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

- In 2017 (updated 2020), Hayes published an evidence review that evaluated high-intensity focused ultrasound (HIFU) for salvage therapy of recurrent prostate cancer.[4] 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."[4] 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.[5] 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.[6] 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 (v2.2021) 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).[7]

American College of Radiology

The 1996 (updated 2016) ACR 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%."[16]

National Institute for Health and Care Excellence (NICE)

The 2014 (updated in 2019), NICE published guidelines on Prostate Cancer, diagnosis and treatment. For local prostate cancer, NICE gives the following recommendation: "Do not offer high-intensity focused ultrasound and cryotherapy to men with localised prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions… There is insufficient evidence of the clinical and cost effectiveness of cryotherapy and HIFU in comparison to established interventions to recommend their routine use."[17]

POLICY SUMMARY

The available evidence does not support the long-term 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. Additionally, the December 2017 AAU/ASTRO/SUO evidence-based guideline for prostate cancer recommends HIFU only be used in the context of a clinical trial and that additional prospective randomized studies are needed. Although the NCCN recommends HIFU, this recommendation is based on a very weak and poor quality body of evidence. All eight studies referenced in the NCCN recommendation were nonrandomized studies encompassing small sample sizes and short follow-up

periods (< 4 years). For these reasons, HIFU is considered investigational for the treatment of prostate cancer.

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 Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

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.

REGULATORY STATUS

Mental Health Parity Statement

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.

U.S. Food and Drug Administration (FDA)

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)[19]	The Sonablate® is indicated for transrectal high intensity focused ultrasound (HIFU) ablation of prostatic tissue.
Ablatherm® (Maple Leaf; Toronto, Canada)[20]	The Ablatherm® Integrated Imaging device is indicated for transrectal high intensity focused ultrasound ablation of prostate tissue.

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