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Favorable long-term oncological and urinary outcomes of incidental prostate cancer following holmium laser enucleation of the prostate

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Abstract. The aim of the present study was to investigate the impact of incidental prostate cancer (IPCa), which was diagnosed by holmium laser enucleation of the prostate (HoLEP), on long-term oncological and functional outcomes. A total of 482 patients who underwent HoLEP for benign prostatic hyperplasia (BPH) between 2008 and 2016 at our institution were retrospectively reviewed. We defined IPCa as prostate cancer (PCa) according to the enucleated tissue of transitional zone. Therefore, 64 patients were excluded for the following reasons: Prostate-specific antigen (PSA) ≥4.0 ng/ml and no prostate biopsy (n=46); and PSA ≥4.0 ng/ml and diagnosed with PCa by prostate biopsy performed during HoLEP (n=18). Notably, 418 patients were included in the study and divided into two groups: The BPH group and the IPCa group. For 5 years, postoperative PSA and functional outcomes were evaluated. Of 418 patients, 25 (6%) were diagnosed with IPCa by HoLEP, 21 patients (84%) had a Gleason score ≤6 and 5 patients (20%) received adjuvant therapy for PCa following HoLEP. No significant differences were observed between groups for preoperative PSA, PSA density, or urinary and sexual function outcomes; however, age at the time of HoLEP significantly differed between groups (71.7 vs. 75.5 years, P=0.026). Long-term (5-year) urinary outcomes demonstrated sustained improvement. Postoperative PSA increased gradually in the IPCa group (3-year, P=0.033; 4-year, P=0.037); International Index of Erectile Function 5 conversely decreased (5-year, P=0.068). According to the present results, if standard PSA screening and prostate biopsy are performed, watchful waiting for IPCa is feasible, and IPCa does not impact on 5-year urinary outcomes.

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Introduction

T1a-T1b prostate cancer (PCa) is called incidental prostate cancer (IPCa); cancer found in the specimens of men undergoing surgery for benign prostatic hyperplasia (BPH) (1). The frequency of IPCa diagnosed during surgery for BPH has been decreasing due to preoperative prostate-specific antigen (PSA) screening and prostate biopsy (2,3). The rate of IPCa detected during transurethral resection of the prostate (TURP) and holmium laser enucleation of the prostate (HoLEP) have been reported to be 5.2-6.4 and 5.6-8.1%, respectively (2-8). It has also been proved that there is no difference between HoLEP and open prostatectomy regarding cancer detection rate for large prostates by a matched pair analysis (9). Some reports have shown that risk factors for IPCa include age and PSA density (4-6). Estimated overall survival for IPCa was described by Elkoushy et al 72.8% at 5-years and 63.5% at 10-years (6). However, the clinical significance of IPCa and the necessity for adjuvant treatment remain to be controversial.

Currently, HoLEP is recommended as BPH surgeries, and is commonly performed for BPH patients with lower urinary tract symptoms (LUTs). The favorable long-term outcomes were reported by several studies (10,11). However, few studies have been conducted to evaluate the postoperative functional outcomes of IPCa. Herein, we investigate the impact of IPCa on long-term oncological and functional outcomes.

Materials and methods

After obtaining Institutional Review Board approval, we retrospectively reviewed 482 patients who underwent HoLEP from 2008 to 2016 and for whom sufficient data on pathological

findings and PSA (preoperative and 1-year postoperative) were available. Patients with a known history of PCa before HoLEP were excluded. Staging of T1a/T1b disease was determined according to a volume threshold of 5% cancer involvement in the specimen.

A flow diagram of patients is shown in Fig. 1. We defined IPCa as PCa by enucleated tissue of transitional zone (TZ). Patients who had a possibility of peripheral zone (PZ) PCa were excluded by transrectal prostate biopsy. Forty-six patients were excluded due to a PSA level ≥4.0 mg/ml without performing prostate biopsy. Eighteen patients who were diagnosed with PZ PCa by prostate biopsy preoperatively or during HoLEP were excluded, and 171 patients without malignancy were included in this study. Consequently, 418 patients were classified into two groups: The BPH group (n=393) and the IPCa group (n=25). These two groups were compared.

Patient characteristics and operative and perioperative variables were collected, including prostate volume estimated by transabdominal ultrasonography, enucleated prostate weight, operative time (morcellation time), estimated blood loss, duration of catheterization, and pathological findings. Baseline (preoperative) and follow-up outcomes were compared using the International Prostate Symptoms Score (IPSS), quality of life (QoL) index, International Index of Erectile Function 5 (IIEF-5), maximum flow rate (Qmax), postvoid residual urine volume (PVR), and PSA. The postoperative urinary and sexual function outcomes (IPSS, QoL, IIEF-5, Qmax, and PVR) were evaluated at 3, 6, 12, 24, 36, 48, and 60 months, and PSA was measured at 12, 24, 36, 48, and 60 months. If patients had undergone curative treatment for IPCa during the follow-up period, all post-treatment variables were excluded.

These data were analyzed using the commercially available Statistical Package for Social Science for Windows, version 20.0 (IBM SPSS, Armonk, NY, USA). The two groups were compared using the Mann-Whitney U test. P-value <0.05 was considered to be statistically significant.

Results

On the whole, 38 out of 482 patients (8%) were diagnosed with IPCa. For the patients who had PSA ≥4 ng/ml at the baseline, 25 out of 235 patients (11%) were diagnosed with IPCa. After patient exclusions, a total of 418 patients were enrolled and 25 patients (6%) were diagnosed with IPCa by HoLEP (Table I). Twenty-one of these patients (84%) had Gleason scores of 2+3 or 3+3, and four patients (16%) had a Gleason score of 3+4. Twenty-four patients (96%) and 1 patient (4%) were T1a and T1b, respectively. No patients had metastasis. Five patients (20%) underwent adjuvant curative treatment for PCa, including prostatectomy (n=2), radiotherapy (n=1), and hormonal therapy (n=2). Three patients underwent curative treatment immediately after HoLEP, whereas 2 patients underwent treatment after PSA rising during the follow-up period. In the BPH group, 4 patients were diagnosed with PCa by prostate biopsy because their PSA was elevated after HoLEP. All of them underwent cancer treatment, including prostatectomy (n=3) and hormone therapy (n=1). Patients in the IPCa group were older and had a slightly higher PSA density (mean age 71.7 vs. 75.5 years; P=0.026 and 0.11 vs. 0.13 ng/ml/ml; P=0.077). No significant differences in the other preoperative and operative variables were observed between the two groups.

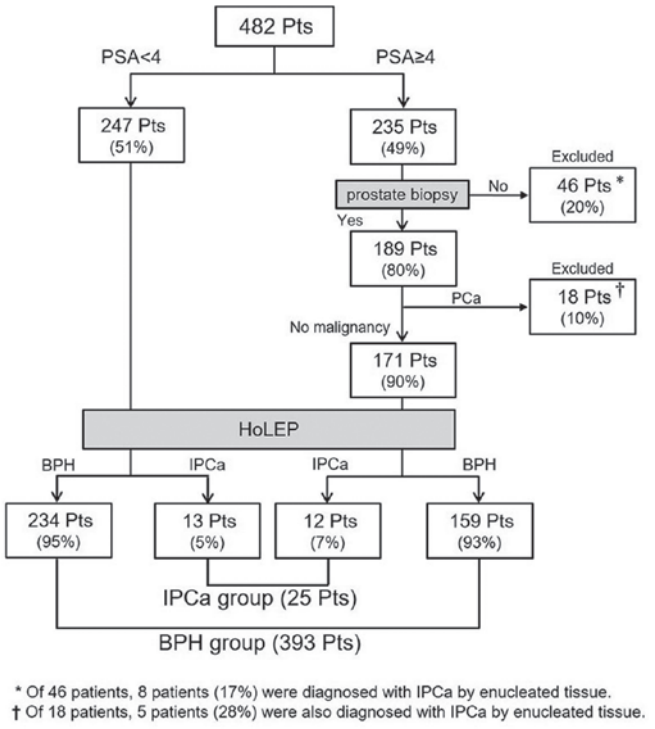

Figure 1. Flow chart of study selection based on the inclusion and exclusion criteria. Pts, patients; PSA, prostate-specific antigen; HoLEP, holmium laser enucleation of the prostate; BPH, benign prostatic hyperplasia; PCa, prostate cancer; IPCa, incidental prostate cancer.

Preoperative and postoperative long-term outcomes are shown in Fig. 2. The definition of watchful waiting (WW) is as follows: In both the BPH (WW) and IPCa (WW) group, the postoperative variables after PCa curative treatment for 9 patients (n=4, BPH group; n=5, IPCa group) were excluded, while those before curative treatment were included in follow-up data. The rate of WW at 5 years was 99% in the BPH group and 80% in the IPCa group. In the IPCa (WW) patients, voiding symptoms improved immediately after HoLEP, as IPSS, QoL, Qmax, and PVR were comparable to those of the BPH (WW) group at any timepoint (P>0.05). However, long-term postoperative PSA increased gradually in the IPCa (WW) group (3-year, P=0.033; 4-year, P=0.037); IIEF-5 conversely decreased (5-year, P=0.068). In contrast, postoperative PSA and IIEF-5 remained stable for 5 years in the BPH (WW) group. All patients in both groups (including patients who underwent cancer treatment) have survived without cancer progression (mean follow-up period 30.4 and 34.7 months, respectively); 5-year overall survival and progression-free survival rates are 100%.

Discussion

In this study, after strict PSA screening and excluding PZ PCa (T1c) by preoperative prostate biopsy, only age was significantly different in the two groups. Postoperative urinary function improved similarly in the BPH (WW) and PCa (WW) groups. In contrast, PSA increased gradually and IIEF-5 decreased in the PCa (WW) group. It is conceivable that undetectable PZ PCa remains after HoLEP and that these cancers are clinically insignificant.

Table I. Summary of patient characteristics and comparison between the BPH and IPCa groups.

Variables [Mean ± SD/No (%)]	Total	BPH	IPCa	P-value
No. patients	418	393	25	
Age (years)	71.9±8.2	71.7±8.2	75.5±7.3	0.026[a]
Estimated prostate volume (ml)	47.0±26.8	46.9±27.0	48.2±24.8	0.631
Enucleated weight (g)	22.5±20.9	22.4±21.2	23.8±17.5	0.403
IPSS	18.9±7.3	18.9±7.3	18.2±7.3	0.684
QoL	4.6±1.3	4.6±1.3	4.4±1.4	0.610
IIEF-5	6.5±6.0	6.5±6.1	6.5±5.1	0.437
Qmax (ml/s)	11.9±6.4	12.0±6.4	10.1±6.5	0.165
PVR (ml)	138.6±222.3	137.9±223.5	148.4±208.9	0.564
PSA (ng/ml)	5.32±6.65	5.29±6.76	5.82±4.61	0.101
PSA density (ng/ml/ml)	0.11±0.10	0.11±0.10	0.13±0.10	0.077
Operative time (min)	74.0±36.8	73.8±37.0	78.4±33.7	0.352
Bleeding volume (ml)	84.4±110.9	84.7±112.0	80.5±94.3	0.891
Morcellation time (min)	10.1±11.6	10.1±11.8	9.8±8.3	0.641
Catheterization time (days)	2.6±1.4	2.6±1.4	2.3±1.1	0.353
Gleason score (%)				
≤6			21 (84%)	
7			4 (16%)	
Clinical stage (%)				
cT1a			24 (96%)	
cT1b			1 (4%)	
Initial treatment (%)				
Watchful waiting			20 (80%)	
Radical prostatectomy			2 (8%)	
Radiation therapy			1 (4%)	
Hormone therapy			2 (8%)	
Mean follow-up period (months)	30.6±18.7	30.4±18.4	34.7±22.3	0.327

[a]P<0.05. SD, standard deviation; BPH, benign prostatic hyperplasia; IPCa, incidental prostate cancer; IPSS, International Prostate Symptoms Score; QoL, quality of life; IIEF, International Index of Erectile Function; Qmax, maximum flow rate; PVR, postvoid residual urine volume; PSA, prostate-specific antigen.

Some risk factors for IPCa have been previously reported: PSA (4,5), PSA density (4,6), PSA velocity (4), prostate volume (4), age (5,6), decreasing specimen weight (5), hypoechoic lesion on transrectal ultrasonography (TRUS) (7), and diabetes (for Gleason score ≥7 or T1b) (8). However, the inclusion criteria in these studies were not unified. The protocol for preoperative PSA screening was not determined uniformly; whether patients with elevated PSA (≥4 ng/ml) would undergo prostate biopsy depended on the physician's discretion. A possibility exists that some high-risk patients, who should have been excluded by prostate biopsy, were included in several studies. Besides, the rate of IPCa for patients with PSA ≥4.0 ng/ml and no prostate biopsy was extremely high (17%) in our study, while they had not been suspected of PCa before HoLEP (Fig. 1). Our criteria was a clinically applicable model, because PSA screening was always performed and PZ PCa (T1c) was excluded as much as possible. This may help to explain BPH patients with elevated PSA cannot be denied IPCa by clinical experience.

HoLEP is associated with more favorable long-term outcomes than monopolar and bipolar TURP in some published Randomized controlled trials (12,13). With respect to postoperative functional outcomes in the IPCa group, voiding symptoms and variables improved in a similar manner as in the BPH group, consistent with a previous report (14), and the improvement was long-term. These results suggest that select clinically insignificant PCa patients with BPH might be good candidates for HoLEP. Becker *et al* reported that HoLEP represented a feasible, safe, and effective treatment option for PCa patents with LUTs unfit or without indication for radical prostatectomy (15). Interestingly, postoperative PSA increased gradually and IIEF-5 conversely decreased in the IPCa group, perhaps due to age, as age significantly differed in the two groups. However, the similar preoperative IIEF-5 scores indicate the existence of factors affecting sexual function, including psychological factors and comorbidities such as diabetes and cardiovascular disease.

Lin *et al* revealed that the overall incidence of PCa was significantly higher in patients with erectile dysfunction (ED)

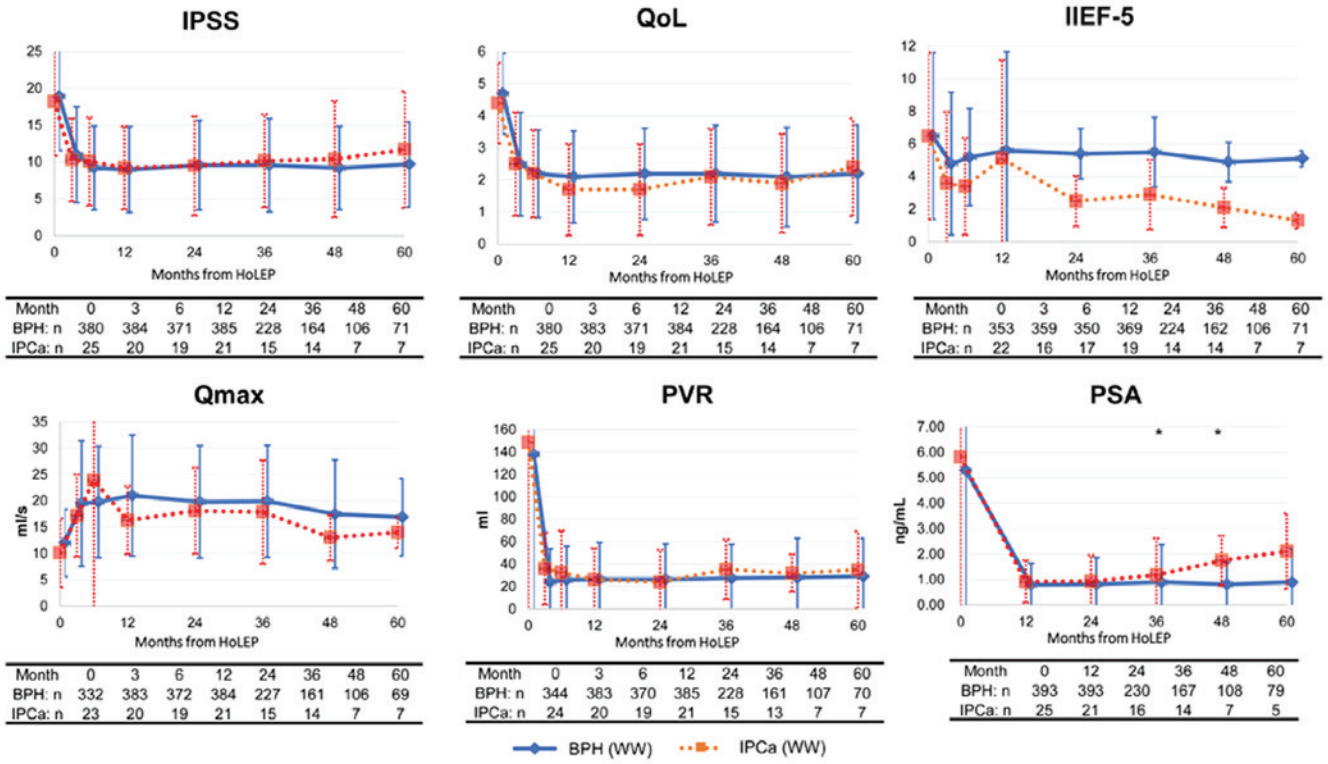

Figure 2. Comparison of long-term urinary, sexual and oncological outcomes in the BPH (WW) and IPCa (WW) groups. IPSS, International Prostate Symptoms Score; QoL, quality of life; IIEF-5, International Index of Erectile Function 5; Qmax, maximum flow rate; PVR, postvoid residual urine volume; PSA, prostate-specific antigen; HoLEP, holmium laser enucleation of the prostate; BPH, benign prostatic hyperplasia; IPCa, incidental prostate cancer; WW, watchful waiting.

compared to patients without ED (adjusted HR, 1.19) (16). These results imply a close relationship between ED and PCa. Therefore, ED should be carefully managed in patients with IPCa.

Previous studies revealed that postoperative PSA in IPCa gradually increases. Elmansy *et al* reported that PSA velocity significantly differed between the IPCa and BPH groups (1.28 vs. 0.13 and 2.4 vs. 0.09, 1-year P<0.022; 3-year P<0.001) (17). Rivera *et al* reported that patients with a Gleason score of ≥8 had significantly elevated postoperative PSA, PSA difference from preoperative PSA and percent change PSA levels compared to patients with a Gleason score of ≤7 at diagnosis (P=0.01, 0.02, and 0.01, respectively) (18). We frequently face the dilemma of overtreatment versus cancer progression. Lee *et al* concluded that according to recent research and guidelines, immediate definite therapy should be avoided without careful assessment (19). There was no patient with a Gleason score of ≥8 enrolled in the present study, although the rate of IPCa (6%) was comparable to previous studies. Furthermore, the 5-year overall survival and progression-free survival rates for IPCa were 100%. These findings suggest that if standard PSA screening is performed and PCa is excluded in PZ, clinically significant cancer is less likely to remain in TZ and IPCa patients should undergo WW until PSA begins to rise. We expect our results may be helpful in watchful waiting even if we have no pathological result of enucleated tissue (e.g. following up after PVP). Additionally, Meeks *et al* estimated that if PSA screening was used, the number of clinically significant tumors missed by ablative therapy was low (average, 0.26% PZ of all procedures) (20). It remains unclear to what extent IPCa patients should undergo WW, and what is the best adjuvant therapy. Further study is required to examine the oncological outcomes of IPCa patients on WW for a longer follow-up period.

Our study has some limitations. First, it was a retrospective and non-randomized study. Second, the sample size of the IPCa group was small. Third, a selection bias existed regarding whether patients with PSA ≥4.0 mg/ml underwent prostate biopsy preoperatively or simultaneously with HoLEP. In addition, the selection of adjuvant cancer therapy or WW was determined by patient's desire and urologist's discretion.

Prostate biopsy prior to HoLEP for patients with PSA ≥4.0 mg/ml cannot completely exclude cancer. However, the results of this study suggest that if standard PSA screening and prostate biopsy are performed, WW for IPCa patients after HoLEP does not impact on 5-year progression-free survival and improved urinary function is sustainable.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YT designed the study, analyzed data and wrote the paper. TS reviewed the results. YMi and YMa assisted in writing the manuscript and constructing the figures. RT and KW contributed to the analysis and interpretation of the result. SM, NK, YNi, TK collected data and contributed to the study design. YNa and SH supervised the study and aided in interpreting the results. All authors approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient consent for publication

Informed consent was obtained from all individual participants included in the present study.

Competing interests

The authors declare that they have no competing interests.

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