INFORMATION BRIEF (RAPID REVIEW)

HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) FOR PROSTATE CANCER

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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Rapid Review

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590, Putrajaya
Tel: 603 8883 1229

Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my

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TITLE: High Intensity Focused Ultrasound (HIFU) for prostate cancer

PURPOSE

To provide scientific evidence on the effectiveness and safety of HIFU treatment for patients with prostate cancer. This review was conducted upon request by a Urologist from Hospital Raja Permaisuri Bainun, Ipoh, Perak in view of using HIFU for patients with prostate cancer.

BACKGROUND

Prostate cancer is the fourth common cancer globally at 7.3% accounting for 1.4 million new cases in 2020 and the third common cancer in Malaysia, with prevalence of 1 in every 117 men.[1,2] Lim J. et al (2021) reported that in Malaysia, the patients were treated by radical prostatectomy, radiotherapy, androgen deprivation therapy (ADT), chemotherapy, and active surveillance or watchful waiting. Radiation therapy and radical prostatectomy are the two most common therapies for prostate cancer, however they have drawbacks, such as the potential for intraoperative bleeding or radiation damage to the surrounding tissues, and inconsistent results.[4]

High Intensity Focused Ultrasound (HIFU) is a non-invasive treatment which uses a high-intensity ultrasound sound wave on the damaged tissue. It heats up the malignant tissues between 65 to 100°C causing the annihilation of the tissue through coagulative necrosis.[3,4] He Y. et al (2020) pointed out the advantages of HIFU:-

i. It allows real-time monitoring by ultrasound during the procedure.
ii. It can be utilised to assess the margin of necrosis using contrast-enhanced ultrasonography immediately postoperatively.
iii. It can be performed multiple times if required.

MRI or ultrasound imaging is frequently used in conjunction with HIFU operations to plan the therapy and track the patient's progress in real time.[5]

EVIDENCE SUMMARY

Previously, there were three (3) Technology Review (TR) reports produced by Malaysian Health Technology Assessment Section (MaHTAS) on HIFU; which focused on the treatment of solid tumours, namely hepatocellular carcinoma, pancreatic cancer and uterine fibroids. The latest TR on HIFU for [redacted], [redacted] reported that HIFU is recommended for research purpose, which requires more high-quality evidence prior its usage as standard treatment for solid tumours. Later, there were two (2) Information Brief prepared on HIFU that focused on gynaecological disorders (breast fibroadenoma, uterine fibroid, endometriosis, adenomyosis) and thyroid nodule. In these two reports, HIFU is found to be safe for uterine fibroid, however, more high-level evidence is required to support the effectiveness and safety of HIFU against breast fibroadenoma, thyroid nodules, adenomyosis and endometriosis.[3,5]

A total of **30** relevant articles titles were retrieved from the scientific databases such as Ovid Medline and general search engines using the following search terms: *prostate cancer, high intensity focused ultrasound, HIFU, prostatic neoplasm, High-Intensity Focused Ultrasound Ablation, Prostatic Hyperplasia*.

EFFICACY/ EFFECTIVENESS

In a systematic review (SR) by Maestroni U et al. (2021), they intended to evaluate the safety and cancer control rates of HIFU following failure of External Beam Radiation Therapy (EBRT) in the treatment of localised prostate cancer. The review included 13 studies involving 1241 patients with localised prostate cancer. It was reported that 38.3% of patients were treated with androgen-deprivation therapy (ADT) at the time of application of HIFU, whereas 24.71% continued with the therapy after the treatment. The PSA nadir level prior to the treatment with HIFU were in between 0 to 62 ng/ml; mean of 5.87 ng/ml; median of 6.7 ng/ml and a SD of ± 5.52. After the treatment with HIFU, the PSA nadir was 1.1 ng/ml (SD of ± 3.39), however it was unclear when the level reached. The authors however emphasised that there were limitations to this study as majority were of retrospective studies and the heterogeneity of the data collected, as well as there were discrepancies in the definition of recurrence. It was concluded that HIFU is effective for clinically localised prostate cancer; supported by 82.5% overall survival throughout 5 years. The author suggested due to lack of robust data, it is advisable that the outcomes have to be supported by large, multicentric and well-designed study.[7]

A systematic review and meta-analysis by Pan Y et al. (2022) reported the oncologic and functional outcomes of combining HIFU with transurethral resection of the prostate (TURP) involving 1861 patients in 15 studies. All studies reported the PSA nadir and the time to PSA nadir post procedure, which ranged between 0.20 to 1.90 ng/ml for an average time of 1.9 to 12 months. There were 11 studies reported positive biopsy ranging from 3% to 29.7% with an average time of 3 to 12 months. Based on functional outcomes, it was reported the pooled rate of urinary incontinence was 4.6%, potency was 43.6%, acute urinary retention 0.9%, urinary tract infections at 1.3% and urethral stricture at 1.4%. The authors concluded that the combination of HIFU and TURP may provide significant outcomes.[8]

Bakavicius A et al. (2022) in another systematic review focused on focal HIFU therapy as the primary therapy for localised prostate cancer patients that has not been treated with other forms of therapy. Twenty studies were included in the review involving 4209 patients treated with focal HIFU. Based on the oncological outcomes, ten studies reported that median time to reach PSA nadir varied between three to 12 months with median PSA reduction ranged between 53 to 84%. Apart from that, the clinically significant in-field recurrence and out of field progression were reported in between 5 to 22% and 2 to 29%, respectively. From the similar literature, the functional outcome of urinary function was reported at the range of 86 to 98% for the first 6 months, while complete continence is achieved between 93 to 97% a year after the procedure. Around 69 to 80% of patients retained sufficient erections during intercourse 6 months after the procedure with slight improvement of the function after two years. Complications were reported to be minor among 80 to 100% patients that does not requires any surgical intervention, such as acute urinary retention, urethral sloughing and urinary tract infection.[9]

A systematic review by He Y et al. (2020) evaluated the evidence on oncological and functional outcomes among localised prostate cancer patients treated using HIFU. The review included 27 articles involving 7393 patients focused on the efficacy and side effects of HIFU as primary treatment. There were 18 studies on whole-gland HIFU treatment, whereas 9 remaining studies were those on treatment with partial-gland HIFU. The overall survival outcomes for whole-gland HIFU based on overall survival (OS) rate ranged between 90 – 100%, whereas for partial-gland HIFU ranged between 97 – 100%. They found the metastasis-free survival rate after whole-gland and partial-gland HIFU for 5 years are 98.4% and 93% respectively. According to the findings, partial-gland ablation is safer than whole-gland ablation, with oncological outcomes remain unaffected. Despite that, given the lack of randomisation in comparing both whole-gland and partial-gland HIFU, more RCTs are required to examine the advantages of HIFU. In terms of urinary incontinence, they found the incidence was 0.1 (95% CI 0.06 to 0.14) for whole-gland HIFU and 0.02 (95% CI 0.01 to 0.03) for partial-gland HIFU. Meanwhile, for the incidences of impotence were at 0.44 (95% CI 0.35 to 0.52) and 0.21 (95% CI 0.14 to 0.29) for whole-gland and partial-gland HIFU, respectively. It was also pointed out that both incidences (urinary incontinence and impotence) were lower than a recent, prospective, controlled, non-randomized controlled trial (RCT) that used robot-assisted laparoscopic prostatectomy (RALP) or retropubic prostatectomy.[4]

A prospective observational study by Yee CH et al. (2021) was conducted to compare the fusion treatment of HIFU with MRI-US Fusion Platform and conventional HIFU in Hong Kong. In this study, 20 patients were subjected to focal or quadrant ablation. At 6-month multi parametric MRI post HIFU, it showed that mean percentage drop of PSA was 44.6% and 63.3% in the fusion and conventional group, respectively. During the same period, it was reported that no suspicious lesion observed for all the patients. Apart from that, there was no issue of incontinence reported among the patients for both treatments.[10] The authors concluded that there was a considerable decrease in PSA and prostatic health index (PHI) as well as an early tumour clearance on MRI scan following HIFU focused therapy for prostate cancer patients. Even though the MRI-US fusion platform for HIFU focused therapy provided clearer view of the lesion, more research is required to determine the benefits of the technique.[10]

A retrospective study conducted by Hong and Lee (2022) included data of 163 patients with clinically unilateral prostate cancer treated with partial gland ablation using HIFU with concurrent TURP in Seoul National University Bundang, South Korea. They found there was no significant difference in the PSA level preoperatively and post-HIFU biopsy. At the postoperative one year follow up biopsy, there were 75.8% and 87.4% patients free of any cancer (regardless cancer grade) and clinically significant cancer (grade group $\geq$ 2), respectively. Out of 163 patients, only four experienced postoperative incontinence. However, the author suggested a larger study is required due to limitations such as possibility of selection / recall bias due to absence of control arm, under estimation of actual patients with remnant disease, shorter follow up. It was concluded that further prospective randomised study is required for better apprehension on the functional and oncological outcomes of the treatment.[6]

SAFETY

As of today, there are two HIFU devices are registered with Malaysia Medical Device Authority (MDA) and allowed to be marketed by United States Food and Drug Administration (US FDA) for the indication of prostate tissue ablation, which are [redacted] and [redacted]. [redacted] is also licensed under Australian Therapeutic Goods Administration (TGA) for the indication of treatment of prostate cancer.[12-14]

COST-EFFECTIVENESS

Benard A et al. (2019) conducted a cost-effectiveness analysis comparing focal HIFU and active surveillance among low- and intermediate-risk prostate cancer from the perspective of the French National Health Insurance using the application of Markov multi-state model. It was reported focal HIFU cost an extra of € 207 520 and yielded 382 less quality-adjusted life years (QALY) than active surveillance (AS) based on fictive cohort of 1000 individuals, which means HIFU is more costly and less effective. Due to lack of comparative evidence between HIFU and AS, there was high uncertainty of the results.[11]

CONCLUSION

Based on the above review, HIFU treatment for localised prostate cancer following failure of EBRT reported significant overall survival after 5 years. Significant functional and oncological outcomes were reported for patients treated by either whole- or partial-gland HIFU. HIFU with combination of TURP may also provide significant outcome in the treatment of prostate cancer. HIFU appeared safe with minor complication without mortality. There are two HIFU devices were registered with Malaysia MDA and has obtained US FDA approval [redacted], [redacted]). However, most evidence retrieved provided short term outcome up to one year with limited evidence retrieved on comparator. Hence, more high-quality studies are needed to ascertain the long-term outcomes of HIFU in treatment of localised prostate cancer. In terms of cost-effectiveness, it was suggested that the focal HIFU is not cost effective against active surveillance.

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Prepared by

Nurul Nashriq Md Hamsin
Pharmacist
Senior Principal Assistant Director
Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia

Reviewed by

Dr. Roza Sarimin
Public Health Physician
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Izzuna Mudla Mohamed Ghazali
Public Health Physician
Deputy Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

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