High Intensity Focused Ultrasound (HIFU)

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DESCRIPTION

This medical policy is addressing high intensity focused ultrasound (HIFU). For magnetic resonance (MR) guided focused ultrasound (MRgFUS), see medical policy 04.01.09 MRI Guided High-Intensity Focused Ultrasound (MRgFUS) Ablation.

High intensity focused ultrasound (HIFU) is a minimally invasive technique that is currently under clinical study for treatment of cancers and other conditions, including but not limited to prostate cancer, renal cancer, pancreatic cancer, breast cancer, central nervous system cancers (gliomas), soft tissue sarcomas, hepatocellular carcinoma, thyroid nodules, benign prostatic hypertrophy (BPH), breast fibroadenoma and vulvar dystrophy (non-neoplastic epithelial disorders of the vulva). Currently, the primary area of study is for use of HIFU in the treatment of prostate cancer.

High intensity focused ultrasound (HIFU) focuses high-energy ultrasound waves on a single location, which increases the local tissue temperature to over 80 degrees Celsius. This causes a discrete locus of coagulative necrosis of approximately 3x3x10 mm. This

causes a discrete locus of coagulative necrosis of approximately 3 x 3 x 10 mm. The surgeon uses a transrectal probe to plan, perform, and monitor treatment in a real-time sequence to ablate the entire gland or small discrete lesions. HIFU can be repeated if necessary. This procedure is typically carried out in an outpatient setting and is performed under a spinal or general anesthesia. A proposed benefit to this method is less adjacent tissue damage.

Breast Cancer/Breast Fibroadenoma

Breast fibroadenoma (FA) is a benign tumor, most often detected during self-examination or clinical breast examination. Usually occurring in women under the age of 30, they are seen in approximately 10% of all women during their lifetime. FA account for between 30% and 75% of all breast biopsies, depending on the age of the population being sampled. Because of the superficial location, breast FA is suitable for minimally invasive ablation techniques. These techniques can be divided into heat-based modalities which include high-intensity focused ultrasound (HIFU), radiofrequency ablation, laser ablation and cryoablation.

(2018) Hahn et al reported a successful reduction in FA volume after 12 months was achieved in 24/27 patients (89%). At baseline 16 patients (59%) had pain, which was resolved in 63% (10/16). All patients were satisfied with the cosmetic related outcome. Twenty-four patients (89%) would repeat the procedure. After 12 months 21 patients with sonographically indistinct residuals underwent a CNB. There were no vital cells in 86%. Three cases showed vital cells of FA. Retrospectively possible reasons in these three cases were an insufficient treatment due to bad visibility and insufficient fixation of the FA during HIFU and/or a too short follow-up time. limitations of the study is that pain levels are generally difficult to distinguish due to individual variability in pain perception which is often mingled with discomfort. Additional limitation include the location of the treated FA was not clip marked, which could result in a false negative histology due to inaccurate localization. To avoid a false biopsy, ultrasound documentation of all visits specifying the precise lump location was compared. Another limitation is that a core needle biopsy might provide a histologically false negative result as it does not excise the complete lesion, but just takes a representative biopsy of three specimens. Another drawback could be that a duration of 12 months is possibly too short for analyzing the complete thermoablative effect in some patients. In conclusion, US-guided HIFU is an effective procedure and a minimally invasive alternative for the treatment of breast FA.

(2015) Peek et al reported on a systematic review of high intensity focused ultrasound (HIFU) ablation in the treatment of breast cancer. Studies were eligible if they were performed on patients with breast cancer and objectively recorded at least one clinical outcome measure of response (imaging, histopathological or cosmetic) to HIFU treatment. Nine studies fulfilled the inclusion criteria. The absence of tumor or residual tumor after treatment was reported for 95.8% of patients (160 of 167). No residual tumor was found in 46.2% (55 of 119; range 17-100%), less than 10% residual tumor in 29.4% (35 of 119; range 0-53%), and between 10 and 90% residual tumor in 22.7% (27 of 119; range 0-60%). The most common complication associated with HIFU ablation was pain

(40.1%) and less frequently edema (16.8%), skin burn (4.2%) and pectoralis major injury (3.6%). MRI showed an absence of contrast enhancement after treatment in 82% of patients (31 of 38; range 50-100%), indicative of coagulative necrosis. Correlation of contrast enhancement on pretreatment and post-treatment MRI successfully predicted the presence of residual disease. The authors concluded, HIFU treatment can induce coagulative necrosis in breast cancers. Complete ablation has not been reported consistently on histopathology and no image modality has been able to confidently predict the percentage of complete ablation. Consistent tumor and margin necrosis with reliable follow-up imaging are required before HIFU ablation can be evaluated within large, prospective clinical trials.

(2017) Twenty patients with 26 FA were selected for US-guided HIFU. The therapy was performed in one or two sessions. FA volume was assessed before and followed up to 24 months after the last HIFU. After each treatment, adverse events were evaluated. In 19/26 FA (73.1%) one HIFU was performed (group 1), whereas 7/26 FA (26.9%) received second HIFU (group 2) 6-9 months (median, 7 months) after the first session. In group 1 and 2, FA volume decreased significantly at 1-month ($p < 0.001$) and 3-month follow-up ($p = 0.005$), respectively, and continued to reduce until 24-month follow-up ($p < 0.001$ and $p = 0.003$, respectively). At 24 months, mean volume reduction was 77.32% in group 1 and 90.47% in group 2 ($p = 0.025$). Mild subcutaneous edema was observed in 4 patients and skin erythema in 3 patients. US-guided HIFU represents a promising non-invasive method with sustainable FA volume reduction and patient's tolerability. Although one treatment is highly efficient, the volume reduction can be increased with second treatment.

Summary of Evidence: Breast Cancer/Breast Fibroadenoma
Based on the review of the peer reviewed medical literature the evidence is insufficient to make any determinations regarding safety and effectiveness for the use of HIFU for breast cancer treatment and further studies with longer follow up are needed to establish the optimal treatment protocol and to assess the long-term efficacy of HIFU for this indication. Further prospective randomized studies to include larger patient populations and longer follow-up are needed. The evidence is insufficient to determine the effects on net health outcomes

Central Nervous System Cancers
(2018) Alkins et al noted that ultrasound (US) in clinical medicine is most commonly associated with imaging but can be harnessed to yield an array of biological effects, including thermal ablation of brain tumors. Therapeutic US has been studied for many years, but only within the past 10 years has the technology reached a point where it is safe and practical for clinical adoption. Using large, multi-element arrays, US can be focused through the skull, and combined with MRI for image guidance and real-time thermometry, to create lesions in the brain with millimeter accuracy. Using this technology, true non-invasive surgery can be accomplished with immediate tumor killing. Combining the ablative capabilities of focused US with its other unique effects, such as

blood-brain barrier (BBB) disruption and radio-sensitization, may eventually result in change of the current glioma treatment paradigm.

Summary of Evidence: Central Nervous System Cancers
Based on the review of the peer reviewed medical literature there have been isolated case series studies, minimal randomized controlled studies, meta-analysis, and systematic reviews published utilizing high intensity focused ultrasound (HIFU) to treat indications such as central nerve system cancers (gliomas). The safety and effectiveness of the use of high intensity focused ultrasound (HIFU) for the treatment of central nervous system cancers i.e., gliomas has not been established. Further studies are needed.

Hepatocellular Carcinoma (HCC)
Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. The only potentially curative treatments are surgical resection and liver transplantation. Most patients with primary or metastatic liver cancers are not suitable candidates for surgical resection at the time of diagnosis. In addition, chemotherapy and radiotherapy rarely produce a complete or sustained response in patients with advanced disease. High intensity focused ultrasound (HIFU) is under investigation for the ablation of unresectable HCC.

(2021) Sehmbi et al noted that HIFU is an emerging non-invasive, targeted treatment of malignancy. In a systematic review, these investigators examined the safety, efficacy, and optimal technical parameters of HIFU in the treatment of malignant lesions of the hepatobiliary system. They carried out a systematic search of the English literature until March 2020, examining PubMed, Embase and Cochrane Library databases. The following keywords were input in various combinations: 'HIFU', 'High intensity focused ultrasound', 'Hepatobiliary', 'Liver', 'Cancer' and 'Carcinoma'. Extracted content included: Application type, exposure parameters, patient demographics, as well as treatment outcomes. A total of 24 articles reported on the clinical use of HIFU in 940 individuals to treat malignant liver lesions; 21 studies detailed the use of HIFU to treat HCC only. Mean tumor size was 5.1 cm. Across all studies, HIFU resulted in complete tumor ablation in 55 % of patients. Data on technical parameters and the procedural structure were very heterogeneous; 10 studies (n = 537 (57 %) patients) described the use of HIFU alongside other modalities including TACE, RFA and PEI; 66 % of which resulted in complete tumor ablation. Most common complications were skin burns (15 %), local pain (5 %) and fever (2 %). The authors concluded that HIFU has shown benefit as a treatment modality for malignant lesions of the hepatobiliary system. Combining HIFU with other ablative therapies, especially TACE, increased the efficacy without increasing complications. These researchers stated that future human clinical studies are needed to determine the optimal treatment parameters, better define outcomes and examine the risks and benefits of combination therapies.

Summary of Evidence: Hepatocellular Carcinoma (HCC)
Based on review of the peer reviewed medical literature HIFU for the treatment of hepatocellular carcinoma (HCC) the literature includes nonrandomized controlled trials,

retrospective cohort study and case series studies with small patient populations. The overall quality of evidence is low due to the lack of randomized controlled trials, and of studies comparing HIFU to other standard treatment modalities. Other limitations include differences between studies in patient characteristics (e.g., tumor size and disease severity), measure of tumor response and length of follow-up also impacted the quality of available evidence. Additional well-designed studies with larger patient populations to include comparative studies are needed to support the safety and effectiveness of high intensity focused ultrasound (HIFU) for the treatment of unresectable hepatocellular carcinoma (HCC). The evidence is insufficient to determine the effects on net health outcomes.

Pancreatic Cancer

(2017) Dababou et al completed a meta-analysis of palliative treatment of pancreatic cancer with high intensity focused ultrasound (HIFU). The meta-analysis includes a total number of 23 studies with 865 patients, 729 with pancreatic cancer. The population enrolled ranges from 3 patients in the smallest series, up to 61 in the largest study. T2 (variance among studies) was 0.195, and I2 (percentage of variation among studies) was 40% (95% CI: 1–64%); the Q test p-value was 0.026, indicating significant heterogeneity among studies. Among 639 patients treated with HIFU, 567 complained of pancreatic pain before the treatment and 459 patients experienced partial or complete pain relief after treatment. The random effects estimate of the proportion of patients with pain reduction was 0.81 (95% CI: 0.76–86). The authors concluded, HIFU appears to be an effective tool for pain palliation in advanced pancreatic cancer. Studies assessing treatment in patients with pancreatic adenocarcinoma are limited by factors such as small sample sizes and heterogeneity in clinical definitions and assessments. Prospective randomized and standardized studies are necessary to confirm the effectiveness of HIFU in relieving pain, and to evaluate for any potential impact on tumor control and patient survival.

Summary of Evidence: Pancreatic Cancer

Based on the review of the peer reviewed medical literature the evidence is insufficient to make any determinations regarding safety and effectiveness for the use of HIFU effective tool for pain palliation in advanced pancreatic cancer. Further prospective randomized studies to include larger patient populations and longer follow-up are needed. The evidence is insufficient to determine the effects on net health outcomes.

Prostate Cancer

Clinical Context and Therapy Purpose

The purpose of focal therapy using high intensity focused ultrasound (HIFU) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Patients
The relevant population of interest are men with primary localized prostate cancer.

Interventions
The therapy being considered is focal therapy using high intensity focused ultrasound (HIFU)

Comparators
The following therapies and practices are currently being used to make decisions about management men with localized prostate cancer, surgery (radical prostatectomy), external beam radiation, and active surveillance.

Outcomes
The general outcomes of interest are overall survival (OS), tumor progression and recurrence, incontinence, and sexual dysfunction.

Methods to manage localized prostate cancer include watchful waiting and active surveillance. Treatment options for localized prostate cancer include radical prostatectomy, radiotherapy (EBRT or brachytherapy) and whole gland cryotherapy. High intensity focused ultrasound (HIFU) has been proposed as a method for treating localized prostate cancer. For treatment of the prostate the physician uses a transrectal probe to plan, perform and monitor treatment in real time sequence to ablate the entire gland or small discrete lesions. A cooling balloon surrounding the probe protects the rectal mucosa from the high temperature. Reported post procedure complications include incontinence, bladder neck/urethral stricture and rectourethral fistulae.

(2021) Bates et al undertook a PRISMA-adhering systematic review that evaluated the evidence base (from January 2000 to June 2020) for focal therapy as a treatment strategy for men with histologically proven, clinically localized prostate cancer as compared to standard management options. Focal therapy interventions included high-intensity focused ultrasound (HIFU), vascular targeted photodynamic therapy, laser ablation, thermal ablation, focal brachytherapy, radiofrequency waves, microwave ablation, focal external-beam radiotherapy, and irreversible electroporation. The comparator intervention included any standard management option such as radical prostatectomy, external beam radiotherapy, whole gland brachytherapy, and active surveillance/monitoring. Overall, 5 articles reporting on 4 primary comparative studies (1 RCT and 3 retrospective nonrandomized comparative studies; N=3961) and 10 eligible systematic reviews were identified. The RCT compared a vascular targeted photodynamic therapy (padeliporfin) versus active surveillance among patients with low-risk prostate cancer and concluded that patients who underwent photodynamic therapy had less progression (28% vs. 58%; adjusted hazard ratio [HR] 0.34; 95% confidence interval [CI], 0.24 to 0.46; p<.0001) and needed less radical therapy (6% vs. 29%; p<.0001) at 24 months. Despite these "positive" results, an FDA staff analysis cited issues with the trial design, endpoints, missing data, and adverse events of padeliporfin therapy, resulting in the decline to recommend for approval by the FDA advisory

committee. One retrospective study comparing focal HIFU with robotic radical prostatectomy found no significant difference in treatment failure at 3 years, with better continence and erectile function recovery with HIFU. The other 2 retrospective cohort studies compared focal laser ablation with radical prostatectomy and external beam radiotherapy and reported significantly worse oncologic outcomes with the focal treatment. Regarding the included systematic reviews, virtually all concluded that there was insufficient high certainty evidence to make definitive conclusions regarding the clinical effectiveness of focal therapy. The authors concluded that the "certainty of the evidence regarding the comparative effectiveness of focal therapy as a primary treatment for localized prostate cancer was low, with significant uncertainties" and that "until higher certainty evidence emerges...focal therapy should ideally be performed within clinical trials or well-designed prospective cohort studies."

(2021) Dosanjh et al stated that HIFU is a novel therapy for PCa. Owing to a lack of long-term data, HIFU is recommended for use only in the context of research. These researchers examined the trend for HIFU use nationally and rates of strictures and fistulae. Patients undergoing HIFU for PCa between April 2007 and March 2018 were studied in an English national database (Hospital Episode Statistics). Data on complications were included for patients with a minimum of 1-year follow-up. Analysis of complications was controlled for other interventions. Descriptive analyses of HIFU rates and the incidence of strictures and fistulae were carried out. Cox and logistic regression models were built for urethral stricture incidence. A total of 2,320 HIFU treatments among 1,990 patients were identified. The median age was 67 years (IQR 61 to 72). Some 1,742 patients met the criteria for follow-up analysis. The highest-volume center performed 1,513 HIFU procedures, followed by 194 at the second highest. The number of HIFU procedures increased annually, rising from 196 to 283 per year. There were 208 patients (11.9 %) who went on to have radiotherapy and 102 (5.9%) radical prostatectomy after HIFU. Following HIFU, stricture developed in 133/1,290 patients (10.3 %) and urinary fistula in 16/1,240 (1.3 %) before any further intervention. More recent years for HIFU were associated with a lower likelihood of stricture formation (2016/2017 versus 2007/2008: hazard ratio [HR] 0.30, 95 % CI: 0.11 to 0.79; p = 0.015). Limitations included the lack of staging information and unknown rates of HIFU outside of publicly funded health care. The authors concluded that HIFU was performed at a large number of low-volume centers and the results suggest that the rate of urethral structural complications may not be lower than that for established prostate cancer treatments.

(2020) Enikeev et al conducted a prospective non-randomized study that evaluated the outcomes of whole gland ablation (high-intensity focused ultrasound [HIFU], cryotherapy and brachytherapy) and active surveillance (AS) in patients with low-risk prostate cancer (PCa). Eligible patients had low-risk prostate cancer according to the D'Amico classification (Gleason score 3 + 3 = 6; PSA < 10 ng/ml; T1-T2a), two or less positive cores in one lobe and a prostate volume of ≤ 50 cc. The patients (n=155) were placed into four groups: HIFU (n=45), cryoablation (n=45), brachytherapy (n=35) or active surveillance (n=30). The primary outcome measured was cancer progression. The

secondary outcome measured was the impact of each treatment on the quality of life. The patients underwent prostate-specific antigen (PSA) tests every three months after surgery or start of AS. Prostate multiparametric-magnetic resonance imaging (MpMRI) was repeated at 12 and 24 months. All patients, regardless of disease progression, underwent repeat prostate biopsy at 12 and 24 months. Functional parameters (IPSS, IIEF-5) and PSA levels were evaluated at three, six, 12, 18 and 24 months after surgery or start of AS. The urinary incontinence rate was assessed with the pad-test. At 12 and 24 months, all patients were assessed by the Hospital Anxiety and Depression Scale (HADS). There was not a statistically significant differences in survival rates between the groups. Biochemical relapse-free survival rates at 24 months were not statistically significant between groups: 81.8% for HIFU, 85% for cryoablation, 93.9% for brachytherapy and 93.3% for AS. Increased anxiety was found in 6.7% of patients after treatment and in 36.7% of patients undergoing AS. There were no statistical differences between the techniques. Author noted limitations included the non-randomized design, short term follow-up and small patient population

(2020) He et al performed a systematic review and meta-analysis on oncological and functional outcomes of high intensity focused ultrasound (HIFU) as the primary treatment for localized prostate cancer (PCa). Twenty-seven articles were included for analysis with a total of 7393 patients. Eighteen studies investigated the whole-gland HIFU, and the duration of follow-up ranged from 2 to 168 months. After whole-gland HIFU, the mean prostate-specific antigen (PSA) nadir was found to be 0.4 to 1.95 ng/mL and the mean time to PSA nadir was 2.4 to 5.4 months. The rate of positive biopsy after HIFU was 4.5% to 91.1%. Meta-analysis revealed the incidences of urinary incontinence, impotence, urinary obstruction, retention, and infection was 10%, 44%, 15%, 11%, 7%, respectively. Nine studies investigated partial-gland HIFU, and the duration of follow-up was 1 to 131 months. After partial-gland HIFU, the mean PSA nadir was 1.9 to 2.7 ng/mL and the mean time to PSA nadir 5.7 to 7.3 months. The rate of positive biopsy after HIFU in the treatment area was 14% to 37.5%. Meta-analysis revealed the incidences of urinary incontinence, impotence, urinary obstruction, retention, and infection was 2%, 21%, 2%, 9%, 11%, respectively. The authors concluded HIFU can be considered to be superior to prostatectomy in terms of urinary and sexual outcomes. The partial-gland HIFU was safer than whole-gland HIFU, and they had similar oncological outcomes. To date, there have been no prospective randomized controlled trials (RCTs) comparing the outcomes of radical prostatectomy, radiation therapy, and HIFU. Furthermore, among the studies on partial-gland HIFU ablation, few have compared partial-gland treatment to whole-gland ablation. Those that do include such comparison are difficult to interpret given the absence of randomization. Therefore, more RCTs are needed investigating the benefits of HIFU for the treatment of PCa.

Ingrosso et al (2020) noted that different non-surgical therapeutic strategies can be adopted for intra-prostatic relapse of PCa after primary RT, including re-irradiation (with brachytherapy [BT] or EBRT), HIFU, and cryotherapy. The main issues to consider when choosing non-surgical salvage local therapies are local tumor control and significant genito-urinary toxicity. These researchers conducted a systematic review and

meta-analysis on the role of non-surgical salvage modalities in patients with radio recurrent PCa and associated clinical outcomes and toxicity profiles. They performed a critical review of the Medline, Scopus, and ClinicalKey databases from January 1, 2000 through February 1, 2018 according to the Preferred Reporting Items and Meta-Analyses (PRIMA) statement. To assess the overall quality of the literature reviewed, these investigators used a modified Delphi tool for case-series studies. A total of 64 case-series studies were included, corresponding to a cohort of 5,585 patients. The modified Delphi checklist evidenced high methodological quality overall (mean quality score of 80.6 %). Biochemical control rates were lowest for patients treated with HIFU (58 %, 95 % CI: 47 % to 68 %) and highest for patients treated with BT (69 %, 95 % CI: 62 % to 76 %) and EBRT (69 %, 95 % CI: 53 % to 83 %). The lowest prevalence of incontinence was for patients treated with BT (3 %, 95 % CI: 0 % to -6 %; I2 = 63.4 %) and the highest was among patients treated with HIFU (28 %, 95 % CI: 19 % to 38 %; I2 = 89.7 %). The authors concluded that non-surgical therapeutic options, especially BT, showed good outcomes in terms of biochemical control and tolerability in the local recurrence setting. The current analysis demonstrated that nonsurgical salvage local therapies offer a chance of a curative local approach in radiorecurrent prostate cancer. However, high-quality data from prospective trials are needed to validate long-term outcomes from nonsurgical strategies for the treatment of intraprostatic recurrence after previous radiotherapy.

(2020) Mantica et al conducted a systematic review of minimally invasive strategies for the treatment of prostate cancer recurrence after radiation therapy. Overall, 545 studies were identified. After duplicate exclusion, initial screening, and eligibility evaluation, a total of 80 studies were included in the qualitative analysis, corresponding to a cohort of 6681 patients. The median age at initial diagnosis ranged from 59 to 75.5. Pre-treatment PSA ranged from 6.2 to 27.4 ng/mL. All patients underwent primary radiotherapy for localized prostate cancer. Cryotherapy, Brachytherapy, EBRT, HIFU were the minimally invasive options mostly used as salvage therapy. They showed to be promising approaches for recurrent prostate cancer (PCa) control, with acceptable toxicities. The authors concluded minimally invasive therapeutic options offer promising results in terms of biochemical control in the local recurrence setting. Unfortunately, the absence of high quality and comparative studies makes it difficult to establish which method is the best in terms of oncological and safety outcomes.

(2020) Nahar et al prospectively reported on the short-term outcomes of focal HIFU as a primary treatment of localized prostate cancer in 52 patients at a single center, with a minimum follow-up of 12 months. Of the 30 patients who underwent biopsy post-ablation, 25 (83.3%) had negative and 5 (16.7%) had positive in-field results. Four (13.3%) patients had a de novo positive out-of-field biopsy and negative in-field biopsy. Prostate-specific antigen was significantly reduced ($p<.001$) below 2 ng/dL at the 3-, 6-, 9-, and 12-month follow-up in 35 (76.1%), 27 (73%), 21 (72.4%), and 13 (56.5%) patients, respectively. Only 5 major complications were noted in 4 patients; all 4 required transurethral resection of necrotic tissue blocking the bladder outlet after HIFU and 1 had concurrent epididymoorchitis complicated with scrotal abscess requiring incision and drainage. Additionally, urinary symptoms returned to near baseline within 3 to 6 months

and sexual function returned to baseline at 12 months. The author's conclusion noted focal high intensity focused ultrasound is a safe and effective treatment for patients with localized clinically significant prostate cancer with acceptable short-term oncologic and functional outcomes. The complications are minimal and patient selection is essential. Short-term oncologic outcomes are promising but longer follow-up is required to establish long-term oncologic outcomes.

(2020) Schmid et al examined focal therapy using HIFU for the treatment of localized PCa in a prospective, cohort, multi-center study; they analyzed the safety and complications of this procedure. This trial included patients who suffered from low-to-intermediate risk localized PCa with no prior treatment. After tumor identification on multi-parametric MRI and in prostate biopsy, the lesions were treated with HIFU observing a safety margin of 8 to 10 mm; AEs after 30 and 90 days, as well as the required interventions were assessed and stratified for treatment localizations. Of the 98 men included in the study in 2 European centers, 35 (35.7 %) experienced AEs in the first 30 days after HIFU intervention with Clavien-Dindo grade of less than or equal to II: 15 pts (15.3 %) had a post-operative urinary tract infection and 26 patients (26.5 %) a urinary retention; 4 patients (4.1 %) underwent subsequent intervention (Clavien-Dindo grade IIIa/b). The number of late post-operative complications occurring between 30 and 90 days after intervention was low (2.0 %). The highest complication rate was associated with tumors located at the anterior base (50.0 %). The inclusion of the urethra in the ablation zone led to AEs in 20 out of 41 cases (48.8 %) and represented a significant risk factor for complications within 30 days (OR = 2.53; 95 % CI: 1.08 to 5.96; p = 0.033). The authors concluded that focal therapy of PCa lesions with a robotic HIFU-probe was safe and rendered an acceptable rate of minor early AEs. The inclusion of the urethra in the ablation zone led to an increase in early complications and should be avoided whenever possible.

(2019) The Emergency Care Research Institute (ECRI) updated their 2004 statement about high-intensity focused ultrasound for treating localized prostate cancer in 2019 stating, case series and nonrandomized comparative studies show HIFU is relatively safe and ablates prostate cancer tissue in patients with low-risk localized disease; however, few comparative studies are available and are very low quality, providing insufficient evidence to determine HIFU's effectiveness compared with that of RP, EBRT, or BT. Large, prospective, randomized controlled trials are needed to address evidence gaps. Additionally, they acknowledged the following guidelines:

- A 2017 European Urology Association guideline and a 2018 guideline endorsed by four American medical societies consider available evidence insufficient to recommend HIFU for localized prostate cancer treatment.
- A 2019 National Comprehensive Cancer Network guideline cites HIFU as an option after RT recurrence in the absence of metastatic disease.

(2018) Guillaumier et al reported on 5-year prostate cancer control following focal high intensity focused ultrasound (HIFU) therapy to treat individual areas of cancer within the prostate. This was a prospective study of 625 consecutive patients with nonmetastatic

clinically significant PCa undergoing focal HIFU therapy (Sonablate) in secondary care centers between January 1, 2006, and December 31, 2015. A minimum of 6-mo follow-up was available for 599 patients. Intermediate- or high-risk PCa was found in 505 patients (84%). Disease was localized using multiparametric magnetic resonance imaging (mpMRI) combined with targeted and systematic biopsies, or transperineal mapping biopsies. Areas of significant disease were treated. Follow-up included prostate-specific antigen (PSA) measurement, mpMRI, and biopsies. The primary endpoint, failure-free survival (FFS), was defined as freedom from radical or systemic therapy, metastases, and cancer-specific mortality. The median follow-up was 56 mo (interquartile range [IQR] 35-70). The median age was 65 yr (IQR 61-71) and median preoperative PSA was 7.2 ng/ml (IQR 5.2-10.0). FFS was 99% (95% confidence interval [CI] 98-100%) at 1 yr, 92% (95% CI 90-95%) at 3 yr, and 88% (95% 85-91%) at 5 yr. For the whole patient cohort, metastasis-free, cancer-specific, and overall survival at 5 yr was 98% (95% CI 97-99%), 100%, and 99% (95% CI 97-100%), respectively. Among patients who returned validated questionnaires, 241/247 (98%) achieved complete pad-free urinary continence and none required more than 1 pad/d. Limitations include the lack of long-term follow-up. The authors concluded, focal therapy for select patients with clinically significant nonmetastatic prostate cancer is effective in the medium term and has low probability of side effect.

(2017) Albisinni et al although still experimental, focal treatment is being increasingly implemented in the management of prostate cancer (PCa). Aim of this study was to compare functional and oncologic outcomes of high intensity focused ultrasound (HIFU) hemiablation of the prostate to robot assisted laparoscopic prostatectomy (RALP) in the management of unilateral PCa. Fifty-five men with unilateral, clinically localized PCa underwent HIFU hemiablation of the affected prostatic lobe between 2007 and 2015. All patients were found to have unilateral disease on the basis on full concordance between multiparametric magnetic resonance imaging (MRI) and MRI-guided biopsies. These patients were matched 1:1 with patients who underwent RALP for PCa in which pT2a-b disease (unilateral) was found on final pathologic analysis. Matching criteria were Gleason score, prostate specific antigen (PSA), and cT stage. Treatment failure was defined as the need for salvage external beam radiotherapy or systemic androgen deprivation therapy (ADT) due to disease progression. Kaplan-Meier curves and log-rank tests were constructed to assess differences in salvage treatment free survival across surgical techniques. Matching was effective with no significant differences across the two groups, although men treated with HIFU were older ($p < 0.001$). Median follow-up was 36 months (interquartile range 16-56). HIFU was associated to better and faster recovery of continence, with most men (82%) showing no signs of urinary incontinence even right after surgery. Moreover, the risk of de novo erectile dysfunction was significantly lower after HIFU. No significant difference was found in the need for salvage external beam radiation therapy or ADT across the two surgical approaches: 7/55 men underwent salvage therapy in the HIFU vs 6/55 in the RALP group ($p = 0.76$). Nonetheless, seven more patients in the HIFU arm required a complementary treatment on the contralateral lobe during follow-up, after developing a contralateral PCa. No patient died of PCa on follow-up, while six men died of other causes (five HIFU vs one RALP, $p = 0.11$). The

authors concluded the following, in this matched pair analysis, HIFU hemiablation was comparable to RALP in controlling localized unilateral PCa, with no significant differences in the need for salvage therapies. HIFU was also associated to significantly better functional outcomes. Accurate patient selection remains vital, and larger prospective trials are needed to confirm our findings.

(2016) The Agency for Healthcare Research and Quality (AHRQ) issued a clinician research summary regarding therapies of clinically localized prostate cancer which concluded the evidence is insufficient to permit conclusions about the comparative effectiveness or adverse effects of all other treatments including brachytherapy, cryotherapy, intensity modulated radiation therapy, proton beam radiation therapy, stereotactic body radiation therapy and high intensity focused ultrasound compared in this review. This summary concluded that evidence from two large studies (the SPCG-4 study and PIVOT) showed that metastases can be reduced with radical prostatectomy versus watchful waiting. Evidence related to the comparative effectiveness of radical prostatectomy and watchful waiting for mortality outcomes was rated as insufficient, largely because of the lack of replication in the two large trials. Evidence for other therapies for clinically localized prostate cancer assessed in this updated systemic review is too limited to determine their comparative effectiveness and adverse effects. Evidence is insufficient to determine which subgroups of patients might benefit most from these therapies based on patient disease characteristics. Clear guidance regarding the appropriate patient population for radical prostatectomy, radiation therapy, hormonal therapy, watchful waiting, active surveillance, or one of the other options is difficult to establish. Physicians might take into consideration age, general health status, stage of tumor, PSA level. Gleason score, logistical factors (timing of surgery versus radiation therapy), use of androgen deprivation therapy (ADT) as a component of the treatment strategy, patient preferences, nuances in patient recovery and quality of life, and other factors in identifying the most appropriate treatment options. Guidelines from NCCN and the American Urological Association may be informative in this regard.

Summary of Evidence: Prostate Cancer
Based on review of the peer reviewed medical literature for high intensity focused ultrasound (HIFU) and the treatment of localized prostate cancer the literature consists for non-randomized studies, systemic reviews and case series. HIFU may provide quality of life (QOL) advantages for patients in comparison to surgery and radiotherapy, however, there is a lack of consensus on objective response criteria, very limited long-term oncologic data, and no comparative effectiveness data versus traditional treatments available for localized prostate cancer. The long-term efficacy, safety, and long-term health outcomes of HIFU for the treatment of localized prostate cancer has not been established in controlled clinical trials. Well-designed prospective comparative studies are needed to evaluate risk/benefit of HIFU for the treatment of localized prostate cancer. The American Urological Association (AUA), American Society of Radiation Oncology (ASTRO) and Society of Urologic Oncology (SUO) on clinically localized prostate cancer which states “the Panel recommends if HIFU is offered as an alternative treatment modality for localized prostate cancer, it should be done within the context of a clinical

trial and clinicians should inform patients considering focal therapy or HIFU that these treatment options lack robust evidence of efficacy". The evidence is insufficient to determine the effects on net health outcomes.

Renal Cancer
Renal cell carcinoma (RCC), also referred to as kidney cancer is a disease in which cancer cells are found in the lining of the tubules in the kidney. Symptoms of renal cell carcinoma may include blood in the urine, loss of appetite, pain in the side that doesn't subside, weight loss and anemia. Standard treatment available for patients with RCC includes surgery, chemotherapy, external or internal radiation therapy, and immunotherapy. Surgical excision in the form of a simple or radical nephrectomy is the accepted, often curative, treatment for stages I, II and III of RCC. HIFU has been proposed as an intervention for small renal masses as well as advanced stage renal malignancy.

Summary of Evidence: Renal Cancer
Based on the review of the peer reviewed medical literature there are a small number of studies, primarily case series with small patient populations and insufficient data to draw conclusions. The safety and effectiveness of the use of high intensity focused ultrasound (HIFU) for the treatment of renal cancer has not been established. The evidence is insufficient to determine the effects on net health outcomes

Soft Tissue Sarcomas
Based on the review of the peer reviewed medical literature well designed studies comparing high intensity focused ultrasound (HIFU) to cryotherapy, radiofrequency ablation, and/or external beam radiotherapy are needed to ascertain the effectiveness of HIFU for the treatment of bone metastases. HIFU may provide another treatment option for patients with primary bone tumors who are not surgical candidates or who refuse surgery, but this data needs to be confirmed as well. The evidence is insufficient to determine the effects on net health outcomes.

Thyroid Nodules
Nodular thyroid tissue is common, however most thyroid nodules are benign. Causes of benign thyroid nodules include goiter and Hashimoto's thyroiditis. The incidence of malignancy, or thyroid cancer, depends on factors such as age, gender, radiation exposure and family history. Treatment of thyroid cancer depends on the type of cancer but may include one or more of the following treatments: radioiodine, thyroid hormone suppression and surgical removal of the thyroid gland. Minimally invasive treatments, such as percutaneous ethanol injection sclerotherapy, laser photocoagulation, and high intensity focused ultrasound (HIFU) ablation have been proposed as an alternative to surgery.

(2017) Lang and Wu comprehensively searched all studies that evaluated the use of HIFU ablation as a treatment of benign thyroid nodules from Medline (PubMed) and Cochrane Library electronic databases using specific keywords. All titles identified by

the search strategy were independently screened by two authors. Case reports, animal studies, editorials, expert opinions, reviews without original data and studies on pediatric population were excluded. Multiple reports of the same dataset were assessed, and the most representative and updated report of a study was included. Five original studies were found. All treated thyroid nodules were confirmed to be benign cytologically and either appeared solid or predominantly (>70%) solid on ultrasonography. Only one type of commercially available US-guided device with an extracorporeal probe (3 MHz) was used in all the reported treatments. No major complications including recurrent laryngeal nerve injury, skin burn, or hematoma were reported in all of the studies. The overall nodule volume reduction after single session of HIFU ablation ranged between 45 and 68%, depending on nodule size and length of follow-up. Despite the few number of studies, our review appeared to suggest that HIFU is a safe and efficacious method of treating symptomatic benign thyroid nodules. However, larger-scale, prospective trials with longer follow-up period are indeed required to confirm this. In terms of the ablation itself, relative to other ablation techniques, there are still much room for improvements in shortening treatment duration and expanding the range of treatable nodules.

Summary of Evidence: Thyroid Nodules
Based on the review of the peer reviewed medical literature there are limited studies, primarily case series with small patient populations. These studies suggest that high intensity focused ultrasound (HIFU) may be promising non-invasive tool for nodular thyroid disease, but the available evidence is insufficient data to draw conclusions regarding HIFU for this indication. The evidence is insufficient to determine the effects on net health outcomes.

Vulvar Dystrophy (Non-Neoplastic Epithelial Disorders of the Vulva)
Lichen sclerosus, lichen planus, and lichen simplex chronicus are three of the most common non-neoplastic epithelial disorders of the vulva. Lichen sclerosus is characterized by intense vulvar itching and can affect women of all ages, but it manifests most commonly in postmenopausal women. Patients with lichen sclerosus have an increased risk of developing squamous cell carcinoma, and they should be monitored for malignancy. Lichen planus is an inflammatory autoimmune disorder that can affect the vulva and the vagina; it peaks in incidence between ages 30 and 60. There are three clinical variants of lichen planus affecting the vulva: erosive, papulosquamous, and hypertrophic. Lichen simplex chronicus is caused by persistent itching and scratching of the vulvar skin, which results in a thickened, leathery appearance. It is thought to be an atopic disorder in many cases and may arise in normal skin as a result of psychological stress or environmental factors. Definitive diagnosis of non-neoplastic disorders depends on the histology of biopsied tissue. All three disorders are treated with topical corticosteroid ointments of varying potency. Lichen sclerosus and lichen planus are not routinely treated with surgery, which is necessary only in patients who have a malignancy or advanced scarring that causes dyspareunia or clitoral phimosis. High intensity focused ultrasound (HIFU) recently has been studied as a treatment modality for non-neoplastic epithelial disorders of the vulva (NNEDV) (vulvar dystrophy).

(2016) Zhou et al reported on the efficacy of high intensity focused ultrasound (HIFU) for the treatment of non-neoplastic epithelial disorders of the vulva (NNEDV). This was a multi-center, randomized controlled trial in women with NNEDV based on histologic alterations. Enrolled patients were clinically diagnosed with NNEDV. They were randomized into 2 treatment groups: 1) halcinonide for 3 months or 2) HIFU once. A total of 123 patients were biopsied both prior to and after the therapy, and 62 and 61 patients were assigned to the HIFU and halcinonide groups, respectively. The histological changes were then analyzed. After the treatments, the therapeutic effects were observed in both groups. Comparing the diagnosis and alterations in lichenoid and sclerotic patterns and in chronic inflammation, we found statistically significant differences. Furthermore, when compared with the halcinonide group, the HIFU group exhibited enhanced curative effects that were statistically significant ($P = 0.039$). The authors concluded, based on the histological evidence from this randomized, controlled trial, HIFU represents an effective method for the treatment of NNEDV.

(2010) Ruan et al evaluated the effectiveness of high intensity focused ultrasound (HIFU) in the treatment of patients with non-neoplastic epithelial disorders of the vulva. These researchers reviewed 41 cases of lichen sclerosus, 38 cases of squamous cell hyperplasia, and 17 mixed cases. Biopsy specimens were assessed with light microscopy before and after treatment. Pruritus and signs of vulvar lesions were dramatically improved after HIFU treatment, without severe complications, and 90.2 % of the patients were cured or had their symptoms improved 6 months after treatment. On light microscopy, pigmentation and epithelial structures were recovered and dermal lymphocytic infiltration was reduced. The response rates were lower and complication rates higher among lichen sclerosus than among squamous cell hyperplasia cases ($p < 0.05$ for both). The authors concluded that treatment with HIFU may be safe and effective in cases of vulvar dystrophy. The findings of this trial need to be validated by well-designed studies with larger number of patients and longer follow-up periods.

Summary of Evidence: Vulvar Dystrophy (Non-Neoplastic Epithelial Disorders of the Vulva)
Based on the review of the peer reviewed medical literature there are limited studies. These studies suggest that high intensity focused ultrasound (HIFU) may be promising non-invasive tool for non-neoplastic epithelial disorders of the vulva (NNEDV). Further studies with longer follow up are needed to establish the optimal treatment protocol and to assess the long-term efficacy of HIFU for this indication. The evidence is insufficient to determine the effects on net health outcomes.

Practice Guidelines and Position Statements

American College of Radiology (ACR) Appropriateness Criteria

- (2016) American College of Radiology Expert Panel on Radiation Oncology-Prostate Work Group's guideline on locally advanced high risk prostate cancer was updated and states, "Ablative treatments including cryotherapy and high-

intensity focused ultrasound (HIFU) are other options available to men with high-risk prostate cancer, though data are limited for these modalities. There was insufficient literature using parameters employed for these modalities to be included in the assessment of high-risk prostate cancer".
    - The panel did not include other treatment options i.e., ablative treatments cryotherapy and high intensity focused ultrasound (HIFU) in their summary of recommendations.

(Accessed December 2021)

American Society of Clinical Oncology (ASCO)

- (2018) The American Society of Clinical Oncology (ASCO) endorsed the clinical practice guideline of an American Urological Association/American Society of Radiation Oncology/Society of Urologic Oncology guideline for clinically localized prostate cancer.
  (Accessed December 2021)

American Urological Association (AUA)

(2017) The American Urological Association (AUA), American Society for Radiation Oncology (ASTRO) and Society of Urologic Oncology (SUO) issued a guideline on clinically localized prostate cancer, which included the following guideline statements regarding high intensity focused ultrasound (HIFU):

- **Care Options by Cancer Severity/Risk Group**
    - Very low/low risk disease
        - Clinicians should inform low-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. (Expert Opinion)
    - Intermediate Risk Disease
        - Clinicians should inform intermediate-risk prostate cancer patients who are considering focal therapy or HIFU that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)
    - High Risk Disease
        - Cryosurgery, focal therapy and HIFU treatments are not recommended for men with high risk localized prostate cancer outside of a clinical trial. (Expert Opinion)

  (*Accessed December 2021*)

- **HIFU and Focal Therapy**
    - Clinicians should inform those localized prostate cancer patients considering focal therapy or HIFU that these treatment options lack robust evidence of efficacy. (Expert Opinion)
    - Clinicians should inform localized prostate cancer patients who are considering HIFU that even though HIFU is approved by the FDA for the destruction of

prostate tissue, it is not approved explicitly for the treatment of prostate cancer. (Expert Opinion)

- Clinicians should advise localized prostate cancer patients considering HIFU that tumor location may influence oncologic outcome. Limiting apical treatment to minimize morbidity increases the risk of cancer persistence. (Moderate Recommendation; Evidence Level: Grade C)
- As prostate cancer is often multifocal, clinicians should inform localized prostate cancer patients considering focal therapy that focal therapy may not be curative and that further treatment for prostate cancer may be necessary.

The Panel recommends that if HIFU is offered as an alternative treatment modality for localized prostate cancer, it should be done within the context of a clinical trial. Prospective randomized or comparative trials with other treatment modalities are lacking. Published five-year oncologic outcomes are variable and attributable to the lack of consensus on objective response criteria. However, it has been recognized that the PSA nadir level after whole gland HIFU is predictive of biochemical recurrence. The Panel awaits the results of well-designed comparative clinical trials in order to define the appropriate role of this technology in the management of localized prostate cancer. Whole prostate ablation utilizing HIFU with or without short term neoadjuvant ADT has been associated with a comparable incidence of post-treatment incontinence, bladder neck/urethral stricture, and rectourethral fistulae. (*Accessed December 2021*)

National Cancer Institute (NCI)
(2020) The NCI provides A Prostate Cancer Treatment Physician Data Query (PDQ®) which notes, high-intensity focused ultrasound has been reported in case series to produce good local disease control. However, it has not been directly compared with more standard therapies, and experience with it is more limited. (*Accessed December 2021*)

provides information on prostate cancer treatments. The NCI indicated that cryoablation, photodynamic therapy, and HIFU were new treatment options currently being studied in national trials. The NCI offered no recommendation for or against these treatments. (*Accessed December 2021*)

National Comprehensive Cancer Network (NCCN)
(All accessed December 2021)

- **Breast Cancer Version 1.2022**
  - The current guideline does not include or indicate the use of high-intensity focused ultrasound (HIFU) in the treatment and management of breast cancer.
- **Central Nervous System Cancers Version 2.2021**
  - The current guideline does not include or indicate the use of high-intensity focused ultrasound (HIFU) in the treatment and management of central nervous system cancers.

- **Hepatobiliary Cancers Version 5.2021**
  - The current guideline does not include or indicate the use of high-intensity focused ultrasound (HIFU) in the treatment and management of hepatobiliary cancers.
- **Kidney Cancer Version 3.2022**
  - The current guideline does not include or indicate the use of high-intensity focused ultrasound (HIFU) in the treatment and management of kidney cancer.
- **Pancreatic Adenocarcinoma Version 2.2021**
  - The current guideline does not include or indicate the use of high-intensity focused ultrasound (HIFU) in the treatment and management of pancreatic adenocarcinoma.
- **Prostate Cancer Version 2.2022**
  - **Other Local Therapies**:
    - Many local 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 matching 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 radiation therapy recurrence in the absence of metastatic disease.

      - HIFU has been studied for the treatment of initial disease. A prospective multi-institutional study used HIFU in 111 patients with localized prostate cancer. The radical treatment-free survival rate was 89% at 2 years, and continence and erectile functions were preserved in 97% and 78% of patients, respectively at 12 months. Morbidity was acceptable with grade III complication rate of 13%. In another prospective multi-institutional study 625 men with localized prostate cancer were treated with HIFU. Eighty-four percent of the cohort had intermediate or high- risk disease. The primary endpoint of FFS was 88% at 5 years (95% CI. 85%-91%). Pad-free urinary continence was reported by 98% of participants. Other case series studies have seen similar results.

      - HIFU also has been studied for treatment of radiation recurrence. Analysis of a prospective registry of men treated with HIFU for radiation recurrence revealed median biochemical recurrence-free survival at 63 months, 5-year OS of 88%, and cancer specific survival of 94%. Morbidity was acceptable with a grade III/IV complication rate of 3.6%. Analysis of a separate prospective registry showed that 48% of men who received HIFU following radiotherapy failure were able to avoid ADT at median follow-up at 64 months.

- **Post-Irradiation Recurrence**
  - Options for primary salvage therapy for those with positive biopsy but low suspicion of metastases to distant organs includes observation or radical prostatectomy with PLND in selected cases by highly experienced surgeons. Salvage radical prostatectomy can result in long-term disease control but is often associated with impotence and urinary incontinence. Other options for localized interventions include cryotherapy, HIFU (category 2B), and brachytherapy. Treatment, however, needs to be individualized based on the patient's risk of progression, the likelihood of success, and the risks involved with salvage therapy.

- **Soft Tissue Sarcoma Version 2.2021**
  - The current guideline does not include or indicate the use of high-intensity focused ultrasound (HIFU) in the treatment and management of soft tissue sarcoma.

- **Thyroid Carcinoma Version 3.2021**
  - The current guideline does not include or indicate the use of high-intensity focused ultrasound (HIFU) in the treatment and management of thyroid cancer.

National Institute for Health and Care Excellence (NICE)
(Accessed December 2021)

- **Breast Adenoma**: (2017: Updated September 2020) NICE issued a guidance development process on high-intensity focused ultrasound for symptomatic breast fibroadenoma recommending the following information:
  - The evidence on high-intensity focused ultrasound for symptomatic breast fibroadenoma raises no major safety concerns. Evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

- **Prostate Cancer** (2019: Updated December 2021) NICE issued a guideline on Prostate cancer: diagnosis and management (NICE guideline [NG131]) stating the following:
  - Do not offer high-intensity focused ultrasound and cryotherapy to people with localized prostate cancer, other than in the context of controlled clinical trials comparing their use with established interventions. [2008]

    - NICE's interventional procedures guidance on high-intensity focused ultrasound for prostate cancer, cryotherapy for recurrent prostate cancer and cryotherapy as a primary treatment for prostate cancer evaluated the safety and efficacy of cryotherapy and high-intensity focused ultrasound for the treatment of prostate cancer. NICE guidelines provide guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS. Because there was a lack of evidence on

quality-of-life benefits and long-term survival, these interventions are not recommended in this guideline.

- NICE's interventional procedures guidance on focal therapy using high-intensity focused ultrasound for localized prostate cancer and focal therapy using cryoablation for localized prostate cancer found no major safety concerns, but evidence on efficacy is limited in quantity and there is a concern that prostate cancer is commonly multifocal.

- **Thyroid Nodule** (2019) NICE issued a guideline on high-intensity focused ultrasound for symptomatic benign thyroid nodules (NICE guideline [IPG643]) stating the following:
  - The evidence on the safety of high-intensity focused ultrasound for symptomatic benign thyroid nodules raises no major safety concerns, however the current evidence on its efficacy is limited in quantity and quality Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedure's guidance page.

Regulatory Status

Device	FDA Clearance Year	Description
Sonablate 450 (SonaCare Medical)	2015	classified the device as class II under the generic name "high intensity ultrasound system for prostate tissue ablation". This device was the first of its kind to be approved in the United States.
Ablatherme (EDAP TMS) / Ablatherm Integrated Imaging High-Intensity Focused Ultrasound (HIFU) device	2015	The Ablatherm was determined to be substantially equivalent to the Sonablate device and is indicated for the ablation of prostate tissue. Ablatherm HIFU is administered via a transrectal probe under imaging guidance. The device uses HIFU to elevate the tissue temperature within the target zone of the prostate, resulting in tissue necrosis, while the surrounding tissue is kept at physiologically safe temperatures. Ablatherm HIFU treatment completely destroys the targeted prostate tissue
Ablatherm® Fusion / Ablatherm® Integrated Imaging and Sonablate®	2017	was determined to be substantially equivalent to Ablatherm® Integrated Imaging and Sonablate® and is indicated for the ablation of prostate tissue. The purpose of the 510(k) submission was to add an optional feature that would provide MRI images and/or biopsies positions fused with the system's

		live ultrasound imaging. This option is referred to as AblaFusion (FDA, 2017).
Focal One®	2018	Focal One was determined to be substantially equivalent to the Ablatherm and Sonablate and is indicated for the ablation of prostate tissue (FDA, 2018). "The Focal One® is an evolution from the previous generation device, designed by EDAP: Ablatherm Integrated Imaging (K153023) and Ablatherm Fusion (K172285). The Focal One consists of the Focal One module with a software control system, an endorectal dynamic focusing probe, a leg holder, a set of single use disposables and a coupling liquid pouch"

This is not an all-inclusive list.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies

- 04.01.09 MRI-Guided High-Intensity Focused Ultrasound (MRgFUS) Ablation
- 07.01.69 Treating Benign Prostatic Hyperplasia

High Intensity Focused Ultrasound (HIFU) is considered **investigational** for all indications including but not limited to the following:

- Breast fibroadenoma
- Breast cancer
- Central nervous system cancers (gliomas)
- Hepatocellular carcinoma (primary or metastatic)
- Pancreatic cancer
- Prostate cancer
- Renal cell carcinoma (RCC)
- Soft tissue sarcomas
- Thyroid nodules
- Vulvar dystrophy (non-neoplastic epithelial disorders of the vulva)

Based on the review of the peer reviewed medical literature the long-term efficacy and safety of high intensity focused ultrasound (HIFU) compared to established interventions for various conditions has not been proven in controlled clinical trials for any indication. Additional randomized clinical trials with larger patient populations comparing established interventions are needed to determine the role of high intensity focused ultrasound (HIFU). The evidence is insufficient to determine the effects on net health outcomes.

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.

- 55880 Ablation of malignant prostate tissue, transrectal, with high-intensity focused ultrasound (HIFU), including ultrasound guidance
- 55899 Unlisted procedure, male genital system
- 76999 Unlisted ultrasound procedure (e.g. diagnostic, interventional)

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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 Revised
January 2019	Annual Review	Policy Revised
January 2018	Annual Review	Policy Revised
January 2017	Annual Review	Policy Revised
January 2016	Annual Review	Policy Revised
February 2015	Annual Review	Policy Revised
March 2014		New Policy Created

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
PO Box 9232
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