvement in tremor severity compared with radiofrequency thalamotomy (GRADE: low). MRgFUS neurosurgery has a favorable safety profile. The assessment concluded, MRgFUS neurosurgery is an effective and generally safe treatment option for moderate to severe, medication-refractory essential tremor. It provides a treatment option for people ineligible for invasive neurosurgery and offers a noninvasive option for all people considering neurosurgery. People with essential tremor who had undergone MRgFUS neurosurgery reported positive experiences. They liked that it was a noninvasive procedure and reported a substantial reduction in tremor that resulted in an improvement in their quality of life.

Mohammed et. al. (2018) conducted a meta-analysis of outcomes and complications of magnetic resonance-guided focused ultrasound (MRgFUS) in the treatment of essential

tremor (ET). Patients with the diagnosis of ET who were treated with MRgFUS were included in the study. The change in the Clinical Rating Scale for Tremor (CRST) score after treatment was analyzed. The improvement in disability was assessed with the Quality of Life in Essential Tremor Questionnaire (QUEST) score. The pooled data were analyzed by the DerSimonian-Laird random-effects model. Tests for bias and heterogeneity were performed. Nine studies with 160 patients who had ET were included in the meta-analysis. The ventral intermediate nucleus was the target in 8 of the studies. The cerebellothalamic tract was targeted in 1 study. There was 1 randomized controlled trial, 6 studies were retrospective, and 2 were prospective. The mean number of sonications given in various studies ranged from 11 ± 3.2 to 22.5 ± 7.5 (mean ± SD). The maximum delivered energy ranged from 10,320 ± 4537 to 14,497 ± 6695 Joules. The mean of peak temperature reached ranged from 53°C ± 2.3°C to 62.0°C ± 2.5°C. On meta-analysis with the random-effects model, the pooled percentage improvements in the CRST Total, CRST Part A, CRST Part C, and QUEST scores were 62.2%, 62.4%, 69.1%, and 46.5%, respectively. Dizziness was the most common in-procedure complication, occurring in 45.5%, followed by nausea and vomiting in 26.85% (pooled percentage). At 3 months, ataxia was the most common complication, occurring in 32.8%, followed by paresthesias in 25.1% of the patients. At 12 months post-treatment, the ataxia had significantly recovered and paresthesias became the most common persisting complication, at 15.3%. The authors concluded, the MRgFUS therapy for ET significantly improves the CRST (clinical rating scale for tremor) scores and improves the quality of life (QOL) in patients with ET, with an acceptable complication rate.

Randomized Controlled Trials (RCTs)

In 2016, Elias et. al. conducted a single high-quality study, a double-blind sham controlled randomized trial of magnetic resonance-guided focused ultrasound (MRgFUS) for the treatment of essential tremor (ET). Enrolled patients had moderate-to-severe essential tremor that had not responded to at least two trials of medical therapy and randomly assigned them in a 3:1 ratio to undergo unilateral focused ultrasound thalamotomy or a sham procedure. The Clinical Rating Scale for Tremor and the Quality of Life in Essential Tremor Questionnaire were administered at baseline and at 1, 3, 6, and 12 months. Tremor assessments were videotaped and rated by an independent group of neurologists who were unaware of the treatment assignments. The primary outcome was the between-group difference in the change from baseline to 3 months in hand tremor, rated on a 32-point scale (with higher scores indicating more severe tremor). After 3 months, patients in the sham-procedure group could cross over to active treatment (the open-label extension cohort). Seventy-six patients were included in the analysis. Hand-tremor scores improved more after focused ultrasound thalamotomy (from 18.1 points at baseline to 9.6 at 3 months) than after the sham procedure (from 16.0 to 15.8 points); the between-group difference in the mean change was 8.3 points (95% confidence interval [CI], 5.9 to 10.7; P<0.001). The improvement in the thalamotomy group was maintained at 12 months (change from baseline, 7.2 points; 95% CI, 6.1 to 8.3). Secondary outcome measures assessing disability and quality of life also improved with active treatment (the blinded thalamotomy cohort) as compared with the sham procedure (P<0.001 for both comparisons). Adverse events in the thalamotomy group

included gait disturbance in 36% of patients and paresthesias or numbness in 38%; these adverse events persisted at 12 months in 9% and 14% of patients, respectively. The authors concluded, MRgFUS thalamotomy reduced hand tremor in patients with essential tremor.

Chang et. al. (2018) published results of a prospective trial of magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy for essential tremor (ET), the study reports results at a 2-year follow-up after MRgFUS thalamotomy for ET. A total of 76 patients with moderate-to-severe ET, who had not responded to at least two trials of medical therapy, were enrolled in the original randomized study of unilateral thalamotomy and evaluated using the clinical rating scale for tremor. Sixty-seven of the patients continued in the open-label extension phase of the study with monitoring for 2 years. Nine patients were excluded by 2 years, for example, because of alternative therapy such as deep brain stimulation (n = 3) or inadequate thermal lesioning (n = 1). However, all patients in each follow-up period were analyzed. Mean hand tremor score at baseline (19.8 ± 4.9; 76 patients) improved by 55% at 6 months (8.6 ± 4.5; 75 patients). The improvement in tremor score from baseline was durable at 1 year (53%; 8.9 ± 4.8; 70 patients) and at 2 years (56%; 8.8 ± 5.0; 67 patients). Similarly, the disability score at baseline (16.4 ± 4.5; 76 patients) improved by 64% at 6 months (5.4 ± 4.7; 75 patients). This improvement was also sustained at 1 year (5.4 ± 5.3; 70 patients) and at 2 years (6.5 ± 5.0; 67 patients). Paresthesias and gait disturbances were the most common adverse effects at 1 year-each observed in 10 patients with an additional 5 patients experiencing neurological adverse effects. None of the adverse events worsened over the period of follow-up, and 2 of these resolved. There were no new delayed complications at 2 years. The authors concluded, tremor suppression after MRgFUS thalamotomy for ET is stably maintained at 2 years. Latent or delayed complications did not develop after treatment.

Follow-Up Results of Magnetic Resonance Guided Focused Ultrasound Thalamotomy for Essential Tremor

In 2019, Park et. al. summarized the 4-year results of previous reports focusing on the durability and effectiveness of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. Following the emergence of magnetic resonance-guided focused ultrasound as a promising tool for movement disorder surgery, thalamotomy for essential tremor using this technique has become a useful tool based on its efficacy and lack of adverse effects. From October 2013 to August 2014, 15 patients with intractable essential tremor were enrolled. Twelve of them completed clinical assessment through 4 years of postoperative follow-up. Tremor severity, task performance, and disability were measured using the Clinical Rating Scale of Tremor. The mean age of the 12 patients was 61.7 ± 8.1 years. Maximally delivered energy was 15,552.4 ± 6574.1 joules. The mean number of sonications was 17.3 ± 1.6. The mean postoperative lesion volume was 82.6 ± 29.023 mm^3 and in 1 year was a mean of 9.667 ± 8.573 mm^3. Four years postoperatively, improvement of the hand tremor score was 56%, that of the disability score was 63%, that of the postural score was 70%, and that of the action score was 63% compared with baseline; all improvements were significant and sustained over the 4-year period after thalamotomy. There was no

permanent adverse effect throughout the 4-year follow-up period. The authors concluded, magnetic resonance-guided focused ultrasound thalamotomy exhibits sustained clinical efficacy 4 years after the treatment of intractable essential tremor. Adverse events are generally transient. A large cohort of patients who have undergone magnetic resonance-guided focused ultrasound thalamotomy with longer follow-up is needed to confirm our findings.

Summary of Evidence
For individuals with medicine-refractory essential tremors who receive magnetic resonance-guided focused ultrasound (MRgFUS), the evidence includes technology assessment, meta-analyses, and a double-blind, sham-controlled randomized trial. The assessment did not pool study results but concluded that, overall, MRgFUS decreased tremor severity and improved quality of life (QOL). One meta-analysis reported significant improvements in hand tremor scores from baseline up to 24 months post-treatment, with evidence of a diminishing treatment benefit over time. Another meta-analysis found similar improvements in tremor severity with MRgFUS to unilateral DBS, but improvements in both were inferior to bilateral DBS. The sham-controlled randomized trial found significant improvements in the treatment group in tremor severity, functional improvement, and quality of life after 3 months of follow-up. The improvements in hand tremor score, function, and quality of life were maintained at the 2 year follow-up. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.

For individuals with medicine-refractory tremor dominant Parkinson's disease (PD) who receive magnetic resonance-guided focused ultrasound (MRgFUS), the evidence includes a pilot randomized controlled trial (RCT). The double-blind, sham-controlled, pilot randomized trial found significant improvements in the treatment group in tremor severity after 3 months of follow-up. However, large, randomized controlled trials are needed to assess the long-term efficacy and safety of MRgFUS relative to other treatments for this indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Chronic Neuropathic Pain
Chronic neuropathic pain is frequently the result of damage to or dysfunction of the nerve fibers which send incorrect signals to pain centers. Pain significantly lowers patients' quality of life and complicates normal functioning. An alternative treatment being investigated for the treatment of chronic neuropathic pain is the use of magnetic resonance-guided focused ultrasound (MRgFUS) to produce thermal ablation of areas within the thalamus. Uncontrolled studies with small patient populations have been completed treating patients with chronic neuropathic pain caused by a range of conditions including post herpetic neuralgia, avulsion of brachial plexus and lumbar nerve root compression. These preliminary uncontrolled studies have shown improvement in mean reduction in pain scores with minimal adverse events. However, large, randomized controlled trials are needed to assess the long-term efficacy and safety of MRgFUS

relative to other treatments for this indication. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

Adult Cancer Pain Version 2.2021
Some patients experience inadequate pain management despite pharmacologic therapy or may not tolerate an opioid titration program because of side effects. Some patients may prefer interventional therapies instead of chronic medication regimen. Interventional techniques have been demonstrated, in some cases, to eliminate or significantly reduce the level of pain, and/or may allow a significant decrease in systemic analgesics. Interventional therapies that can be useful in the relief of cancer pain include nerve blocks, vertebral augmentation, regional infusion of analgesics, image-guided ablation and other techniques.

Ablation techniques may also be helpful for pain management in patients who receive inadequate relief from pharmacologic therapy. Prospective trials of percutaneous ablative techniques, many using thermal energy, have shown decreased patient pain from bone metastases in patients who did or did not receive prior radiation therapy.

Ablation therapy (e.g., image guided ablation, US ablation) for bone lesions can also be helpful in reducing pain.

Breast Cancer Version 2.2022
The current NCCN guideline does not mention or indicate the use of magnetic resonance-guided high intensity focused ultrasound (MRgFUS) in the treatment of breast cancer.

Central Nervous System Cancers Version 2.2021
The current NCCN guideline does not mention or indicate the use of magnetic resonance-guided high intensity focused ultrasound (MRgFUS) in the treatment of central nervous system cancers (i.e. brain cancer to include glioblastoma).

Prostate Cancer Version 2.2022
Many Therapies have been investigated for the treatment of localized prostate cancer in the initial disease and recurrent settings with the goals of reducing side effects and mating the cancer control of other therapies. Cryotherapy or other local therapies are not recommended as routine primary therapy for localized prostate cancer due to lack of long-term data comparing these treatments to radiation or radical prostatectomy. At this time, the panel recommends only cryosurgery and high-intensity focused ultrasound (HIFU; category 2B) as local therapy options for RT recurrence in the absence of metastatic disease.

Soft Tissue Sarcoma Version 2.2021
The current NCCN guideline does not mention or indicate the use of magnetic resonance-guided high intensity focused ultrasound (MRgFUS) in the treatment of soft tissue sarcomas (i.e., desmoid tumors).

American College of Radiology (ACR)
In 2012, the American College of Radiology (ACR) issued appropriateness criteria for radiologic management of uterine leiomyomas that states: MR-guided high intensity ultrasound is another uterine sparing option to treat focal leiomyomas. It is noninvasive, though each treatment may take several hours to be completed. Its use currently is restricted to patients with fewer than six leiomyomas or leiomyoma volume less than 900 cm^3. To date, there is little long-term information on the efficacy of this technology.

American College of Obstetricians and Gynecologists (ACOG)
In 2021, the American College of Obstetricians and Gynecologists **(**ACOG) reaffirmed in a practice bulletin on the management of symptomatic uterine leiomyoma states "while limited, low quality data suggests MRgFUS is associated with a reduction in leiomyoma and uterine size, smaller randomized comparative data suggests when compared with UAE, MRgFUS is associated with less improvement in symptoms and a higher rate of reintervention."

American Society of Radiation Oncology (ASTRO)
In 2017, the American Society of Radiation Oncology (ASTRO) issued an updated evidence-based guideline on palliative radiation therapy for bone metastases. The updated guideline analysis confirms that radiation therapy provides excellent palliation for painful bone metastases and that retreatment is safe and effective. The guideline does not mention magnetic resonance-guided focused ultrasound.

National Institute for Health and Clinical Excellence (NICE)
In 2018, NICE issued an interventional procedure guidance (IPG617) on unilateral MRI-guided ultrasound thalamotomy for the treatment of resistant essential tremor that stated the following: The evidence on the safety of unilateral MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor raises no major safety concerns. However, current evidence on its efficacy is limited in quantity. Therefore, this procedure should not be used unless there are special arrangements for clinical governance, consent, and audit or research.

Regulatory Status
In October 2004, the U.S. Food and Drug Administration (FDA) approved via the premarket application (PMA) process, the ExAblate® 2000 System (Insightec, Inc., Haifa, Israel) for "ablation of uterine fibroid tissue in pre- or perimenopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure." Treatment is indicated for women with a uterine gestational size of less than 24 weeks who have completed childbearing.

In October 2012, the U.S. Food and Drug Administration (FDA) approved the ExAblate® System, Model 2000/2100/2100 VI via the PMA process. The intended use of the device is for pain palliation 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 U.S. Food and Drug Administration (FDA) approved the ExAblate Neuro system for use in the unilaterally thalamotomy treatment of idiopathic essential tremor patients with medication refractory tremor. Patients must be at least age 22. The designated area in the brain responsible for the movement disorder symptoms (ventralis intermedius) must be identified and accessible for targeted thermal ablation by the ExAblate device. ExAblate Neuro uses magnetic resonance images taken during the procedure to deliver focused ultrasound to destroy brain tissue in a tiny area thought to be responsible for causing tremors.

PRIOR APPROVAL

Not applicable.

POLICY

See related medical policies

- 02.01.53 High Intensity Focused Ultrasound (HIFU)
- 07.01.69 Treating Benign Prostatic Hyperplasia

Magnetic resonance-guided high intensity focused ultrasound (MRgFUS) ablation may be considered **medically necessary** for pain palliation in adult patients with metastatic bone cancer who failed or are not candidates for radiotherapy.

Magnetic resonance-guided high intensity focused ultrasound (MRgFUS) unilateral thalamotomy ablation (ventralis intermedius nucleus thalamus) may be considered **medically necessary** in adult patients with essential tremor and meet **ALL** of the following criteria:

- Documented diagnosis of essential tremor; **AND**
- Medication refractory essential tremor defined as refractory to at least two trials of medical therapy to include the following:
    - Beta blockers (such as propranolol)
    - Anticonvulsants (such as primodone, gabapentin or topiramate)
    - Benzodiazepines (such as clonazepam or diazepam)

Magnetic resonance-guided high intensity focused ultrasound (MRgFUS) ablation is considered **investigational** for all other indications including but not limited to the following, as the safety and/or effectiveness cannot be established by review of the

available published peer reviewed literature. The evidence is insufficient to determine the effects of the technology on net health outcomes:

- Treatment of uterine fibroids
- Treatment of essential tremors except as indicated above
- Treatment of chronic neuropathic pain
- Brain cancer (to include but not limited to glioblastoma)
- Prostate cancer
- Breast cancer
- Desmoid tumors
- Treatment of pain palliation for patients with metastatic bone cancer except as indicated above

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0071T Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume less than 200 cc of tissue
- 0072T Focused ultrasound ablation of uterine leiomyomata, including MR guidance; 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
- C9734 Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance

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POLICY HISTORY

Date	Reason	Action
January 2022	Annual Review	Policy Renewed
January 2021	Annual Review	Policy Renewed
January 2020	Annual Review	Policy Renewed
January 2019	Annual Review	Policy Revised
January 2018	Annual Review	Policy Revised
January 2017	Annual Review	Policy Renewed
January 2016	Annual Review	Policy Revised
February 2015	Annual Review	Policy Revised
March 2014	Annual Review	Policy Revised
May 2013	Annual Review	Policy Renewed
May 2012	Annual Review	Policy Renewed
August 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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