

02.01.53 High Intensity Focused Ultrasound (HIFU)

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Related Policies:

- [04.01.09 MRI-Guided High-Intensity Focused Ultrasound \(MRgFUS\) Ablation](#)
- [07.01.96 Transurethral Water Vapor Thermal Therapy \(Rezum\) and Transurethral Waterjet Ablation \(Aquablation\) for Benign Prostatic Hypertrophy](#)

Summary

Description

Note: 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 which 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 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.

High intensity focused ultrasound (HIFU) 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.

Summary of Evidence

For individuals who have primary localized prostate cancer who receive high intensity focused ultrasound (HIFU) the evidence includes prospective reviews. Relevant outcomes are overall survival (OS), disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life (QoL), and treatment-related morbidity. The evidence is highly heterogeneous and inconsistently reports clinical outcomes. No prospective, comparative evidence was found versus current standard treatment of localized prostate cancer, including radical prostatectomy, external-beam radiotherapy, or active surveillance. Methods have not been standardized to determine which and how many identified cancerous lesions should be treated for best outcomes. No evidence supports which, if any, of the focal techniques leads to better functional outcomes. Although high disease-specific survival rates have been reported, the short follow-up periods and small sample sizes preclude conclusions on the effect of any of these techniques on OS rates. The adverse event rates associated with focal therapies appear to be superior to those associated with radical treatments (e.g., radical prostatectomy, external-beam radiotherapy); however, the evidence is limited in its quality, reporting, and scope. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other miscellaneous cancers/conditions who receive HIFU, the evidence includes systematic reviews, randomized controlled trials, nonrandomized controlled trials, and single-arm case series. Relevant outcomes are overall survival (OS), disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life (QoL), and treatment-related morbidity. The evidence is highly heterogeneous and inconsistently reports health outcomes. Further prospective randomized studies are needed that evaluate health outcomes in larger patient populations with longer follow-up. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome however based on support from the National Comprehensive Cancer Network (NCCN) consensus (see [Practice Guidelines and Position Statements](#) below) category 2A recommendations HIFU will be considered medically necessary in select individuals when the criteria have been met, see [Policy](#) below.

Additional Information

Not applicable.

OBJECTIVE

The objective of this evidence review is to determine whether the use of high intensity focused ultrasound (HIFU) improves the net health outcomes in individuals with various conditions including but not limited to breast cancer/breast fibroadenoma, central nervous system cancers, hepatocellular carcinoma,

pancreatic cancer, prostate cancer, renal cancer, thyroid nodules, and Vulvar dystrophy (non-neoplastic epithelial disorders of the vulva).

PRIOR APPROVAL

Not applicable.

POLICY

Medically Necessary

High intensity focused ultrasound (HIFU) is considered **medically necessary** for **one of the following** scenarios:

- Individuals who have metastatic soft tissue sarcoma
- For palliative therapy for individuals who have pancreatic adenocarcinoma

Investigational

High intensity focused ultrasound (HIFU) is considered **investigational** when the above criteria has not been met and for all other conditions including but not limited to the following because the evidence is insufficient to determine the technology results in an improvement in the net health outcomes:

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

ALL Category III codes will be considered investigational unless the code is explicitly addressed as a covered service in a Wellmark BlueCross BlueShield Medical Coverage Policy.

POLICY GUIDELINES

Coding

See the [Codes](#) table for details.

Category III codes are a set of temporary (T) codes for emerging technologies, services, and procedures that allow for data collection by the American Medical Association's (AMA). If a Category III code is available, providers must use that code instead of an unlisted or deleted Category I code. The services or procedures represented by Category III codes may not have FDA approval, may not be performed by many health care professionals across the country, and the service or procedure may not have proven clinical efficacy. Certain T codes may be addressed as a covered service in a Wellmark BlueCross BlueShield Medical Coverage Policy. But, unless there is explicit Policy criteria that specifically extends coverage to a particular Category III code, the code would generally be considered experimental, investigational, or unproven.

BACKGROUND

High-Intensity Focused Ultrasound

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

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 HIFU, radiofrequency ablation, laser ablation and cryoablation.

Central Nervous System Cancers

According to the American Society of Clinical Oncology, "in most instances, CNS tumors start from the normal cells of the brain and spinal cord called "neurons" and "glia." Tumors that start from neurons include medulloblastoma and primitive neuroectodermal tumors (PNETs). Tumors that start from glia include glioma, astrocytoma, oligodendroglioma, and ependymoma. The tumor's specific name often reflects the CNS tumor's tissue of origin.

In addition to the tumor's name, CNS tumors are described by their grade. This means that each tumor is given a grade on a scale of I to IV (1 to 4). The tumor's grade reflects whether the tumor is likely to behave aggressively and whether it is likely to spread to other parts of the brain and spine. There are also specific factors within each tumor type that affect how quickly the tumor will grow. Many of these differences depend on genetic changes found within the tumor."

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.

Pancreatic Cancer

According to Sofuni et al. Pancreatic cancer (PC) has one of the poorest prognoses among solid cancers, and its incidence has increased recently. Satisfactory outcomes are not typically achieved with current therapies and High intensity focused ultrasound (HIFU) is being reviewed as a novel therapy for individuals with PC with unresectable advanced cancer that is not indicated for or does not respond to conventional local therapies or whose pain can only be controlled by increasing the dose of analgesics. HIFU for PC has several limitations and further study is needed, this technique can be safely performed on unresectable advanced PC. Moreover, HIFU therapy is hoped to improve the QOL of individuals by preventing local complications such as duodenal obstruction through local control and symptom relief effects such as pain relief. In future, HIFU could be utilized as a minimally invasive treatment strategy for PC individuals with a poor prognosis.

Prostate Cancer

Prostate cancer is the second most common cancer diagnosed among men in the U.S. According to the American Cancer Society, nearly 313,780 new cases are estimated to be diagnosed in the U.S. in 2025, associated with around 35,770 deaths. Prostate cancer is more likely to develop in older men and in non-Hispanic Black men. About 6 in 10 cases are diagnosed in men who are ≥ 65 years of age, and it is rare in men < 40 years of age. Autopsy studies in the pre-prostate-specific antigen (PSA) screening era identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years. The prostate cancer death rate declined by about half from 1993 to 2022, likely due to earlier detection and improved treatment.

High Intensity Focused Ultrasound for Localized Prostate Cancer

Given significant uncertainty in predicting the behavior of individual localized prostate cancers, and the substantial adverse events associated with definitive treatments, investigators have sought a therapeutic middle ground. The latter seeks to minimize morbidity associated with radical treatment in those who may not actually require surgery while reducing tumor burden to an extent that reduces the chances for rapid progression to incurability. This approach is termed focal treatment, in that it seeks to remove, using any of several ablative methods described next, cancerous lesions at high-risk of progression, leaving behind uninvolved glandular parenchyma. The overall goal of any focal treatment is to minimize the risk of early tumor progression and preserve erectile, urinary, and rectal functions by reducing damage to the neurovascular bundles, external sphincter, bladder neck, and rectum.

Prostate Cancer: Modalities Used to Ablate Lesions

The following ablative methods for which clinical evidence is available are considered herein: focal laser ablation; high-intensity focused ultrasound (HIFU); cryoablation; radiofrequency ablation (RFA); photodynamic therapy; and irreversible electroporation. Each method requires placement of a needle probe into a tumor volume followed by delivery of some type of energy that destroys the tissue in a controlled manner. All methods except focal laser ablation currently rely on ultrasound guidance to the tumor focus of interest; focal laser ablation uses MRI to guide the probe. This evidence review does not cover focal brachytherapy.

Renal Cell Carcinoma

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.

Soft Tissue Sarcoma

Soft tissue sarcoma (STS) can arise from various tissue types and is comprised of over 50 tumor types. Although STS is treated with a combination of surgery, radiotherapy and chemotherapy, the prognosis is relatively poor. High intensity focused ultrasound (HIFU) is being studied as a non-invasive way of treating soft tissue sarcoma (STS) with minimal side effects, low complication rate and quick recovery.

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.

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).

Regulatory Status

In October 2015, the Sonablate® 450 (SonaCare Medical) was cleared for marketing through the 510(k) process after approval of a de novo request and classification 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 U.S. In November 2015, Ablatherm®-HIFU (EDAP TMS) was cleared for marketing by the FDA through the 510(k) process. In June 2018, EDAP received 510(k) clearance for its Focal-One® HIFU device designed for prostate tissue ablation procedures. This device fuses magnetic resonance and 3D biopsy data with real-time ultrasound imaging, allowing urologists to view detailed images of the prostate on a large monitor and direct high-intensity ultrasound waves to ablate the targeted area.

This is not intended to be an all-inclusive list.

RATIONALE

This evidence review was created in March 2014 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through November 2025.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QoL), and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will

be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Prostate Cancer

This review only assesses evidence on focal therapy for individuals who have primary localized prostate cancer; it does not consider the recurrent or salvage setting.

Clinical Context and Therapy Purpose

The purpose of focal therapy using high intensity focused ultrasound (HIFU) in individuals who have primary localized prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

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

Diagnosis of Prostate Cancer

From a clinical standpoint, different types of localized prostate cancers may appear similar during initial diagnosis. However, prostate cancer often exhibits varying degrees of risk progression that may not be captured by accepted clinical risk categories (e.g., D'Amico criteria) or prognostic tools based on clinical findings (e.g., PSA titers, Gleason grade, or tumor stage). In studies of conservative management, the risk of localized disease progression based on prostate cancer-specific survival rates at 10 years may range from 15% to 20% to perhaps 27% at 20-year follow-up. Among elderly individuals (≥ 70 years) with this type of low-risk disease, comorbidities typically supervene as a cause of death; these men will die from the comorbidities of prostate cancer rather than from cancer itself. Other very similar-appearing low-risk tumors may progress unexpectedly and rapidly, quickly disseminating and becoming incurable.

Patient Selection in Individuals with Prostate Cancer

A proportion of men with localized prostate cancer have been reported to have (or develop) serious misgivings and psychosocial problems in accepting active surveillance, sometimes leading to inappropriately discontinuing it. Thus, the appropriate patient selection is imperative for physicians who must decide whether to recommend active surveillance or focal treatment for individuals who refuse radical therapy or for whom it is not recommended due to the risk/benefit balance.

Prostate Cancer: Lesion Selection

Proper lesion selection is a second key consideration in choosing a focal treatment for localized prostate cancer. Although prostate cancer is a multifocal disease, clinical evidence has shown that between 10% and 40% of men who undergo radical prostatectomy for presumed multifocal disease actually have a unilaterally confined discrete lesion, which, when removed, would “cure” the patient. This view presumably has driven the use of regionally targeted focal treatment variants, such as hemiablation of half the gland containing the tumor, or subtotal prostate ablation via the “hockey stick” method. While these approaches can be curative, the more extensive the treatment, the more likely the functional adverse outcomes would approach those of radical treatments.

The concept that clinically indolent lesions comprise most of the tumor burden in organ-confined prostate cancer led to the development of a lesion-targeted strategy, which is referred to as “focal therapy” in this evidence review. This involves treating only the largest and highest-grade cancerous focus (referred to as the “index lesion”), which has been shown in pathologic studies to determine the clinical progression of the disease. This concept is supported by molecular genetics evidence that suggests that a single index tumor focus is usually responsible for disease progression and metastasis. The index lesion approach leaves in place small foci less than 0.5 cm³ in volume, with a Gleason score less than 7, that are considered unlikely to progress over a 10- to 20-year period. This also leaves available subsequent definitive therapies as needed should disease progress.

Identification of prostate cancer lesions (disease localization) particularly the index lesion, is critical to the oncologic success of focal therapy; equally important to success is the ability to guide focal ablation energy to the tumor and assess treatment effectiveness. At present, no single modality reliably meets the requirements for all 3 activities (disease localization, focal ablation energy to the tumor, assessment of treatment effectiveness). Systematic transrectal ultrasound-guided biopsy alone has been investigated; however, it has been considered insufficient for patient selection or disease localization for focal therapy.

Multiparametric magnetic resonance imaging (mpMRI), typically including T1-, T2-, diffusion-weighted imaging, and dynamic contrast-enhanced imaging, has been recognized as a promising modality to risk-stratify prostate cancer and select patients and lesions for focal therapy. Evidence has shown mpMRI can detect high-grade, large prostate cancer foci with performance similar to transperineal prostate mapping using a brachytherapy template. For example, for the primary endpoint definition (lesion, ≥ 4 mm; Gleason score, $\geq 3+4$), with transperineal prostate mapping as the reference standard, sensitivity, negative predictive value, and negative likelihood ratios with mpMRI were 58% to 73%, 84% to 89%, and 0.3 to 0.5, respectively. Specificity, positive predictive value, and positive likelihood ratios were 71% to 84%, 49% to 63%, and 2.0 to 3.44, respectively. The negative predictive value of mpMRI appears sufficient to rule out clinically significant prostate cancer and may have clinical use in this setting. However, although mpMRI technology has the capability to detect and risk-stratify prostate cancer, several issues constrain its widespread use for these purposes (e.g., mpMRI requires highly specialized MRI-compatible equipment; biopsy within the magnetic resonance imaging (MRI) scanner is challenging; interpretation of prostate MRI images requires experienced urologists) and it is still necessary to histologically confirm suspicious lesions using transperineal prostate mapping.

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 managing men with primary localized prostate cancer, surgery (radical prostatectomy), external beam radiation, and active surveillance.

Treatments of Prostate Cancer

The divergent behavior of localized prostate cancers creates uncertainty about whether to treat immediately. A patient may choose definitive treatment up front. Surgery (radical prostatectomy) or external-beam radiotherapy are frequently used to treat patients with localized prostate cancer. Complications most commonly reported with radical prostatectomy or external-beam radiotherapy and with the greatest variability are incontinence (0% to 73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically $\leq 5\%$); gastrointestinal and bowel toxicity, including nausea and loose stools (25% to 50%); proctopathy, including rectal pain and bleeding (10% to 39%); and erectile dysfunction, including impotence (50% to 90%).

American Urological Association guidelines state that for individuals with low-risk prostate cancer, clinicians should recommend active surveillance. With this approach, individuals forego immediate therapy but continue regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted

Outcomes

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

As a therapy situated between active surveillance and definitive therapy, focal therapy is a tissue-sparing procedure intended to maximize QoL (e.g., incontinence, sexual dysfunction) by treating the index lesion.

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.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Prostate Cancer

No prospective, comparative studies were identified for the majority of the ablative technologies; however, RCTs comparing focal therapy to radical therapy are underway for HIFU (NCT03531099). The current evidence primarily comprises systematic reviews of noncomparative studies, case series, and other observational studies.

Duwe et al (2023) described a prospective series of 29 patients with unilateral prostate cancer treated with focal HIFU between 2016 and 2021 at a single institution in Germany. Median follow-up after HIFU was 23 months. Median age at time of HIFU was 67 years. Prostate cancer was detected in 13/29 (45%) patients histologically at one year. Another 7/29 patients (24%) were diagnosed with prostate cancer at two years. One patient developed local metastatic disease 2 years after HIFU. 70% of patients maintained sufficient erectile function for intercourse and 97% reported maintenance of urinary continence.

Reddy et al (2022) reported results of 1379 participants with 6 months or more of follow-up in the HIFU Evaluation and Assessment of Treatment (HEAT) registry from 2005-2020 in 13 centers in the United Kingdom. Median follow-up was 32 months; 325 (24%) participants had 5 or more years of follow-up. The median age was 66 years. Failure-free survival at 7 years was 69% (95% CI, 64% to 74%). 252 participants had repeat focal treatment due to residual or recurrent cancer. 92 participants required salvage whole-gland treatment.

Nahar et al (2020) 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 epididymo-orchitis 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.

Miscellaneous Cancers/Conditions

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.

Populations

The relevant population of interest are individuals with conditions including but not limited to breast cancer/breast fibroadenoma, central nervous system cancers, hepatocellular carcinoma, pancreatic cancer, prostate cancer, renal cancer, thyroid nodules, and Vulvar dystrophy (non-neoplastic epithelial disorders of the vulva).

Interventions

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

Comparators

Therapies and practices being used to make decisions about management individuals with conditions including but not limited to breast cancer/breast fibroadenoma, central nervous system cancers, hepatocellular carcinoma, pancreatic cancer, renal cancer, thyroid nodules, and Vulvar dystrophy (non-neoplastic epithelial disorders of the vulva).

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life (QoL), and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Breast Cancer

Review of Evidence

Systematic Review

Zulkifli et al (2023) conducted a systematic review on the application of high-intensity focused ultrasound (HIFU) ablative therapy in the treatment of primary breast cancer. “Two randomized controlled trials and seven non-randomized clinical trials fulfilled the inclusion criteria. The percentage of patients who achieved complete (100%) coagulation necrosis varied from 17% to 100% across all studies. Eight of the nine studies followed the treat-and-resect protocol in which HIFU-ablated tumors were surgically resected for pathological evaluation. Most breast cancers were single, solitary, and palpable breast tumors. Haematoxylin and eosin stains used for histopathological evaluation showed evidence of coagulation necrosis. Radiological evaluation by MRI showed an absence of contrast enhancement in the HIFU-treated tumor and 1.5 to 2 cm of normal breast tissue, with a thin peripheral rim of enhancement indicative of coagulation necrosis. All studies did not report severe complications, i.e., hemorrhage and infection. Common complications related to HIFU ablation were local mammary oedema, pain, tenderness, and mild to moderate burns. Only one third-degree burn was reported. Generally, the cosmetic outcome was good. The five-year disease-free survival rate was 95%, as reported in two RCTs.” The authors concluded that, “HIFU ablation can induce tumor coagulation necrosis in localized breast cancer, with a favorable safety profile and cosmetic outcome. However, there is variable evidence of complete coagulation necrosis in the HIFU-treated tumor. Histopathological evidence of coagulation necrosis has been inconsistent, and there is no reliable radiological modality to assess coagulation necrosis confidently. Further exploration is needed to establish the accurate ablation margin with a reliable radiological modality for treatment and follow-up. HIFU therapy is currently limited to single, palpable breast tumors. More extensive and randomized clinical trials are needed to evaluate HIFU therapy for breast cancer, especially where the tumor is left in situ.”

There are additional studies which evaluated the immunohistochemical analysis however these studies do not include the health outcomes of interest. (Zhu, 2021; Lu, 2008; Xu, 2008; Wu 2003).

Breast Fibroadenomas

For breast fibroadenomas and HIFU there are no published systematic reviews or randomized controlled trials.

Central Nervous System Cancers

For central nervous system cancers and HIFU there are published systematic reviews or randomized controlled trials.

Hepatocellular Carcinoma (HCC)

Review of Evidence

Systematic Review

Sehmbi et al (2021) 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 %). Overall survival data, as a percentage of all patients treated with HIFU, was provided by eleven studies reporting on 480 (51%) patients. Median follow up was three years, however four studies followed up patients for 5 years. At 3 years, survival ranged from 6% to 81% and at 5 years, survival ranged from 8% to 18%. Survival data is difficult to compare across the cohort, given unreported heterogeneity across prognostic factors. 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.

Pancreatic Cancer

Review of Evidence

Systematic Review/Meta Analysis

Fergadi et al (2022) completed a meta-analysis evaluating the role of high-intensity focused ultrasound (HIFU) as a fourth treatment modality for patients with locally advanced pancreatic cancer. They reviewed nineteen articles met the inclusion criteria, incorporating 939 patients. This study reveals that patients in the HIFU group presented increased median overall survival (OS), along with higher OS at 6 and 12 months after treatment compared with the control group ($p < 0.05$). Furthermore, patients treated with HIFU in conjunction with chemotherapy presented reduced levels of pain ($p < 0.05$) compared to the traditional treatment group. In addition, HIFU contributed to significant tumor responsiveness, in terms of CA19-9 reduction ($p < 0.05$). Finally, HIFU was a considerably safe treatment modality with a low incidence of complications. The authors concluded these outcomes suggest that HIFU is a feasible and safe treatment modality for patients with advanced pancreatic cancer and provides enhanced outcomes regarding survival and quality of life. Given the lack of a significant number of randomized clinical trials, this meta-analysis represents the best currently available evidence. New randomized trials assessing HIFU are necessary to further evaluate their outcomes.

Dababou et al (2017) 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. T^2 (variance among studies) was 0.195, and I^2 (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.

Renal Cancer

Renal cancers and HIFU had no published systematic reviews or randomized controlled trials.

Thyroid Nodules

Review of Evidence

Systematic Review/Meta-Analysis

We identified no comparative studies for using HIFU for treatment of benign thyroid nodules.

Benaim et al (2023) published a systemic review and meta-analysis on HIFU for benign thyroid nodules. They identified 8 studies (N=297) that met their inclusion criteria after searching OVID-Medline, PubMed, Scopus, and Cochrane in August of 2021. The researchers found a reduced total nodule volume from 1 to 24 months (weighted mean difference [WMD], 47.68, 95 % confidence interval [CI], 34.13–59.66, $p < 0.0001$) for individuals who received HIFU. A significant proportion of patients achieved a 50% reduction in volume following HIFU risk ratio [RR], 1.49, 95 % CI, 1.15–1.84, $p < 0.001$). Overall the researchers concluded HIFU may be a treatment modality for individuals with benign thyroid nodules, however, due to the mixed quality and lack of RCTs additional studies are needed to identify appropriate patient selection and standardized treatment protocols.

Cheong et al completed a systematic review and meta-analysis from 1990 to 2021. The authors noted, “o date, there have only been 2 systematic reviews, and 1 systematic review and meta-analysis on high-intensity focused ultrasound (HIFU) for benign thyroid nodules. The present systematic review and meta-analysis seeks to evaluate the efficacy and safety of HIFU in the treatment of benign thyroid nodules. Pubmed, Embase and Cochrane databases were searched for relevant studies from 1990 to 2021. Nine studies were included in the systematic review and 6 in the meta-analysis. Pooled volume reduction rates (VRRs) at 3, 6 and 24 months after HIFU were assessed. This systematic review and meta-analysis showed that pooled VRRs at 3, 6, and 24 months after HIFU were 42.14 (95% confidence interval [CI] 28.66-55.62, $I^2=91\%$), 53.51 (95% CI 36.78-70.25, $I^2=97\%$) and 46.89 (95% CI 18.87-74.92, $I^2=99\%$), respectively. There was significant heterogeneity in the pooled VRRs at 3, 6 and 24 months after HIFU. No studies recorded complete disappearance of the nodules. Common side effects included pain, skin changes and oedema. There were no major complications except for transient vocal cord paralysis and voice hoarseness (0.014%) and transient Horner syndrome (0.5%).” The authors concluded, “HIFU may be an effective and safe alternative treatment modality for benign thyroid nodules. Larger clinical trials with longer follow-up are needed to evaluate the effectiveness of HIFU in treating benign thyroid nodules.” The key limitation of these findings is that these studies lacked comparator groups.

Vulvar Dys trophy (Non-Neoplastic Epithelial Disorders of the Vulva)

Vulvar Dys trophy (Non-Neoplastic Epithelial Disorders of the Vulva) and HIFU have no identified well designed systematic reviews or randomized controlled trials.

Section Summary: Miscellaneous Cancers/Conditions

For miscellaneous cancers/conditions such as breast cancer, central nervous system, hepatocellular carcinoma, (HCC), pancreatic dc, renal cancer, thyroid nodules, and vulvar dys trophy (non-neoplastic epithelial disorders of the vulva) the evidence is highly heterogeneous and inconsistently reports health outcomes. Further prospective randomized studies are needed that evaluate health outcomes in larger patient populations with longer follow-up.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Urological Association (AUA) et al.

The American Urological Association, in collaboration with the American Society for Radiation Oncology (ASTRO) with additional representation from the American Society of Clinical Oncology (ASCO), and Society of Urologic Oncology (SUO) published updated guidelines on the management of clinically localized prostate cancer in 2022. The guidelines included the following recommendation on focal treatments:

- "Clinicians should inform patients with intermediate-risk prostate cancer considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance. (Expert Opinion)"
- "Clinicians should not recommend whole gland or focal ablation for patients with high-risk prostate cancer outside of a clinical trial. (Expert Opinion)"

National Cancer Institute

The National Cancer Institute (NCI; 2024) updated its information on prostate cancer treatments. The NCI indicated that cryosurgery, photodynamic therapy, and HIFU were new treatment options currently being studied in national trials. The NCI offered no recommendation for or against these treatments.

National Comprehensive Cancer Network (NCCN)

- **Breast Cancer Version 4.2025**
 - The current guideline does not include or support the use of high-intensity focused ultrasound (HIFU) in the treatment and management of breast cancer.
- **Central Nervous System Cancers Version 2.2025**
 - The current guideline does not include or support the use of high-intensity focused ultrasound (HIFU) in the treatment and management of central nervous system cancers.
- **Hepatocellular Carcinoma Version 1.2025**
 - The current guideline does not include or support the use of high-intensity focused ultrasound (HIFU) in the treatment and management of hepatobiliary cancers.
- **Kidney Cancer Version 1.2026**
 - The current guideline does not include or support the use of high-intensity focused ultrasound (HIFU) in the treatment and management of kidney cancer.
- **Pancreatic Adenocarcinoma Version 2.2025**

- Principles of Palliation and Supportive Care
 - Symptom: Pain
 - Severe tumor-associated abdominal pain unresponsive to optimal, around-the-clock analgesic administration, or if patient experiences undesirable analgesic-associated side effects
 - High-intensity focused ultrasound
 - Consider palliative radiation with or without chemotherapy if not already given as part of primary therapy regimen.
- **Prostate Cancer Version 2.2026**
 - The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer recommend only cryosurgery and high-intensity focused ultrasound (HIFU) as local therapy options for radiotherapy *recurrence* in the absence of metastatic disease (category 2B). 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.
- **Soft Tissue Sarcoma Version 1.2025**

Under Principles of Interventional Oncology, it notes, “Tumor ablation involves application of thermal or non-thermal therapies of a tumor to achieve cell death. Thermal ablation achieves tissue destruction by the induction for extreme hypothermia (cryoablation) or hyperthermia (radiofrequency [RFA], microwave ablation, laser ablation, and high-intensity focused ultrasound [HIFU]).” This does not provide further recommendations for the use of HIFU in Soft Tissue Sarcoma.
- **Thyroid Carcinoma Version 1.2025**
 - 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)

- **Breast Adenoma**

The National Institute for Health and Care Excellence (NICE) issued guidance (2017) on high-intensity focused ultrasound for symptomatic breast fibroadenoma [IPG592] that reported, “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**

In 2019, NICE issued a guideline on Prostate cancer: diagnosis and management [NG131] that was last updated December 2021 that reported 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**

In 2019, NICE issued a guideline on high-intensity focused ultrasound for symptomatic benign thyroid nodules [IPG643] stating, “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](#).”

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	19499	Unlisted procedure, breast [when specified as high intensity focused ultrasound]
	20999	Unlisted procedure, musculoskeletal system, general [when specified as high intensity focused ultrasound]
	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)

Codes	Number	Description
	1099T	Ablation of incompetent vein(s), extremity, transcutaneous, high intensity–focused ultrasound (HIFU), inclusive of all imaging guidance and monitoring
HCPCS		
	No code(s)	
Type of Service	Surgery	
Place of Service	Outpatient/Inpatient	

POLICY HISTORY

Date	Reason	Action
November 2025	Annual Review	Policy Renewed
November 2024	Annual Review	Policy Revised
November 2023	Annual Review	Policy Renewed
January 2023	Annual Review	Policy Revised
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
Des Moines, IA 50306-9232

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