Anthem

Clinical UM Guideline

Subject: Ultrasound Ablation for Oncologic Indications
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Description

This document addresses ultrasound ablative therapy for the treatment of oncologic conditions. There are currently two ultrasound ablative techniques. High intensity focused ultrasound (HIFU) or magnetic resonance guided focused ultrasound (MRgFUS) involves the use of a focused high-intensity convergent ultrasound beam to destroy targeted tissue in a small, focused area via sonication. HIFU has been proposed as a treatment for multiple oncologic conditions. Transurethral ultrasound ablation (TULSA), which delivers directional thermal ultrasound via a catheter inserted into the urethra, is specific to prostate cancer.

Note:

- See the following related document for HIFU treatment non-oncologic indications:
  - MED.00057 MRI Guided High Intensity Focused Ultrasound Ablation for Non-Oncologic Indications
- For information regarding other palliative treatments of metastatic bone lesions, please see the following:
  - CG-SURG-61 Cryosurgical, Radiofrequency, Microwave or Laser Ablation to Treat Solid Tumors Outside the Liver

Clinical Indications

Medically Necessary:

The use of high intensity focused ultrasound (HIFU) is considered **medically necessary** for pain palliation in individuals with localized metastatic bone pain when **all** the following criteria are met:

A. Age 18 years or older; **and**
B. Metastatic lesions located 1 centimeter (cm) or greater from skin and major nerve bundles; **and**
C. Individual does not present an increased risk of fracture from the procedure (for example, a score of 7 or less on Mirel's fracture risk score); **and**
D. Individual does not require surgical stabilization or have clinically significant comorbidities; **and**
E. Individual is not a candidate for other therapies as evidenced by pain refractory to previous radiation therapy.

Not Medically Necessary:

High intensity focused ultrasound (HIFU) is considered **not medically necessary** when the above criteria are not met and for all other indications, including but not limited to, the treatment of prostate cancer.

TULSA is considered **not medically necessary** for any indication, including but not limited to prostate cancer.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Bone metastases
When services may be Medically Necessary when criteria are met:

CPT

20999	Unlisted procedure, musculoskeletal system, general [when specified as high intensity focused ultrasound ablation for pain palliation for bone metastases]

HCPCS

C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance

ICD-10 Diagnosis

C79.51	Secondary malignant neoplasm of bone

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met.

Treatment of other oncologic indications
When services are Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure designated in the Clinical Indications section as not medically necessary.

CPT

19499	Unlisted procedure, breast [when specified as destruction of breast tissue by high intensity focused ultrasound]
53899	Unlisted procedure, urinary system [when specified as transurethral MRI directional ultrasound ablation of prostate tissue (TULSA)]
55880	Ablation of malignant prostate tissue, transrectal, with high intensity-focused ultrasound (HIFU), including ultrasound guidance

HCPCS

C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance

ICD-10 Diagnosis

C00.0-C79.49	Malignant neoplasms
C79.52-C80.2	Malignant neoplasms
D00.00-D09.9	In situ neoplasms

Discussion/General Information

HIFU

Ultrasound, the use of low-intensity sound waves to produce images, is an established diagnostic tool. When high-intensity ultrasound waves are used in place of low-intensity, body tissue absorbs, rather than reflects the energy. The resulting heat and cavitation destroys the targeted tissue. Temperatures within the targeted area increase to 60-95°C, which destroys the targeted tissue without damaging the adjacent tissue. HIFU is a non-invasive ablative procedure which has the advantage of sparing surrounding tissue which may reduce postoperative morbidity and hasten recovery.

HIFU treatment is combined with a visualization method, frequently MR guidance, to better guide treatment in real time. Ultrasound is currently being used as a therapeutic treatment, for example, lithotripsy to disintegrate kidney stones. HIFU or MRgFUS has also been studied as a potential treatment of various cancers.

Pain palliation for localized metastatic bone pain

Bone pain is a common complaint for individuals with metastatic cancer to the bone. Approximately 30% of all individuals with cancer develop metastatic bone lesions and 50-75% of these individuals report significant pain. Bone metastases are common in breast and prostate cancer (Liberman, 2009). The current standard treatment is external beam radiation therapy (EBRT). However, EBRT is ineffective in approximately 20-30% of cases and pain recurs in 27% of the treated population (Liberman, 2009). There are limitations associated with EBRT. Sites which have been previously irradiated have limited tissue tolerance to further radiation. Individuals who fail, are not eligible for, or refuse radiation therapy may be managed pharmacologically or with other therapies such as surgery or percutaneous cryoablation. These options carry their own risks and side effects.

Although the exact mechanism of analgesic action of MRgFUS in pain palliation is unknown, studies have pointed to possible explanations. As the bone cortex absorbs high ultrasound energy, periosteal denervation may ensue, resulting in pain relief. Alternatively, the reduced tumor mass caused by thermal ablation may have an analgesic effect. It is likely that both of these treatment effects contribute to pain relief.

In 2012, the FDA approved via the Premarket Application (PMA) process, the ExAblate® System (InSightec, Ltd, Dallas, TX) for pain palliation in individuals 18 years and older who have metastatic bone cancer pain and have failed, are not candidates for or have refused standard radiation therapy.

Early prospective studies evaluating MRgFUS reported promising results. Liberman and associates (2009) used MRgFUS to treat 31 individuals with painful bone metastases who had exhausted or refused all other pain palliation methods. The bone metastases arose from a variety of primary tumors including renal, colorectal, lung, breast and prostate. Researchers used the visual analog pain score (VAS) to measure pain levels. In the 25 participants that were able to tolerate a complete treatment, 72% (18/25) reported significant pain reduction of at least 2 points on the VAS scale, 24% (6/25) reported no reduction in pain and 4% (1/25) reported an increase in pain levels. In those individuals who reported a decrease in pain levels, 50% (9/18) reported complete relief of pain, with 52% reporting significant pain relief beginning 3 days post treatment. There were no reported treatment related severe adverse events (AEs). In 2013, Napoli and colleagues treated 18 individuals with painful bone metastases with MRgFUS. Participants included those who could not undergo or refused all other available options for pain palliation. Pain severity was measured using a 10-point pain scale questionnaire. The pain severity score was significantly reduced from a baseline mean of 7.1 (Standard Deviation[SD] ± 2.08) (4-10; 95% confidence interval [CI], 6.07-8.15), to 2.5 (SD ± 1.4) (0-5; 95% CI, 1.81-3.2) at 1 month. Pain severity was further reduced at the 3-month follow-up to 1 (SD ± 1.1) (0-3; 95% CI, 0-1.85) (p=0.001). At 3 months, 72.2% (13/18) reported no pain without the use of pain medication, and 16.7% (3/18) reported a drop of at least 2 points on pain scale without an increase in pain medication. The remaining 11.1% (2/18) reported pain reoccurrence which required pharmacological care. There were no treatment-related AEs. In a prospective, non-randomized single arm trial, MRgFUS was used on 5 individuals with painful bone metastatic lesions with a pain rating of 4 or higher. At 2 weeks follow-up, all individuals experienced a decrease in VAS pain scores from baseline (1.5-5). A complete resolution of pain at 1 year follow-up was shown in 2 participants (Joo, 2015).

In the first phase III study published, Hurwitz and colleagues (2014) conducted a randomized, placebo-controlled, single-blind, multicenter, pivotal trial which included 147 participants with bone metastases from breast, prostate, kidney, lung or other primary tumors. Eligibility included those at least 18 years old with at least a 3-month life expectancy with bone metastases which were painful despite previous radiation therapy (RT) but unsuitable for further RT. In addition, eligible participants reported a numerical rating scale (NRS) pain score of 4 or greater in spite of maximal pain medication therapy, and a score of 7 or less on the Mirel's fracture risk scale. Participants received either MRgFUS (n=112) or placebo (n=35) treatment. The identified primary endpoint was the improvement in self-reported pain score without an increase in pain medication utilization at 3 months. The difference in response rates between MRgFUS and placebo at 3 months was significant (64.3% versus 20.0%). In addition, 21% of individuals in the MRgFUS group reduced their morphine equivalent daily dose (MEDD) intake and another 26% completely stopped their MEDD consumption. Of note, 65.7% (23/35) of individuals in the placebo group did not complete the 3-month follow-up compared to approximately 21% (26/112) of the MRgFUS group. After excluding the drop-out groups the results remained similarly statistically significant. The study also included a crossover component; 17 of the 23 individuals in the placebo group who did not complete follow-up chose to receive rescue MRgFUS after a lack of response to placebo. A statistically significant pain response was reported in 70.7% of this group. These results were not included in the primary efficacy analysis. The mean reduction in the NRS score was significant between MRgFUS and placebo (3.6 ± 3.1 versus 0.7 ± 2.4). However, the change from baseline in MEDD intake was not statistically significant, although the authors noted a trend towards a statistically significant change. The treatment group reported an AE frequency of 76.2% versus 23.8% in the sham group. The majority of events were minor and reversible. The authors noted these results compared well to the radiation therapy complication rate.

While the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines (CPG) in Oncology for Adult Cancer Pain (V2.2023) document notes that the palliative effects of HIFU have been demonstrated in several small studies, no recommendation for or against the use of HIFU for pain palliation was given.

Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in men, accounting for 19% of all new cancer cases. Prostate cancer is the second leading cause of death with approximately 39,430 deaths in 2018 (Bekelman, 2018). HIFU has been evaluated as a minimally invasive treatment of whole gland or a focal treatment of prostate cancer, both in the initial treatment of clinically localized prostate cancer and following recurrence.

In 2015, The U.S. Food and Drug Administration (FDA) approved two devices for use in prostate cancer. On October 9, the FDA granted *de novo* clearance to Sonablate Corp. (formerly known as SonaCare Medical, LLC; Charlotte, NC) to market the Sonablate® 450 for prostate tissue ablation. Sonablate was classified as a class II device. In November, the FDA approved the use of Ablatherm® (Maple Leaf; Toronto, Canada) to treat prostate cancer in individuals who previously failed radiation therapy.

Reddy and colleagues (2022) reported on the up to 15-year outcomes of a prospective study of individuals who underwent HIFU to treat nonmetastatic prostate cancer. Individuals with greater than 6 months of follow-up were analyzed (n= 1379). The primary outcome, failure-free survival (FFS), was defined as "evidence of cancer requiring whole-gland salvage treatment or third focal therapy treatment, systemic treatment, development of prostate cancer metastases or prostate-cancer specific death". The FFS at 7 years was 69% with the specific FFS for intermediate risk cancer at 68% (95% CI: 62–75%) and 65% for high-risk cancer (95% CI: 56–74%). While the authors concluded that this modality shows good medium-term control within 7 years, the median follow-up was 32 months. The median follow-up was not adequate to adequately evaluate recurrence rates.

There are a number of uncontrolled case series and prospective studies which address HIFU for prostate cancer (Ahmed, 2009, 2011, 2012; Beerlage, 1999b; Blana, 2004; Chaussy, 2001; Gelet, 2000; Gelet, 2004; Guillaumier; 2018; Lawrentschuk, 2011; Muto, 2008; Napoli, 2013; Poissonnier, 2007; Shoji, 2010; Thuroff, 2003; Uchida, 2002; Uchida, 2005; Uchida, 2006a; Uchida, 2006b; Zacharakis, 2008). One of the largest of these studies was conducted by Ganzer and colleagues (2011). This study was a retrospective case series involving 804 subjects who underwent HIFU and were included in an industry-sponsored registry. The focus of this study was the use of prostate specific antigen (PSA) as a predictor of disease-free survival after HIFU, not the outcomes related to HIFU treatment. The study has several methodological flaws, including lack of a comparison group, and uncertainty regarding the percentage of subjects who completed the follow-up period.

Crouzet and colleagues (2014) conducted a large prospective case series (n=1002) to evaluate rates of survival and morbidity over the long term in subjects treated with HIFU (Ablatherm) for localized disease. The mean follow-up period was 6.4 years (range, 0.2-13.9). Approximately 98% of subjects received 1 (60%) or 2 treatments (38%). Post-treatment biopsies were available in 77% of subjects. The overall survival (OS) rate was 80%, the progression-free survival (PFS) rate was 94%, and the disease-specific survival rate was 97%. The most commonly reported complications included "Stress 1" urinary incontinence (18.7%), followed by obstruction of the bladder outlet (16.6%), and acute urinary retention (7.6%). Late complications included occurrences of stenosis (9%) and fistula (0.4%). This prospective case series did not compare HIFU long-term survival and morbidity rates with the rates of other standard treatments.

The NCCN Prostate Cancer CPG (V1.2023) includes a recommendation for individuals with tumor recurrence following radiation therapy to include HIFU as a treatment option (2B recommendation). Previously, this recommendation was graded as a 2A. This recommendation is based upon prospective and retrospective studies (Ahmed, 2012; Baco, 2014; Crouzet, 2012; Crouzet, 2017; Kanthabalan, 2017; Palermo, 2017; Rischmann, 2017; Shah, 2016; Siddiqui, 2016; Uddin 2012).

Focal therapies using modalities such as HIFU have been evaluated by appropriate medical societies including the American Urological Association (AUA), the American Society for Radiation Oncology (ASTRO), the American Society of Clinical Oncology (ASCO) and the Society of Urologic Oncology (SUO). The societies cite a continued lack of high quality data with long-term outcomes comparing ablation with standard therapies (Eastham, 2022; re, 2017; Sanda, 2018; Thompson, 2007).

HIFU therapy was included in a comparative effectiveness review of clinically localized prostate cancer treatments (Dahm, 2020; Wilt, 2021). Focal therapies are proposed as less invasive treatment options when compared to radical prostatectomy or radiation therapy. However, comparisons involving HIFU were limited to radical prostatectomy because of a lack of studies comparing HIFU to other therapies. There is insufficient evidence to draw conclusions about the effect of HIFU on urinary incontinence, erectile dysfunction or fecal incontinence when compared to radical prostatectomy. The authors concluded, "Although… newer modalities hold promise, we need higher quality studies to assess patient important outcomes to guide evidence-based clinical practice."

Although use of HIFU or MRgFUS for primary prostate cancer or for prostate cancer metastatic to locations other than bone has not entered the generally accepted standard care for these conditions, treatment of pain related to prostate cancer metastatic to bone may provide benefits to affected men.

Other Oncologic Indications

Peek and associates (2015) conducted a systematic review of the use of HIFU in breast cancer. The authors reviewed 9 studies with a total of 167 participants. Following treatment, no residual tumor was found in 46.2% of cases. However, residual tumors of less than 10% were found in 29.4% of cases and residual tumors between 10-90% were found in 22.7% of cases. The authors noted that incomplete tumor ablation could be related to poor accuracy in determining the target area or movement during the procedure. The use of HIFU in the setting of breast cancer treatment may not allow for an adequate collection of tumor specimens to evaluate the tumor histopathology. The limited examination of small biopsies as well as the lack of a reliable means of assessing some prognostic factors, such as potential lymphovascular invasion, may not provide adequate information for the determination of adjuvant systemic therapies.

In a systematic review, Li and colleagues (2014) performed a meta-analysis on the use of HIFU in combination with radiotherapy or chemotherapy in the treatment of pancreatic cancer. A total of 23 studies comprised of 1157 individuals were included. While the analysis showed superior survival rates at 6 and 12 months in the groups which included HIFU in combination therapy, the authors noted that the overall quality of the studies was poor. A second systemic review in which HIFU was compared to other ablative therapies in the treatment of locally advanced pancreatic cancer was done by Rombouts and colleagues (2015). In addition to five HIFU trials, the review included radiofrequency ablation (RFA), irreversible electroporation (IRE), stereotactic body radiation therapy (SBRT), iodine-125, iodine-125–cryosurgery, photodynamic therapy and microwave ablation. Results indicated that median survival in RFA, IRE and SBRT was more favorable compared to HIFU. HIFU was comparable to the median survival in standard chemotherapy. The five HIFU trials included a total of only 136 individuals. While some trials using HIFU to treat pancreatic or liver cancer have shown some promising results, these trials have lacked a comparator group (Chen, 2015; Dupré, 2015; Shi, 2015; Sofuni, 2014). Similar to prostate cancer, there is a lack of randomized trials comparing HIFU to standard treatment options. The current evidence is insufficient to support the use of HIFU as a generally accepted oncological treatment.

The 2021 American Urological Association (AUA) published a guideline on renal mases and localized renal cancer. The guideline addresses several non-extirpative therapies and concluded that these therapies, including HIFU, are investigational for the treatment of renal masses. There are concerns about inconsistent treatment coverage within renal masses resulting in incomplete ablation. Management of renal masses using this modality is poorly defined due to a lack of published studies and lack of long-term follow-up

(AUA, 2021).

TULSA

TULSA was developed as an alternative method of prostate tissue ablation. TULSA is delivered by a system which includes real-time MR thermometry as well as robotically-driven directional thermal ultrasound in a closed loop system to ablate whole gland or targeted areas of the prostate. The system protects the urethra and rectum via a water cooling system pumped through the applicator. The TULSA-PRO® (Profound Medical Corp., Fort Myers, FL) received 510(k) clearance by the FDA in 2019. The clearance was based upon the Ablatherm device as the predicate device. TULSA has been proposed as a localized treatment of unilateral intermediate risk prostate cancers in individuals not interested in active surveillance (Klotz, 2021).

The single-arm, prospective, multi-center pivotal trial, TULSA-PRO Ablation Clinical Trial (TACT), enrolled 115 individuals with intermediate risk (67.0%) or low risk (33.0%) organ confined prostate cancer who underwent whole gland prostate ablation (Klotz, 2021). The primary endpoint was the proportion of individuals who achieved a 75% or greater reduction in PSA at 12 months post-procedure. Participants were followed for up to 5 years post-procedure. The primary endpoint was achieved in 96% (110/115) of participants. The PSA decreased from a median of 6.26 to 0.53 at 12 months. In an intent-to-treat analysis, 63% (72/115) were reported to have a complete histological response and had no evidence of cancer. There were 12 grade 3 adverse events (AEs) attributable to the TULSA-PRO, all of which were resolved by 12 months. The majority of attributable AEs were grade 1 or 2. This study was defined by the regulatory agency to evaluate the effectiveness of the device to ablate prostate tissue. The current evidence does not show that clinical outcomes of those undergoing TULSA is similar to those undergoing established alternatives.

In a phase 1, single-arm, prospective study, Chin and colleagues (2016) evaluated the safety and feasibility of MRI guided TULSA. Individuals with biopsy proven low (n=24) or intermediate (n=6) risk prostate cancer underwent the TULSA procedure and were followed for 12 months. Adverse events included grade 1 or 2 hematuria, urinary tract infections or acute urinary retention, and grade 3 epididymitis. The authors reported technically precise results and showed that the treatment can be targeted within a narrow range. Bonekamp and associates (2019) performed a quantitative analysis of viable prostate tissue volume reduction at 12 months post-procedure. MRI-TULSA resulted in an 88% reduction of viable prostate tissue volume. This early study focused on safety and technical feasibility rather than clinical outcomes.

In 2021, Nair and colleagues reported the 3-year outcomes of the participants in the Chin study. A total of 22 individuals participated in the follow-up. There were no new reported serious AEs. The PSA level, which had dropped following treatment, remained low. A total of 29 individuals underwent a follow-up biopsy, either at 12 months only, or at 12 and 36 months. A clinically significant biopsy was reported in 34% (10/29) of participants with 59% (17/29) of participants reporting any positive biopsy. A set of individuals who were positive for insignificant disease at 12 months (n=4) or clinically significant disease at 12 months (n=5) required salvage treatment. The authors theorized that the high rate of salvage treatment at 3 years follow-up could be attributed to suboptimal staging and treatment.

Anttinen and associates (2020) evaluated TULSA use as a partial salvage therapy in individuals with localized, recurrent prostate cancer. The prospective, nonrandomized, investigator-initiated, single-arm, single-center phase 1 study included 11 individuals with localized, histopathologically verified, radio-recurrent prostate cancer. Individuals received either whole gland (n=8) or partial (n=8) ablation. An mpMRI, a transrectal ultrasound guided biopsy and a cystoscopy were performed at 12 months post-procedure. Grade 3 (n=1) and grade 2 (n=3) AEs related to urinary retention and urinary tract infection were reported. At 12 months, the majority of participants (10/11) were cancer free in the ablated area and maintained a low stable PSA. There was 1 in-field and 2 out-of-field recurrences reported at that time. An individual with out-of-field recurrence underwent a repeat salvage TULSA. The baseline median PSA of 7.6 ng/ml decreased to 0.23 ng/ml at 12 months follow-up. The authors reported that salvage TULSA was technically feasible and showed encouraging early results but have not been compared to standard therapy.

The use of TULSA has been evaluated in several prospective and retrospective studies, with participants being treated for whole gland or partial gland ablation and as primary or salvage treatment as well as combined therapy for individuals with prostate cancer (Elterman, 2021; Lumiani, 2021; Ramsay, 2017). These studies have a number of methodological limitations, including a lack of randomization of participants, a lack of a comparator group and limited follow-up for oncologic outcomes. The available evidence does not support that the use of TULSA is clinically appropriate and an effective therapy compared to the standard treatments.

Definitions

Bone metastasis: When cancer cells have broken off from the primary tumor and have settled and started growing on bones.

High intensity focused ultrasound (HIFU): A surgical procedure that uses focused high energy sound waves to destroy target tissues in the body.

Mirel's scoring system: A scoring system based upon lesion characteristics and pain levels used to classify pathologic fracture risk.

Score	Site of Lesion	Size of Lesion	Nature of Lesion	Pain
1	Upper limb	<1/3 of cortex	Blastic	Mild
2	Lower limb	1/3-2/3 of cortex	Mixed	Moderate
3	Trochanteric region	>2/3 of cortex	Lytic	Functional

* From Jawad MU, Scully SP. In brief: classifications in brief: Mirels' classification: metastatic disease in long bones and impending pathologic fracture. Clin Orthop Relat Res. 2010; 468(10):2825-2827.

Palliative treatment: Treatment given for relief of symptoms and pain rather than attempting to cure.

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Index

Ablatherm®
ExAblate
Sonablate 450
TULSA-PRO

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Discussion, References and Websites for Additional Information sections.
Reviewed	11/10/2022	MPTAC review. Updated Description, Discussion and References sections.
Revised	11/11/2021	MPTAC review. Added not medically necessary statement for TULSA. Revised title from *High Intensity Focused Ultrasound (HIFU) for Oncologic Indications* to *Ultrasound Ablation for Oncologic Indications*. Updated Description, Coding, Discussion and References sections.
Reviewed	11/05/2020	MPTAC review. Updated Description, Discussion, References and Websites for Additional Information sections. Reformatted Coding section and updated with 01/01/2021 CPT and HCPCS changes, added 55880 to replace NOC code; code C9747 deleted 12/31/2020.
Reviewed	11/07/2019	MPTAC review. Updated Description, Discussion, References and Websites for Additional Information sections.
New	03/21/2019	MPTAC review.
New	03/20/2019	Hematology/Oncology Subcommittee review. Moved content of MED.00119 High Intensity Focused Ultrasound (HIFU) for Oncologic Indications to new clinical utilization management guideline document with the same title.
