High-Intensity Focused Ultrasound (HIFU)

MEDICAL POLICY NUMBER: 199

Effective Date: 11/1/2023
Last Review Date: 8/2023
Next Annual Review: 8/2024

INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance and Providence Plan Partners Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

I. High-intensity focused ultrasound (HIFU) may be considered **medically necessary** as a local treatment for radiation-treated recurrent prostate cancer when all of the following criteria are met (A.-C.):

   A. Patient is a candidate for local therapy; **and**
   B. Transrectal ultrasound guided (TRUS) biopsy is positive; **and**
   C. Patient lacks metastatic disease.

II. High-intensity focused ultrasound (HIFU) may be considered **medically necessary** for pain palliation of pancreatic adenocarcinoma when the patient experiences either of the following:

   A. Severe tumor-associated abdominal pain unresponsive to optimal, around-the-clock analgesic administration; **or**
   B. Undesirable analgesic-associated side effects.

III. High-intensity focused ultrasound (HIFU) is considered **not medically necessary** when criteria I.-II. above is not met.

Link to Evidence Summary

POLICY CROSS REFERENCES

None

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

BACKGROUND

Prostate Cancer

In the United States, prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in men. Prostate cancer is more common in older men and men of African American ethnicity. Approximately 1 in 7 men will be diagnosed with prostate cancer in his lifetime. In 2018, it is estimated that 164,690 men will be diagnosed with prostate cancer and 29,430 will die of the disease in the United States.[1]

Although almost all prostate cancers are adenocarcinomas, there are several other types of prostate cancer, including sarcomas, small cell carcinomas, neuroendocrine tumors and transitional cell carcinomas. Prostate cancer is a heterogeneous disease with tumors ranging from indolent to very aggressive. Survival differs according to disease stage at diagnosis. The majority of prostate cancers are discovered prior to becoming metastatic and therefore the 5-year relative survival rate is close to 100%. However, men with metastatic disease have a 5-year survival rate of approximately 30%.[2]

Currently, the treatment of prostate cancer varies depending on the stage and grade of disease. Usual treatment options include surgery, radiation therapy, hormone therapy, chemotherapy, biologic therapy, and bisphosphonate therapy.

Pancreatic Adenocarcinoma

Pancreatic cancer is a common gastrointestinal malignancy, and is often associated with a poor prognosis. Challenges to effective screening for pancreatic cancer include low disease prevalence and high cost of screening modalities such as endoscopic ultrasound and cross-sectional imaging. Pancreatic cancer is the second most common gastrointestinal malignancy in the United States. Approximately 53,000 people are diagnosed with pancreatic cancer every year.[3]

High-Intensity Focused Ultrasound (HIFU)

HIFU is a minimally invasive prostate cancer treatment that ablates abnormal prostatic tissue using high-intensity convergent ultrasound delivered via an endorectal probe. The entire prostate gland is ablated using a series of ultrasonic shots, which causes a sharp rise in temperature. Visualization of the procedure is possible through real-time guidance provided by diagnostic ultrasound or MRI. During real-time monitoring, computer software calculates target volume, with the aim of delivering a wave beam with a high degree of precision. This may be beneficial due to minimizing the impact on surrounding

tissue and intervening structures. Since ultrasound has no maximum dose, HIFU can be repeated as needed.

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

In 2015 FDA approved two high-intensity focused ultrasound devices for use in the prostate: Sonablate® 450 (SonaCare Medical, LLC) and Ablatherm® (Maple Leaf; Toronto, Canada).

Device & Manufacturer	Indications for Use
Sonablate® 450 (SonaCare Medical, LLC)[4]	The Sonablate® is indicated for transrectal high intensity focused ultrasound (HIFU) ablation of prostatic tissue.
Ablatherm® (Maple Leaf; Toronto, Canada)[5]	The Ablatherm® Integrated Imaging device is indicated for transrectal high intensity focused ultrasound ablation of prostate tissue.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of high-intensity focused ultrasound (HIFU) for treatment of prostate cancer. Below is a summary of the available evidence identified through July 2023.

High-Intensity Focused Ultrasound for Primary Treatment of Localized Prostate Cancer

In 2022, Hayes published an evidence review that evaluated ultrasound-guided high-intensity focused ultrasound (HIFU) for primary treatment of localized prostate cancer.[6] The literature review identified 19 nonrandomized uncontrolled studies (12 nonrandomized comparative studies included 6 prospective comparative cohort studies, 5 retrospective comparative cohort studies, and 1 retrospective matched-pair analysis) as eligible for inclusion. Sample sizes ranged from 40 to 1002 patients and follow-up times varied from 6 months to 43 months for comparative studies and 47 to 120 months for noncomparative studies. Outcomes of interest included serum prostate specific antigen (PSA), negative prostate biopsy rate, prostate cancer survival, disease-free survival (DFS), recurrence, postoperative urinary and sexual function, quality of life, prostate cancer mortality, and treatment related complications.

Evidence regarding the effectiveness of HIFU for primary treatment of localized prostate cancer was limited and, "(n)one of the comparative studies evaluated the efficacy and safety of HIFU compared with standard radical prostatectomy, external beam radiotherapy (EBRT), or active surveillance—therapies

that are considered usual care for patients with localized, early-stage prostate cancer. No randomized controlled trials evaluating HIFU for prostate cancer were identified in the literature searches."[6]

Summary of Outcomes in Comparative Studies

Outcome	Evidence
Postoperative PSA	• Mixed results: ○ In 4 studies, PSA was significantly lower for HIFU; however, in 4 other studies HIFU had similar efficacy for reducing PSA as its comparator.
Negative Prostate Biopsy Rate	• Results do not favor HIFU: ○ In 2 studies, the negative prostate biopsy rate was significantly higher for HIFU; however, there was no difference in rates between HIFU and comparator groups in 4 other studies.
Disease-free Survival Rate	• Mixed results: ○ The rate was significantly higher for HIFU plus ADT (androgen depravation therapy) versus HIFU alone (78.0% versus 53.8%) and for HIFU with prostatic compression versus HIFU alone (92.6% versus 76.5%) in 2 studies. Whole-gland versus focal HIFU was similar in efficacy in 2 studies.
Recurrence-free Survival Rate	• Results do not favor HIFU: ○ The rate was significantly lower for HIFU relative to brachytherapy in 1 study; however, rates did not differ between HIFU and other therapies in 3 other studies.
Prostate Cancer-Specific Survival	• Similar results ○ HIFU and brachytherapy had similar outcomes in 1 comparative study.
Overall Survival Rate	• Similar results ○ HIFU and brachytherapy had similar outcomes in 1 comparative study.
Biochemical Recurrence	• Similar results ○ In 2 studies there was no significant difference between HIFU and comparator therapies.
Prostate Cancer Mortality	• Similar results ○ Rates were very low (0% to 0.4%) and similar for HIFU and the comparator therapy in 5 studies.
Urinary Incontinence	• Similar results ○ Postoperative rates were similar after HIFU and comparator therapies in 7 studies.
Prostate and Urinary Symptoms	• Mixed results: ○ Reflecting differences in early and late effects between HIFU and its comparators in 7 studies.
Sexual Function and Erectile Dysfunction	• Similar results

	○ Outcomes were similar in 7 studies between HIFU and its comparator; 6 studies compared variations of HIFU and 1 study compared HIFU with brachytherapy.

Overall, HIFU was relatively safe with no major treatment-related complications or deaths reported for HIFU or its comparators. The overall quality of evidence was determined to be low due to individual study limitations and the absence of well-designed, randomized controlled trials. Individual factors that contributed to the low quality of evidence include that lack of randomization, the lack of control or comparator groups, retrospective analyses, small or unequal sample sizes between groups, lack of statistical analysis for some outcomes, and lack of blinded assessment of results in most studies.

The Hayes review concluded that, "additional, well-designed studies are needed to further compare HIFU for localized prostate cancer with alternative and established therapies before a determination can be made as to its long-term safety and effectiveness, particularly with regard to survival and prostate cancer mortality."[6] The following rating was assigned:

- ○ C (potential but unproven benefit): For use of ultrasound-guided high-intensity focused ultrasound (HIFU) for treatment of localized prostate cancer.

High-Intensity Focused Ultrasound for Salvage Therapy of Recurrent Prostate Cancer

- In 2021 (archived 2022), Hayes published an evidence review that evaluated high-intensity focused ultrasound (HIFU) for salvage therapy of recurrent prostate cancer.[7] The literature review identified 14 studies (1 retrospective comparative study and 13 noncomparative studies) as eligible for inclusion. All studies involved patients with prostate cancer recurrence following primary external beam radiation therapy (EBRT)(12 studies) or radical prostatectomy (RP)(2 studies). Sample sizes ranged from 19 to 418 patients and follow-up times varied from 14 to 53 months. Outcome measures included serum prostate specific antigen (PSA), negative prostate biopsy rate, disease-free survival (DFS), prostate cancer-specific survival, overall survival, recurrence-free survival, recurrence, treatment-related complications, and quality of life.

  Evidence evaluating the effectiveness of HIFU for salvage treatment of localized, recurrent prostate cancer is limited and of poor quality.

  Salvage HIFU for Recurrent Prostate Cancer Following EBRT

Outcome	Evidence
Treatment Failure	Rates ranged from 33% to 60.9%.
Serum PSA Level	Mean serum PSA levels post-HIFU were consistently lower than baseline.
Negative Biopsy	Rates ranged from 73% to 83%.
Overall Survival	Rates ranged from 52% to 100%.
Prostate Cancer Mortality	Rates ranged from 2.7% to 10%.
Recurrence	Rates range from 31.1% to 70%.
Prostate and Urinary Symptoms	• In the one comparative study, salvage HIFU resulted in lower rates of morbidity

	compared with cryoablation. In noncomparative studies, urinary incontinence ranged from 20% to 49% and lower urinary tract symptoms ranged from 1.4% to 76.5%. • In general, prostate symptoms increased following HIFU.
Sexual Function and Erectile Dysfunction	In general, there was a decline in sexual and erectile function from baseline.

Salvage HIFU for Recurrent Prostate Cancer Following RP

Outcome	Evidence
Treatment Failure	Rates ranged from 10.5% at 3 months to 47% to 54.5% at later follow-ups.
Disease Free Survival	Only one study reported. Rate of 47.4%.
Prostate Cancer Mortality	Only one study reported. Rate of 0%.
Prostate and Urinary Symptoms	Urinary incontinence rates were 21% and 22% and urinary retention rates were 4.5% and 10.5%.
Sexual Function and Erectile Dysfunction	In 1 study, 28.5% of patients with an International Index of Erectile Function (IIEF) score ≥ 20 before HIFU reported erectile dysfunction after HIFU salvage therapy.

Overall, HIFU for salvage therapy was relatively safe with no major treatment-related complications or deaths reported. The overall quality of evidence was determined to be low (HIFU following EBRT) or very low (HIFU following RP) due to individual study limitations and the absence of well-designed, randomized controlled trials. Individual factors that contributed to the low quality of evidence include lack of randomization, lack of control or comparator groups, retrospective design, small sample sizes, lack of statistical analysis, loss to follow-up, and lack of blinding.

The Hayes review concluded, "(a)dditional, well-designed studies are needed to further compare HIFU for localized, recurrent prostate cancer with alternative and established salvage therapies before a determination can be made as to its long-term safety and effectiveness, particularly with regard to prostate cancer recurrence and mortality."[7] The following ratings were assigned:

- C (potential but unproven benefit): For use of ultrasound-guided high-intensity focused ultrasound (HIFU) for salvage therapy of localized, recurrent prostate cancer in patients with no signs of metastatic disease who were treated with primary external beam radiotherapy.
- D2 (insufficient evidence): For use of ultrasound-guided HIFU for salvage therapy of localized, recurrent prostate cancer in patients with no signs of metastatic disease who were treated with primary radical prostatectomy.

- In 2020, Ingrosso and colleagues published a systematic review and meta-analysis on nonsurgical salvage local therapies for radio-recurrent prostate cancer.[8] The review investigated

re-irradiation with brachytherapy, external beam radiotherapy (EBRT), HIFU, and cryotherapy. Sixty-four case series were included, totalling 5585 patients. Patients treated with HIFU had the lowest biochemical control rates at 58% (95% CI: 47-68%) and patients treated with brachytherapy and EBRT had the highest at 69% (95% CI: 62-76%) and 69% (95% CI: 53-83%), respectively. Patients treated with HIFU were also found to have the highest prevalence of incontinence (28%; 95% CI: 19-38%; I^2= 89.7%). The authors noted limitations of the review included retrospective, case series study design, limited follow-up for the majority of the studies, and high risk of bias. They concluded that nonsurgical therapeutic options, especially brachytherapy, showed good outcomes and tolerability in the local recurrence setting for individuals with prostate cancer.

- In 2020, Khoo and colleagues published a systematic review of salvage focal therapies for localized, non-metastatic radiorecurrent prostate cancer. Fifteen studies were included in the review, consisting of 14 case series and 1 comparative study.[9] Similar to Ingrosso et al (2020), salvage brachytherapy showed the most beneficial outcomes, with a biochemical disease-free survival rate ranging from 61% to 71.4% at 3 years, compared to a 48% rate after salvage HIFU. Others note great variability and heterogeneity across studies in demographics, follow up, and sample sizes. They conclude that salvage focal ablation of radiorecurrent prostate cancer may provide acceptable outcomes and tolerability, but high level research comparing salvage focal therapies to existing whole-gland strategies is needed to determine efficacy and safety.

CLINICAL PRACTICE GUIDELINES

The American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology (AUA/ASTRO/SUO)

The 2017 AUA/ASTRO/SUO evidence-based clinical practice guideline for localized prostate cancer gave the following recommendations regarding HIFU:

- "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.
- 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)
    - As most men with low-risk disease have favorable outcomes with active surveillance, it is unclear whether focal therapy or HIFU improve survival outcomes or provide comparable QoL as the preferred management for most low-risk men. Prospective randomized or comparative trials of HIFU with active surveillance or other treatment modalities are lacking. Published five year oncologic outcomes are variable and attributable to the lack of consensus on objective response criteria. 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 low-risk prostate cancer.
- 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)

    - The Panel recognizes that novel therapies including HIFU and focal prostate ablation may provide QoL advantages for patients in comparison to surgery and radiotherapy. However, there are no prospective randomized or comparative effectiveness data versus traditional treatments available. Published five year oncologic outcomes for HIFU are variable and attributable to the lack of consensus on objective response criteria. The Panel awaits the results of well-designed comparative clinical trials of HIFU in order to define the appropriate role of this technology in the management of intermediate risk prostate cancer.
- Panel recommends that if focal therapy or HIFU is offered as an alternative treatment modality for intermediate risk prostate cancer, it should preferably be offered within the context of a clinical trial.
- Cryosurgery, focal therapy and HIFU treatments are not recommended for men with **high-risk** localized prostate cancer outside of a clinical trial. (Expert Opinion)
- 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)"[1]

National Comprehensive Cancer Network

The NCCN guidelines for prostate cancer (v 1.2023) recommend HIFU for patients with prostate-specific antigen (PSA) persistence/recurrence after radiation therapy who are TRUS biopsy positive with studies negative for distant metastases (2B recommendation- lower-level evidence).[10]

The NCCN guidelines for pancreatic adenocarcinoma (v 1.2023) recommended HIFU for pain palliation in patients with pancreatic adenocarcinoma in patients with either severe tumor-associate abdominal pain unresponsive to optimal, around-the-clock analgesic administration; or undesirable analgesic-associated side effects.[11]

American College of Radiology

In 2016, ACR published appropriateness criteria for locally advanced, high-risk prostate cancer stated, "(a)blative treatments including cryotherapy and high-intensity focused ultrasound (HIFU) are other options available for men with high-risk prostate cancer, though data are limited for these modalities… The results of HIFU are similar to those of cryotherapy… The morbidity of HIFU is considerable, with rates of urinary obstruction up to 24% and impotency in previously potent men of 45%."[12]

National Institute for Health and Care Excellence (NICE)

In 2023, the NICE published guidelines on focal therapy using high-intensity focused ultrasound for localized prostate cancer, diagnosis and treatment.[13] NICE stated that evidence on the safety of focal therapy using high-intensity focused ultrasound for localized prostate cancer is adequate, but evidence on its efficacy is limited, recommending that the procedure should only be used with special arrangements for clinical governance, consent, and audit or research.

EVIDENCE SUMMARY

Low-quality evidence supports the efficacy and safety of high intensity focused ultrasound (HIFU) compared to other established therapies for prostate cancer. Additional long-term studies of good methodological quality are required to establish the clinical utility and safety of this treatment. Clinical practice guidelines including the NCCN recommends HIFU for select patient populations. For these reasons, HIFU may be considered medically necessary for the treatment of prostate cancer as well as pain palliation in patients with pancreatic adenocarcinoma.

BILLING GUIDELINES AND CODING

CODES*		
CPT	55880	Ablation of malignant prostate tissue, transrectal, with high intensity-focused ultrasound (HIFU), including ultrasound guidance
	55899	Unlisted procedure, male genital system

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
11/2023	Changed denial type to “not medically necessary.” Added medical necessity criteria for pancreatic adenocarcinoma. Policy title change to reflect broadened scope.