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Effect of Holmium Laser Enucleation of the Prostate on Prostate-Specific Antigen Kinetics in Patients with Known Prostate Cancer on Active Surveillance

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Abstract

Objectives: To evaluate the effect of Holmium Laser Enucleation of the Prostate (HoLEP) on Prostate-Specific Antigen (PSA) kinetics in men with preoperatively known Prostate Cancer (PCa) on Active Surveillance (AS).

Methods: We retrospectively reviewed a prospectively maintained database of patients undergoing HoLEP for the management of lower urinary tract symptoms secondary to Benign Prostatic Hyperplasia (BPH) at a single institution. Patients on AS for PCa undergoing HoLEP were compared to all other patients without a diagnosis of PCa with regards to postoperative PSA kinetics, complications, and functional outcomes. A group of AS patients who underwent monopolar Transurethral Resection of the Prostate (TURP) was also compared to our study cohort. Univariate and multivariate analyses were performed using linear regression models.

Results: Of the 1,445 HoLEP cases, 124 (8.6%) patients were identified to have PCa and 25 (2%) were managed under AS. Median age at the time of surgery was 72.5 (69 to 79) years and with a baseline prostate volume of 64.5 mL. After a follow-up of 7.3 years, the absolute median decline in the first PSA measurement post-HoLEP was 4.7 ng/ml with a relative decrease of 47.4%. The median lowest PSA reached post-HoLEP was 1.1 ng/ml within the first year after HoLEP. During follow-up, there were no significant differences in PSA values between the study cohort and the BPH group who underwent HoLEP ($p<0.05$). PSA variation remained low in AS patients during the duration of the post-HoLEP follow-up (0.4 ng/ml). On univariate analysis, higher baseline primary Gleason score and a lower percentage of cancer in HoLEP specimen were found to significantly increase relative PSA changes post-operatively (P=0.004 and 0.022, respectively). Additionally, most AS patients who underwent HoLEP were found to have lower postoperative PSA values and when compared to AS patients in the TURP group (1.1 ng/ml *vs.* 3.2 ng/ml, p=0.019). Functional outcomes and complications of patients undergoing HoLEP were similar in both the PCa on AS and non-PCa cohorts.

Conclusion: Patients with PCa under AS experience a significant decline in PSA after HoLEP. There is low PSA variation during follow-up, suggesting that cancerous cells in low-grade PCa contribute little to overall serum PSA levels. HoLEP is a safe and effective procedure for low-grade PCa patients on AS with bothersome LUTS secondary to BPH.

Keywords: Prostate cancer; Holmium laser; HoLEP; Active surveillance

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Introduction

The emergence of the Holmium Laser Enucleation of the Prostate (HoLEP) technique marked a turning point in the management of Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH) [1]. HoLEP is not only a safe, efficient, size-independent, and durable option for the surgical management of BPH, but it also provides adequate tissue for pathological examination, which may yield incidental findings of Prostate Cancer (PCa) [2]. The characterization and management of patients with incidentally discovered PCa diagnosed after HoLEP is well established [3-5].

However, there is limited literature on patients with a preoperative diagnosis of PCa on Active

Surveillance (AS) undergoing HoLEP for LUTS due to BPH. There is namely a paucity of data on the effect of HoLEP on postoperative PSA kinetics in this population. This is especially important considering that PSA kinetics are used to monitor PCa progression and guide the clinical management of patients on AS [6,7]. Theoretically, increases in PSA of patients with PCa diagnosed before or after HoLEP can be attributable to PCa disease progression as the PSA-producing and LUTS-causing transition zone has been enucleated.

Considering that the surgical treatment of bladder outlet obstruction in known low-risk PCa patients with LUTS who are on Active Surveillance (AS) is not well defined, we sought to evaluate the effect of HoLEP on postoperative PSA kinetics in PCa patients on active surveillance. We hypothesized that prostatic adenoma contributes more to serum PSA kinetics compared to cancerous cells, thus significantly reducing PSA and reducing its variation postoperatively. We also examine the safety and functional outcomes of HoLEP in this patient population of PCa patients on AS.

Methods

Data source

We used a prospectively maintained database for patients undergoing HoLEP between 1998 and 2016. All patients were preoperatively assessed, operated, and followed-up by three expert surgeons.

Study design and cohort

We conducted a retrospective observational study of PCa patients on AS undergoing HoLEP for the managements of LUTS secondary to BPH compared to patients without a PCa diagnosis undergoing HoLEP. We excluded patients with a postoperative diagnosis of PCa.

Data collection

Demographic information was collected at baseline. Baseline prostate volume was determined by Transrectal Ultrasound (TRUS). Total PSA Density (PSAD) was calculated by dividing preoperative PSA by prostate volume. Clinical, laboratory, and pathological data were also collected at baseline, preoperatively, and postoperatively and included pathological features and cancer progression. Perioperative parameters were reported, including total energy used, operative time (enucleation and morcellation times), catheter time, and hospital length of stay.

Study endpoints

The primary endpoint was PSA kinetics which included PSA Doubling Time (PSADT), PSA velocity, and PSA variation which was defined as the difference between the first PSA measurement after HoLEP and the last documented measurement (or the last measurement before a new treatment was initiated) divided by the time between the two measurements. In addition, a sensitivity analysis was performed comparing the study cohort to a group of men on AS undergoing monopolar TURP to address the effect of the technique (enucleation *vs.* resection) on PSA kinetics during the same intervals.

Statistical analysis

Descriptive statistics were presented in terms of number and percentages or means and Standard Deviations (SDs) for categorical and continuous variables, respectively. Fisher's exact test and Mann-Whitney U-test were used for categorical and continuous variables, respectively. PSA comparisons were analyzed using Wilcoxon's rank-sum test. Univariable and multivariable logistic regression were performed. Two-tailed p-value of <0.05 was considered statistically significant. Data was analyzed using Statistical Package for Social Sciences (SPSS) version 20 (IBM SPSS, Armonk, NY, USA).

Results

Cohort characteristics

Of the databases 1445 HoLEP cases, 124 (8.6%) patients were identified to have PCa of which 74 patients (5.1%) were incidentally diagnosed via the HoLEP specimens, 21 (1.5%) were diagnosed during the follow-up after HoLEP, and 25 (1.9%) patients had PCa being managed by AS prior to HoLEP. At the time of PCa diagnosis, the AS cohort had a median age of 68 years, a median PSA of 5.7 ng/ml, a median prostate volume of 64.5 mL (IQR). The median age at the time of HoLEP was 72.5 years (IQR) and preoperative PSA was 6.1 ng/ml (SD). Patients' demographics and perioperative data are presented in Table 1.

PSA kinetics

Postoperatively, there was a sharp decline of the PSA value immediately after HoLEP (Figure 1). The absolute median decline in first PSA measurement post HoLEP was 4.7 ng/mL. After the first year after HoLEP, PSA values of the AS group tend to be stationary and parallel to the regular HoLEP group during 7.3 years of follow-up (Figure 1). The lowest PSA achieved post-HoLEP was 1.1 ng/mL within the first year. On univariable analysis, higher baseline primary Gleason score and a lower percentage of cancer in HoLEP specimen were found to significantly increase relative PSA changes post-HoLEP (p=0.004 and 0.022, respectively.

Comparison to the TURP cohort

With regards to technique (HoLEP *vs.* monopolar TURP), both groups were comparable in terms of baseline and preoperative characteristics (Table 2). However, most AS patients who underwent

Table 1: Baseline and perioperative data for prostate cancer patients under active surveillance who underwent HoLEP.

Variable	Value
Age at diagnosis (median, IQR), years	68 (62-71)
Age at surgery (median, IQR), years	72 (66-73)
Median follow-up (median, IQR), years	7.3
Prostate volume (mL)	63 (49-250)
Gleason score	6 (6-7)
PSA density (median, 95% CI)	0.08 (0.04-0.15)
Cores (median, 95% CI)	8 (6-10)
- Positive (# of patients, %)	20 (100%)
- % of positive cores (median, 95% CI)	18 (17-33)
- % of cancer (median, 95% CI)	10 (5-20)
Gleason primary (median, 95% CI)	3 (3)
Gleason secondary (median, 95% CI)	3 (3-4)
Enucleation time (median, IQR), (min)	81.2 ± 32.1
Morcellation time (median, IQR), (min)	14.9 ± 7.8
Hospital length of stay	1.3 ± 1.7
Baseline PSA ng/mL	5.7 (3.4-7.3)
Peak flow (mL/s)	6.9 ± 4.9
IPSS score	18 (14-20)
QoL score	3 (3-4)
PVR	84 ± 67

Table 2: Comparison between active surveillance patients who underwent either HoLEP vs monopolar TURP.

Variable	HoLEP*	TURP**	P-value
Age at diagnosis (median, IQR)	68 (62-71)	67 (60-71)	0.78
Age at surgery (median, IQR)	72 (66-73)	73 (70-79)	0.29
Baseline data/data at diagnosis			
PSA (median, 95% CI)	5.7 (3.4-7.3)	7.3 (4.1-9.3)	0.25
Prostate volume (median, 95% CI)	64.5 (49-83)	37 (32-71)	0.06
PSA density (median, 95% CI)	0.08 (0.04-0.15)	0.17 (0.07-0.30)	0.08
Cores (median, 95% CI)	8 (6-10)	6 (6-10)	0.11
- % of positive cores (median, 95% CI)	18 (17-33)	23 (15-33)	1
Gleason total (median, 95% CI)	6 (6-7)	6 (6)	0.34
Gleason primary (median, 95% CI)	3 (3)	3 (3)	1
Gleason secondary (median, 95% CI)	3 (3-4)	3 (3)	0.34
Preoperative data			
IPSS (median, 95% CI)	18 (14-20)	17 (14-20)	0.71
QoL (median, 95% CI)	3 (3-4)	4 (3-5)	0.35
Urine catheter present (# of patients, %)	8 (40%)	2 (25%)	0.45
PSA (median, 95% CI)	6.1 (4.6-10.9)	8.2 (5.6-15.3)	0.19
Prostate volume (median, 95% CI)	74 (53-86)	58 (48-100)	0.83
PSA density (median, 95% CI)	0.12 (0.06-0.15)	0.11 (0.09-0.34)	0.46
Time between preoperative data and surgery (median (days), 95% CI)	74 (23-89)	65 (21-111)	0.92
Time between diagnosis and surgery (median (years), 95% CI)	1.9 (1.2-3.5)	6.1 (2.1-12.3)	**0.05**
Postoperative data			
No cancer in tissue (# of patients, %)	13 (52%)	6 (75%)	**0.04**
Gleason total (median, 95% CI)	7 (6-7)	7 (6-7)	0.59
Gleason primary (median, 95% CI)	3 (3)	3 (3)	1
Gleason secondary (median, 95% CI)	4 (3-4)	4 (3-4)	0.59
Specimen volume (median, 95% CI)	48 (24-58)	23 (14-42)	**0.02**
- Percentage of cancer (median, 95% CI)	0 (0-17)	0 (0-20)	0.97
- Percentage of volume left (median, 95% CI)	35 (30-51)	68 (28-79)	**0.05**
First postoperative PSA measurement (median, 95% CI)	1.4 (1.0-3.2)	4.3 (2.5-9.0)	**0.01**
Time between surgery and next PSA measurement (median (days), 95% CI)	103 (77-123)	88 (39-145)	0.51
Follow-up duration (median (years), 95% CI)	7.3 (5.0-11.1)	4.7 (2.7-8.2)	**0.04**
# Patients alive	19 (96%)	8 (100%)	0.71
Post-surgery			
PSA velocity total	0.40 (0.19-1.25)	1.16 (-0.91-2.81)	0.068
PSA doubling time in first two years	1.36 (-0.30-2.53)	1.59 (-2.30-4.80)	0.68
Lowest PSA value	1.1 (0.7-2.0)	3.2 (1.0-8.4)	**0.019**
Time to lowest PSA postoperatively (months)	5.2 (3.7-10.1)	4.8 (2.9-17.2)	0.76
Lowest PSA within 1st year	1.1 (0.7-3.1)	3.2 (1.4-8.4)	**0.045**

*HoLEP, N=25; **TURP, N=8

HoLEP were found to have lower postoperative PSA values when compared to the TURP group (Table 2 and Figure 3). In addition, the HoLEP group had a slower PSA variance as well as a slower doubling time when compared to the monopolar TURP group (Table 2 and Figure 3).

There were no significant differences in PSA values between the study cohort and the BPH group undergoing HoLEP, ($p<0.05$; Figure 1) during follow-up. Likewise, there were no significant differences between both groups in terms of functional outcomes after HoLEP (All $p>0.05$; Figure 2).

Discussion

The role of HoLEP in the urologists' armamentarium is substantial due to its durability and safety compared to other treatment modalities of BPH [2]. To date, there is paucity in the literature addressing PCa patients on AS undergoing HoLEP for symptomatic BPH. We hypothesized that in low-risk and intermediate-risk PCa patients, prostatic adenoma contributes more to serum PSA kinetics compared to cancerous cells. Hence, the main objective of our study was to the

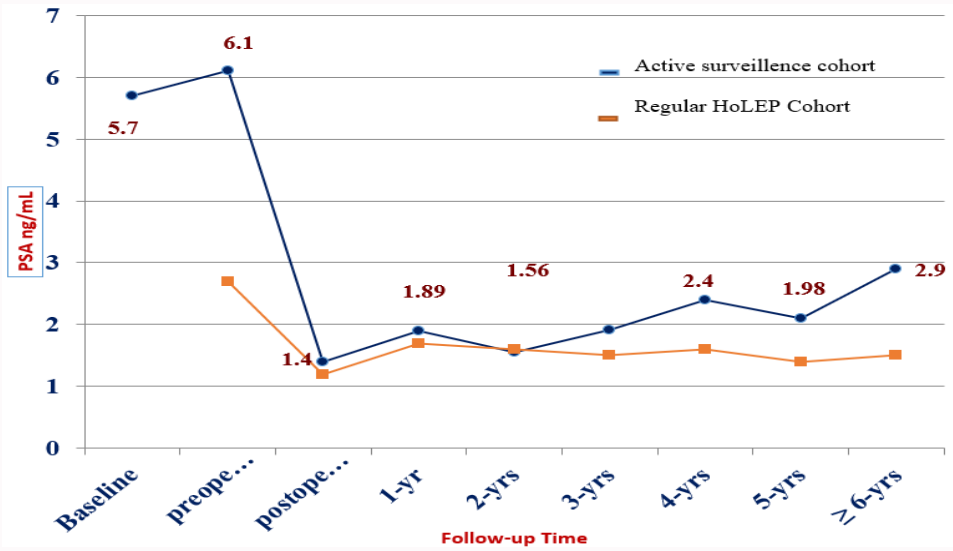

Figure 1: Comparison of PSA values at different follow-up visits (study cohort *vs.* regular HoLEP cohort).

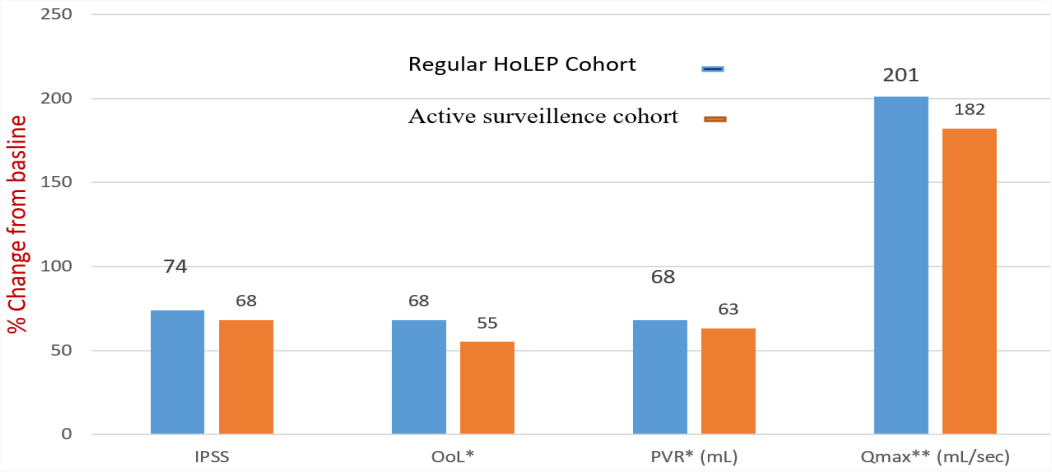

Figure 2: Functional outcomes of AS cohort *vs.* BPH cohort after HoLEP (median follow-up of 7.3 years).

effect of HoLEP on PSA kinetics in PCa patients on AS. We found that, compared to patients without PCa undergoing HoLEP, there were no statistically significant differences in terms of PSA reduction after HoLEP. After a median follow-up of 7.3 years, there were no disease progression in our primary study cohort, with similar long-term functional outcomes between PCa patients on AS undergoing the procedure and the rest of the non-PCa HoLEP patients. This demonstrates that HoLEP is a good treatment option for patients under AS for low-grade PCa and who suffer from bothersome LUTS.

This implies that adenomatous prostate tissue, rather than cancerous cells, play a more important role in PSA secretion in such patients with low Gleason score PCa. Unlike monopolar TURP procedure, HoLEP implies separation of the prostatic adenoma from surgical capsule. Therefore, we assumed that the HoLEP technique would help understand whether postoperative PSA changes are principally due to adenoma *vs.* cancerous cells. Additionally, the primary cohort was compared to a group of AS patients who underwent monopolar TURP for LUTS to address the technical impact (enucleation *vs.* resection) on PSA kinetics. We found that most AS patients undergoing HoLEP were found to have lower postoperative PSA values when compared to TURP group. These results reflect the fact that enucleation removes more adenomatous tissue than resection. HoLEP may be a more favorable technique to use in AS patients, as the post-operative PSA may be more sensitive to variance due to PCa impact rather than adenoma regrowth. This may avoid unnecessary re-biopsies due to eventual PSA increase. Nevertheless, neither cohort showed any increased risk of cancer-specific mortality over the follow-up period.

In the present report, higher baseline primary Gleason score and a lower percentage of cancer in post-HoLEP specimen were found to significantly increase relative PSA changes post-HoLEP. However, none our patients' PCa progressed to requiring treatment during the study period. This could be due to the small number of eligible patients included in the present study, as well as relatively short-term follow-up for PCa (7.3 years). Nevertheless, our cohort had low PSA variation and a slow doubling time post-HoLEP when compared to the monopolar TURP group.

The findings of the present study have provided a window for further understanding the concept of cancer cell contribution to serum PSA in PCa patients under AS, which will be reinforced by

ongoing research. Furthermore, most of the HoLEP patients had lower postoperative PSA values when compared to TURP patients. This may allow for more accurate monitoring of PSA in AS patients.

Functional outcomes and complication rates were similar in both AS patients and BPH patients, indicating that HoLEP is a safe and effective treatment for patients with low grade PCa with bothersome LUTS.

Our study is not without limitations. First, our study is limited by its retrospective nature which introduces several biases, namely selection bias. For example, it was not possible to determine if PCa patients on AS undergoing HoLEP for LUTS differed significantly from PCa patients on AS with LUTS but that didn't undergo HoLEP. Second, our small sample size and short follow-up time relative to the natural history of low-grade of history limits the generalizability of our findings. Despite its limitations, our study contributes important data on a unique subgroup of PCa and HoLEP patients.

Conclusion

Patients with PCa under AS experience a significant decline in PSA following HoLEP for the management of LUTS secondary to BPH. There is a low PSA variation during follow-up, suggesting that cancerous cells in low-grade PCa contribute little to overall serum PSA levels. HoLEP is a safe and effective procedure for low-grade PCa patients with bothersome LUTS. HoLEP provides a greater decline in postoperative PSA compared to monopolar TURP, theoretically allowing for a more sensitive monitoring of PSA in PCa patients on AS.

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