Holmium laser enucleation of the prostate followed by high-intensity focused ultrasound treatment for patients with huge prostate adenoma and localized prostate cancer: 5-Year follow-up

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Background: To evaluate the efficacy of holmium laser enucleation of the prostate (HoLEP) followed by high-intensity focused ultrasound (HIFU) for patients with huge prostate adenoma and localized prostate cancer (CaP) and compare the morbidity and efficacy results with those observed in a similar population treated only with HIFU for a follow-up period of up to 5 years.

Methods: The present retrospective study included 30 CaP patients who underwent HIFU alone and 10 patients who underwent HoLEP followed by HIFU. Selection criteria for this study were no previous treatment for CaP, aged 60 years or older, cT1c-T2N0M0, prostate volume of 30 mL or more, and a follow-up period of 5 years or more. Prostate-specific antigen (PSA) biochemical recurrence-free survival (RFS) rates and functional outcomes including complications and urodynamics after HIFU were compared between the HIFU monotherapy and HoLEP + HIFU groups.

Results: The enrolled patients had a mean age of 70.3 years and 68.8 years in the HIFU monotherapy and HoLEP + HIFU groups, respectively. The 5-year PSA biochemical RFS rates of the two groups were similar (HIFU monotherapy group: 57.2%; HoLEP + HIFU group: 67.5%). The duration of indwelling urethral catheter after HIFU significantly decreased in the HoLEP + HIFU group compared with the HIFU monotherapy group (15.5 ± 2.7 days vs. 27.5 ± 3.8 days, P = 0.022). In terms of functional outcomes, patients who received HoLEP + HIFU had significantly higher maximum (12 months: P = 0.015, 36 months: P = 0.014) and average (36 months: P = 0.002, 60 months: P = 0.047) flow rates than those who received HIFU monotherapy. The frequency of urethral stricture (13.3% vs. 0%), symptomatic urinary tract infection (10.0% vs. 0%), and bladder stone and urethrectal fistula (3.3% vs. 0%) tended to be higher in the HIFU monotherapy group as compared with the HoLEP + HIFU group.

Conclusion: The HoLEP + HIFU treatment decreases urinary catheterization time and improves post-treatment urinary status without additional morbidity.

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TURP continues to be refined. Consequently, TURP will soon be relegated to the past. Moreover, even in combination with TURP, 8% of cases needed additional deobstruction procedure. We therefore evaluated the efficacy of HoLEP followed by HIFU for patients with huge prostate adenoma and localized CaP and compared the morbidity and efficacy results with those observed in a similar population treated only with HIFU for a follow-up period of up to 5 years.

2. Materials and methods

2.1. Patients

We included patients with huge prostate adenoma and localized CaP who underwent HoLEP followed by a single HIFU session from November 2006 to April 2010 in this retrospective study. The selection criteria for this study were age older than 60 years, cT1c-T2N0M0, prostate volume of ≥ 30 mL, and follow-up periods of > 5 years. All patients were either unsuitable for radical prostatectomy because of comorbidities or preferred HIFU treatment over surgery or radiation therapy. All patients provided written informed consent before entering the study. We selected patients who underwent only single session of HIFU monotherapy with a prostate volume of over 30 mL as the control group. All patients in both groups underwent a prostate biopsy including more than 14 cores. None of the patients who received androgen-deprivation therapy before the HoLEP and HIFU was selected for treatment and analysis.

2.2. HoLEP treatment

A 26-Fr Storz endoscope (KARL STORZ Inc., Tuttingen, Germany) with a continuous saline irrigation system equipped with a device for fixing the 550-μm fiber was used. A pulsed, high-powered holmium neodymium:yttrium—aluminum garnet laser beam was generated by Versa Pulse Select 80 (Lumenis Inc., San Jose, CA, USA). Transurethral mechanical morcellation was performed.

2.3. HIFU treatment

All patients received HIFU treatment using the Sonablate® under general anesthesia. Patients were placed in the supine position with their legs apart to receive transrectal HIFU. Treatment was performed using a transrectal probe including a 4-MHz piezoelectric treatment transducer and a 4-MHz ultrasound imaging probe. Contiguous HIFU shots were delivered 1.8 mm apart with a 4-second shot duration and a 12-second interval between shots. Treatment volume was determined by the urologist, who used a longitudinal and transverse ultrasound imaging system. The patients were discharged the day following HIFU.

2.4. Follow-up

During the follow-up period, prostate-specific antigen (PSA) was measured every 6 months for 5 years. Serum PSA was analyzed with the chemiluminescent enzyme-linked immunoassay (normal range ≤ 4 ng/mL). We used two PSA biochemical failure definitions: (1) the ASTRO II “Phoenix” biochemical failure-free survival 2006 consensus definition of a PSA increase of 2 ng/mL above the nadir PSA, and (2) the Stuttgart definition of a PSA increase of 1.2 ng/mL above the nadir PSA. Distributions of PSA biochemical recurrence-free survival (RFS) rates were calculated according to the Kaplan–Meier curves, and the log-rank test were used to determine the differences between the curves. The risk classification was based on that reported by D’Amico et al. “Low risk” was defined as clinical T stages T1c and T2a, Gleason score of ≤ 6, and PSA < 10 ng/mL. Conversely, patients with clinical stage T2c disease or a PSA > 20 ng/mL or a biopsy Gleason score of ≥ 8 were identified to be in a “high-risk group.” The remaining patients with PSA levels > 10 ng/mL but < 20 ng/mL, a biopsy Gleason score of 7, or clinical stage T2b were identified to be at “intermediate risk.”

We recorded medical information, including adverse events exceeding Grade 3, according to The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Uroflowmetry was performed at 1 year, 3 years, and 5 years after HIFU.

2.5. Statistical analysis

Paired t test and Fisher’s exact test were used to compare quantitative and categorical variables, respectively. All P values < 0.05 reflected statistically significant differences.

3. Results

3.1. Patient characteristics

Table 1 summarizes the baseline clinical characteristics of the patients. We included 30 patients in the HIFU monotherapy group and 10 patients in the HoLEP + HIFU group. There were no significant differences in age, prostate volume, initial PSA, clinical T stage, Gleason score, or D’Amico et al’s risk stratification between groups. Although we consider that low-risk disease is the best candidate for HIFU, because of the retrospective nature of this study, we were compelled to include patients with intermediate or high risk as well. These patients had a preference for HIFU because they were older than 80 years and had severe comorbidities including thrombosis, which required continuous treatment with antiplatelet drugs. The HIFU operation and ablation time in the HoLEP + HIFU group were significantly shorter than in the HIFU.
monotherapy group (HIFU operation time: \( P = 0.002 \); HIFU ablation time: \( P = 0.030 \), Table 1). The mean duration between HoLEP and HIFU in the HoLEP + HIFU group was 96.5 days.

3.2. Oncological results

Pathological findings of all HoLEP specimens showed benign disease. Compared with the HIFU monotherapy group, PSA levels drastically decreased significantly in the HoLEP + HIFU group after HIFU (at 6 months, \( P = 0.009 \); at 12 months, \( P = 0.030 \); at 24 months, \( P = 0.046 \); at 36 months, \( P = 0.040 \); and at 60 months, \( P = 0.027 \); Fig. 1). Although there were no significant differences in time to PSA nadir (\( P = 0.171 \)), PSA nadir in the HoLEP + HIFU group (median, 0.003 ng/mL) was significantly lower than in the HIFU monotherapy group (median, 0.014 ng/mL, \( P = 0.033 \)). The 5-year PSA biochemical RFS rates according to the Phoenix ASTRO definition in the HIFU monotherapy and HoLEP + HIFU groups were 57.2% and 67.5%, respectively (Fig. 2A). The 5-year PSA biochemical RFS rates according to the Stuttgart definition in the HIFU monotherapy and HoLEP + HIFU groups were 48.8% and 67.5%, respectively (Fig. 2B). No significant differences in the 5-year PSA biochemical RFS rates between both groups were noted using the Phoenix ASTRO (\( P = 0.618 \)) or the Stuttgart definition (\( P = 0.297 \)). There were no significant differences in PSA biochemical RFS rates between the HIFU monotherapy and HoLEP + HIFU groups (Table 2) in any of the D’Amico et al. risk groups. In the HIFU monotherapy group, five patients progressed to require further treatment. By contrast, no patient in the HoLEP + HIFU group needed any adjuvant treatment. At the time this study was undertaken, no patient had lymphatic or distant metastasis.

3.3. Functional results

No patient in either group complained of more than Grade 3 incontinence (as defined by CTCAE version 4.0). The duration of indwelling urethral catheter after HIFU significantly decreased in the HoLEP + HIFU group compared with the HIFU monotherapy group (15.5 \( \pm \) 2.7 days vs. 27.5 \( \pm \) 2.3 days, \( P = 0.022 \); Table 3). In terms of uroflowmetry, maximum \( (Q_{\text{max}}) \) (12 months, \( P = 0.015 \); 36 months, \( P = 0.014 \), and average flow rates \( (Q_{\text{ave}}) \) (36 months, \( P = 0.002 \); 60 months, \( P = 0.047 \) in the HoLEP + HIFU group were significantly higher than those in the HIFU monotherapy group (Fig. 3). The frequency of urethral stricture, symptomatic urinary tract infection, and bladder stone and urethrorectal fistula tended to be higher in the HIFU monotherapy group as compared with the HoLEP + HIFU group, although statistically nonsignificant (Table 3). Transient urinary retention due to urethral stricture was noted in four patients (13.3%) in the HIFU monotherapy group who received TURP.

4. Discussion

Although the number of patients included in this study was very small, we could show that HoLEP prior to HIFU can decrease adverse events for patients with HIFU. One of the main drawbacks of HIFU is the need for prolonged indwelling urethral catheterization following HIFU. Because of HIFU-related edema, patients underwent urethral catheterization for 2–3 weeks following the procedure.3 Generally speaking, this catheterization may be a frequent cause of urethral stricture, urinary tract infection, bladder stone, and similar complications. Considering that previously reported HIFU caused high incidences of urinary stricture, many HIFU specialists have reported new concepts and methodologies to decrease the duration of indwelling catheterization.4 TURP is now becoming the standard procedure. The combination of HIFU and TURP reduces postoperative sloughing of urethral tissue, thereby achieving improvement in urination after HIFU.10 Many notable groups have performed TURP as a fixed protocol.11,12 It may be performed before or immediately after the HIFU procedure. The time when TURP was the gold standard for BPH is now long past. As technology has advanced, BPH treatment has expanded past TURP to HoLEP, which enables the immediate relief of bladder outlet obstruction and produces an excellent outcome in terms of feasibility, safety, and efficacy. The favorable hemostatic characteristics of the holmium procedure have significantly shortened median catheterization time and median postoperative hospital stay.13

We could show that the indwelling urethral catheterization period after HIFU was significantly decreased in the HoLEP + HIFU group compared with the HIFU monotherapy group in this study. Although not statistically significant, no patient with HoLEP + HIFU experienced urinary retention due to urethral stricture in the HoLEP + HIFU group compared with four cases (13.3%) in the HIFU monotherapy group. Previous reports indicated that the frequency of urethral stricture was 4–24.6% after HIFU.14–15 Therefore, it is safe to say that HoLEP followed by HIFU could decrease the periods of indwelling urethral catheterization after HIFU, and consequently decrease the frequency of urethral stricture. In addition, in many

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**Fig. 1.** Comparison of PSA levels after HIFU between the HIFU and HoLEP + HIFU groups. PSA levels after HIFU in the HoLEP + HIFU group were generally significantly lower than in the HIFU monotherapy group. \( P < 0.05 \). HIFU, high-intensity focused ultrasound; HoLEP, holmium laser enucleation of the prostate; PSA, prostate-specific antigen.
In this study, however, the HoLEP + HIFU procedure never required cystostomy. The combination of HoLEP before HIFU had more advantages. HoLEP allows removal of calcifications of the transitional zone that would otherwise preclude HIFU treatment. It also facilitates treatment of enlarged prostate by reducing the anterior–posterior diameter and allowing complete treatment of the peripheral zone with HIFU in a single session. In the case of TURP, while we must consider the certain frequency of post-TURP bleeding, it is clear that HoLEP has a lower frequency of postoperative bleeding.15

In this study, the 5-year PSA biochemical RFS rates according to the Phoenix ASTRO definition in the HIFU and HoLEP + HIFU groups were 57.2% and 67.5%, respectively, with no statistically significant differences. Previously, it was reported that the overall 5-year PSA biochemical RFS rate of HIFU according to the Phoenix definition was 21.2%.11,13 Because of the small sample size, we could not estimate the exact and appropriate oncological effects of the HoLEP + HIFU treatment. Our study results are clearly superior to previous reports in terms of the PSA biochemical RFS rate (Fig. 2 and Table 2). We therefore consider that our study results revealed equal and effective oncological outcomes for HIFU monotherapy and HoLEP + HIFU therapy. To our knowledge, this is the first report to indicate the efficacy of HoLEP followed by HIFU.

Our methods do have some serious disadvantages. Patients experienced two hospital admissions to undergo HoLEP and HIFU on separate occasions. It would clearly be preferable to decrease the number of operations. Previous paper reported that TURP and HIFU treatments were performed under the same spinal anesthesia.3 We also hope to perform HIFU immediately after HoLEP during a single operation in the future. A second disadvantage is the oncological outcome. We have not confirmed the real effect of HoLEP on CaP. Declines in serum PSA are well-known to occur after HoLEP, but rather due to HoLEP. However, Koguchi et al19 reported a case of dissemination of CaP after HoLEP in an 80-year-old patient. More precise analyses of oncological effects, including longitudinal PSA data, are thus required.

This study had some limitations. First, this was not a randomized trial and the follow-up was admittedly short. Second, no patient received a prostate biopsy after HIFU in this study. We therefore have no pathological data to establish pathological recurrence. As HIFU is a minimally invasive surgery, it seems like a contradiction to evaluate its efficacy by using prostate biopsy with a
maximally invasive technique. In addition, we could not evaluate the cost-effectiveness of adding HoLEP to HIFU. The cost–benefit performance should be analyzed in the future.

In conclusion, HoLEP + HIFU can be considered as a feasible and minimally invasive therapy for localized CaP. Pre–HIFU HoLEP could decrease the duration of indwelling catheterization after HIFU. As a result, it may also be able to decrease the frequency of urethral stricture and UTI. HoLEP + HIFU was equivalent to HIFU mono-therapy with respect to the 5-year efficacy of cancer control. We are still collecting data on more patients to evaluate long-term efficacy.

Conflicts of interest

None declared.

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