

Subject: High-Intensity Focused Ultrasound (HIFU) for Prostate Cancer		Original Effective Date: 5/17/2017
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.¹

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

HIFU, also known as focused ultrasound surgery, acoustic ablation, or sonablation, is a minimally invasive treatment that ablates prostatic tissue using high-intensity convergent ultrasound delivered via an endorectal probe. HIFU signifies an intensity of > 5 watts per square centimeter, which produces coagulation necrosis of tissue and is most often utilized for HIFU ablation. When HIFU is deposited via an ultrasound transducer in a focal area, the induced thermal lesions are well circumscribed, with an intermediate zone comprising a few layers of cells between the intact and ablated cells. The entire prostate gland is ablated using a series of ultrasonic “shots.” Surrounding normal tissue is not affected due to the low acoustic energy density in these areas. The ultrasound causes a sharp rise in temperature of up to 90 degrees Celsius. A

cooling balloon surrounding the transrectal probe protects the rectum from thermal damage. Real-time guidance is provided by diagnostic ultrasound or MRI. Computer guidance software defines the exact target volume such that the sound wave beam is delivered with a high degree of precision, thus minimizing the impact on surrounding tissue and intervening structures.

Food and Drug Administration (FDA): High-intensity focused ultrasounds (HIFUs) are regulated as class II devices under the product code PLP (high intensity ultrasound system for prostate tissue ablation). These devices are designed to use high intensity ultrasound to heat target tissue within the prostate gland, causing coagulation necrosis of the tissue. The following HIFU devices have received FDA clearance ² for marketing in the United States:

- Sonablate (SonaCare Medical LLC; K160942: Approved December 21, 2016 for the indication of transrectal HIFU ablation of prostatic tissue.
- Ablatherm Integrated Imaging High-Intensity Focused Ultrasound (HIFU) device; K153023: Approved November 6, 2015 for transrectal HIFU ablation of prostate tissue.

POSITION STATEMENT

HIFU is considered experimental, investigational and unproven for the treatment of prostate cancer due to insufficient evidence in the peer reviewed literature.

SUMMARY OF MEDICAL EVIDENCE ³⁻³⁷

A small body of low-quality evidence found that salvage HIFU leads to acceptable efficacy outcomes in patients with localized prostate cancer that has recurred following primary treatment with EBRT or RP. There are no RCT's comparing HIFU with other standard therapies for primary localized prostate cancer such as prostatectomy, EBRT, or active surveillance. The best available studies of ultrasound-guided salvage HIFU for localized, recurrent prostate cancer in patients with no signs of metastatic disease at the time of treatment have found that most patients experience a reduction in serum PSA level, acceptable local tumor control, remain free of disease progression, and survive for 5 years or longer after treatment. The treatment appears to be relatively safe, although it can negatively affect urinary and sexual function, as can primary treatments for prostate cancer. The body of evidence is from uncontrolled prospective and retrospective studies, systematic reviews ^{3-5, 7-9} and comparative studies ^{6, 23} that evaluated HIFU with an alternative technology (salvage cryoablation). Additional, well-designed studies are needed to further compare HIFU for localized, recurrent prostate cancer with alternative and established salvage therapies before a determination can be made as to its long-term safety and effectiveness, mainly with regard to prostate cancer recurrence and mortality.

Comparative Studies

Siddiqui et al (2015) compared the morbidity of whole gland salvage ablation using cryotherapy (CRYO) and high-intensity focused ultrasound (HIFU) for radio recurrent prostate cancer at a single centre over a 17-year period. Patients were divided in 3 cohorts. Group 1 included the first 65 patients treated with CRYO (1995-1998); Group 2 included the last 65 patients treated with CRYO (2002-2004), and Group 3 included 65 patients treated with HIFU (2006-2011). We analyzed the complications reported within at least 90 days of treatment or up to the last follow-up. The results outlined Clavien grade complications. For Groups 1, 2 and 3, the following Clavien I-II complications were recorded: 78, 49 and 13, respectively. For Clavien grade IIIa, 2, 5 and 4 for Groups 1, 2 and 3, respectively. For Clavien grade IIIb, 8, 2 and 3 for Groups 1, 2 and 3, respectively. Clavien grade II complications were statistically higher in Group 1 versus Group 2 ($p = 0.005$) and in Group 2 versus Group 3 ($p = 0.0001$). The rate of mild-moderate incontinence was significantly higher in the CRYO group compared to the HIFU cohort ($p \leq 0.05$). The rate of urinary retention was significantly higher in Group 2 compared to Group 3 ($p = 0.0005$). The rates of severe incontinence (range: 1.5%-5%), need for surgical intervention (uniform at 1.5%), and recto-urethral fistulae (range: 1.5%-3%) were not statistically different. CRYO was associated

with higher overall morbidity. The morbidity during the early experience with HIFU was lower than both subgroups of CRYO and may reflect the advancement of technology or cumulative learning experience.⁶

Liu et al (2016) conducted a prospective, single-institutional comparison for primary whole-gland cryoablation and high-intensity focused ultrasound (HIFU) in localized prostate cancer with respect to oncological and functional outcomes. A total of 114 and 120 patients with primary whole-gland cryoablation and HIFU for localized prostate cancer, respectively, were enrolled in the study. Functional outcomes included complications and serial International Index of Erectile Function (IIEF)-5 scores, International Prostate Symptom Score (IPSS), and related quality of life (QoL) scores. During the mean follow-up duration of approximately 2 years, the PSA biochemical recurrence rates of the two groups were similar (cryoablation 25.4 %, HIFU 18.3 %). In terms of functional outcomes, patients with HIFU had significantly lower IPSS (5.70 vs. 9.04 at 24 months; $p = 0.030$), lower erectile dysfunction rate (65.6 vs. 88.0 %; $p = 0.015$), and higher IIEF-5 score (9.36 vs. 4.18 at 24 months; $p = 0.028$) than patients with cryoablation. In this study, both primary whole-gland cryoablation and HIFU demonstrated good oncological outcomes for localized prostate cancer. We validated the safety of the two treatment modalities and identified the importance of combined HIFU and transurethral resection of the prostate. The HIFU patients experienced better urinary function improvement and more possible sexual function preservation than the cryoablation patients; therefore, HIFU may provide better quality of life for patients with localized prostate cancer.²⁵

Systematic Reviews³⁻⁹

Two systematic reviews from 2017 summarized that longer term data are needed to evaluate oncologic efficacy and functional outcomes, and will aid in identifying the optimal candidates for therapy. Standardization of outcomes definitions will allow for better comparison between studies and among treatment modalities and that the oncological outcome has yet to be evaluated against standard of care.⁸⁻⁹

A recent systematic review (Duijzentkunst et al., 2016) assessed the safety and efficacy of focal salvage therapy for treatment of localized, recurrent prostate cancer following radiotherapy. The review compared partial salvage therapy with whole-gland salvage therapy. A total of 8 studies were included, 2 of which evaluated the use of HIFU for focal salvage treatment. Several limitations are noted, including small sample sizes, lack of RCTs, lack of blinding, lack of standardized definitions, and variations in assessment modalities. Despite these limitations, the researchers concluded that focal salvage therapy is comparable to whole-gland salvage therapy, with the benefit of a decrease in severe toxicity and preservation of erectile function, and highlight the need for additional research.³

Another systematic review by Veereman et al. (2015) examined the safety and efficacy of ultrasound-guided HIFU for treatment of localized prostate cancer. This review of low-quality evidence suggested an OS rate after HIFU with the Ablatherm device (accounting for 14 primary studies) ranging from 80% to 89% for > 5 years. The prostate cancer-specific survival rate ranged from 97% to 99% for > 5 years. Biochemical disease-free survival (BDFS) ranged from 64.2% to 85% within 5 years of follow-up, and from 60% to 79% for > 5 years of follow-up.⁷

A third systematic review (Ramsay et al. 2015) aimed to determine the relative clinical effectiveness and cost-effectiveness of ablative therapies compared with radical prostatectomy (RP), external beam radiotherapy (EBRT) and active surveillance (AS) for primary treatment of localized prostate cancer, and compared with RP for salvage treatment of localized prostate cancer which has recurred after initial treatment with EBRT. For primary therapy, the ablative therapies were cryotherapy, HIFU, brachytherapy and other ablative therapies. The comparators were AS, RP and EBRT. For salvage therapy, the ablative therapies were cryotherapy and HIFU. The comparator was RP. Outcomes were cancer related, adverse effects (functional and procedural) and quality of life. Two reviewers extracted data and carried out quality assessment. Meta-analysis used a Bayesian indirect mixed-treatment comparison. Data were incorporated into an individual simulation Markov model to estimate cost-effectiveness. There was no robust evidence that mortality (4-year survival 93% for cryotherapy, 99% for HIFU, 91% for EBRT) or other cancer-specific outcomes differed between

treatments. For functional and quality-of-life outcomes, the paucity of data prevented any definitive conclusions from being made, although data on incontinence rates and erectile dysfunction for all ablative procedures were generally numerically lower than for non-ablative procedures. The safety profiles were comparable with existing treatments. Studies reporting the use of focal cryotherapy suggested that incontinence rates may be better than for whole-gland treatment. Data on AS, salvage treatment and other ablative therapies were too limited. The cost-effectiveness analysis confirmed the uncertainty from the clinical review and that there is no technology which appears superior, on the basis of current evidence, in terms of average cost-effectiveness. The analyses suggest that a number of ablative techniques are worthy of further research. The main limitations were the quantity and quality of the data available on cancer-related outcomes and dysfunction. The findings indicate that there is insufficient evidence to form any clear recommendations on the use of ablative therapies in order to influence current clinical practice. Research efforts in the use of ablative therapies in the management of prostate cancer should now be concentrated on the performance of RCTs and the generation of standardized outcomes. ⁴

PROFESSIONAL SOCIETY GUIDELINES

National Comprehensive Cancer Network (NCCN): The NCCN’s most recent guidelines on treatment of prostate cancer, released in February 2017, recommend HIFU and cryosurgery as options for treating localized, biopsy-confirmed recurrence following external beam radiotherapy (EBRT) in the absence of metastatic disease. HIFU is included as an option for salvage therapy in patients with a positive prostate biopsy and low suspicion of distant metastases, along with observation or radical prostatectomy with lymph node dissection. ⁴⁰

American Urological Association (AUA): The AUA 2007 guidelines (reaffirmed 2011) for the management of prostate cancer state that there are minimal data available on the following interventions: HIFU, cryotherapy, high-dose-rate interstitial prostate brachytherapy, and primary hormonal therapy. Conclusions regarding outcomes of these treatments cannot be made. The panel did not include these treatment options in the analysis and recommendations due to a combination of factors, including limited published experience and short-term follow-up, as well as the similar issues that affected evaluations of other treatment options. The 2017 AUA/ASTRO/SUO Guidelines states for low, intermediate and high risk prostate cancer patients who are considering focal therapy or high intensity focused ultrasound (HIFU) that these interventions are not standard care options because comparative outcome evidence is lacking. ³⁸

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
55899	Unlisted procedure, male genital system

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

ICD-10	Description: [For dates of service on or after 10/01/2015]
C61	Malignant neoplasm of prostate
D07.5	Carcinoma in situ of prostate
D40.0	Neoplasm of uncertain behavior of prostate

RESOURCE REFERENCES**Government Agency**

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REVIEW/REVISION HISTORY

5/17/17: *New Policy*

7/10/18 & 6/19/19: *Policy reviewed, no changes to criteria, updated professional society guidelines and references.*

6/17/20: *Policy reviewed, no changes.*

4/5/21: *Policy reviewed, no changes. Updated references.*