

Prostatic-specific Antigen Velocity After Holmium Laser Enucleation of the Prostate: Possible Predictor for the Assessment of Treatment Effect Durability for Benign Prostatic Hyperplasia and Detection of Malignancy

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OBJECTIVES	To evaluate the prostate-specific antigen velocity (PSAV) as an indicator for effectiveness and durability of size reduction after holmium laser enucleation of the prostate (HoLEP). Additionally, PSAV monitoring in the detection of prostate cancer was also evaluated.
METHODS	Between 1998 and 2006, we reviewed the prostate-specific antigen (PSA) data of 335 men who underwent HoLEP and had a complete PSA data including preoperative PSA, postoperative PSA (reset), and a minimum of 2 annual PSA readings after PSA reset. PSAV was calculated by 3 methods—simple arithmetic method, linear regression method, and rate method.
RESULTS	In the benign group, the mean PSA dropped from 5.44 to 0.91 ng/mL ($P < 0.001$). The prostate cancer patients who were newly discovered in the follow-up period had significantly higher baseline PSA ($P = .032$) and significantly lower PSA reduction than that of the benign group (75.39% vs 47.49%, $P < .001$). PSAV was calculated by 3 different methods and produced identical results; however, linear regression method produced significantly lower estimates at 7 years. In the malignant group, the mean PSAV at 1 and 3 years was higher than that of the benign group (1.28 vs 0.13 and 2.4 vs 0.09, $P < 0.022$, 0.001, respectively).
CONCLUSIONS	HoLEP results in a significant reduction in PSA that remained at lower levels during follow-up, suggesting that the glandular size reduction after HoLEP is durable. Monitoring of PSAV is important in long-term follow-up of patients for prostatic carcinoma detection after prostatic surgery. UROLOGY 74: 1105–1110, 2009. © 2009 Elsevier Inc.

Holmium laser enucleation of the prostate (HoLEP) is one of the most investigated laser procedures for the treatment of patients with symptomatic benign prostatic hyperplasia (BPH). It can be used safely in high surgical risk patients with no size limits of the treated prostate, as it is suitable for small-to-moderate size prostates as well as larger glands.¹ HoLEP seems to be a suitable endourologic alternative to open prostatectomy.² The Holmium: Yttrium-aluminum-garnet (Ho: YAG) laser (Versa Pulse; Lumenis Inc., Santa Clara, CA) allows

precise removal of obstructing prostatic tissue with a hemostatic effect that limits bleeding during resection.³ HoLEP produces sustained improvement of objective and subjective outcomes. The procedure is safe and effective with low morbidity, short catheterization time, and duration of hospitalization.⁴

The HoLEP technique has been shown to produce significant reductions in prostate-specific antigen (PSA), which correlates with the amount of prostate tissue removal. As PSA reduction is similar to that achieved with open prostatectomy, HoLEP can be considered the minimally invasive technique with maximal tissue removal.⁵

After treatment, the PSA levels are reduced to new lower levels (reset) that should be sustained during follow-up of the patient with BPH. Increases in the PSA levels even within the normal range would indicate prostate biopsy as this is associated with an increased risk for

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malignant disease.⁶ Therefore, monitoring change of PSA over time or PSA velocity (PSAV) apart from absolute normal values is essential in the detection of prostate cancer for patients who have been treated for BPH.⁶ The rate of change in PSA over time or PSAV was originally described by Carter et al⁷ who reported a sensitivity of 72% and a specificity of 95% for prostate cancer diagnosis at a PSAV cut off 0.75 ng/mL/y the most accurate cut-off of PSAV to be used for the diagnosis of cancer remains a topic of controversy,^{8,9} whereas others have suggested that measurement of PSAV provides no additional benefit over and above a single PSA measurement.¹⁰⁻¹² However, the weight of the evidence available now shows that PSAV is higher in men with prostate cancer as compared with those with benign disease, irrespective of the method of PSAV calculation.¹³⁻¹⁵ It follows that the validity of the methods used for calculating PSAV requires careful assessment.

The published data have shown that there is significant variation associated with the method used to calculate PSAV from the same PSA data. This is of importance because the decision to proceed with prostate biopsy is dependent on this assessment. Mathematical logic and clinical evidence support linear regression as the method of choice for calculating PSAV.¹⁵ However, others have reported that using a simple arithmetic PSAV calculation yields results comparable with of the more complicated regression and would be more practical for daily clinical use.¹⁶ The aim of this study was to assess the durability of response to treatment as measured by PSAV in patients treated with HoLEP for BPH and the association between PSAV and risk of malignant disease. Finally, the differences observed on the measurements of PSAV depending on the method of calculation were assessed.

MATERIAL AND METHODS

Study Design

This is a longitudinal study of patients treated with HoLEP between March 1998 and March 2006 for complete PSA data, including preoperative PSA, PSA after treatment, and a minimum of 2 available PSA readings after treatment. A total of 335 patients fulfilling these criteria were identified and were included in our study. All patients were treated or supervised by 1 surgeon (M. M. E.) at the Department of Surgery, Division of Urology of the McGill University Health Sciences Center. Patients were excluded if there was a history of prostate cancer. In cases of elevated preoperative PSA > 4 ng/mL, carcinoma of the prostate had to be excluded by biopsy. The number of patients who underwent preoperative biopsy was 5 of 9 in the malignant group and 50 of 326 in the benign group, and all the results were negative for malignancy. All cases with confirmed prostatic carcinoma were excluded. A total of 35 newly discovered prostatic carcinoma cases during pathologic examination after HoLEP were excluded. The technical details of the HoLEP have been reported previously.^{17,18}

Patient Follow-Up and Assessments

All patients underwent preoperative evaluation including the International Prostate Symptom Score (IPSS), uroflowmetry, and transrectal ultra sound for prostatic volume. Serum PSA was obtained within 1 month before HoLEP. The weight of the resected tissue was recorded intraoperatively. Patients were followed at 1, 3, 6, and 12 months, and then annually. The PSA measurements were obtained at 3 months after treatment to establish the first post treatment value or PSA reset, and then annually. PSA levels were obtained by the Hybritech method at the same laboratory at our institution.

PSAV was calculated as the rate of change of PSA using the following 3 methods. First, is the simple arithmetic method that is based on the calculation of the sum of the differences between consecutive PSA measurements divided by the interval between them using the following formula: $\Sigma ((PSA_{t1} + 1 - PSA_{t1/t2-t1}))$. Second, PSAV was calculated on the basis of linear regression analysis in which the slope of the linear equation $PSA = C + b \times (\text{Time})$ was used to determine PSAV. Third, PSAV was estimated using the rate of change according to the following formula: $PSAV = (PSA_f - PSA_0)/t$.

Where

P = PSA value, t1 = baseline (reset),

t = duration of the interval (years),

Σ = sum overall values,

C = linear regression constant,

B = linear regression slope,

PSA_f = PSA at end of the interval,

PSA₀ = baseline (reset) PSA.

Statistical Methods

Descriptive statistics were produced for all relevant study variables, including demographics and baseline characteristics. The mean values of postoperative outcome parameters were compared with those before surgery using the paired Student *t* test; $P < .05$ was considered significant. The nonparametric test Wilcoxon signed rank test was used to assess the difference in the PSAV estimates produced by the 3 different methods. The difference with respect to PSAV measures between patients with BPH and malignant disease was assessed for statistical significance with the nonparametric Mann-Whitney *U* test. The nonparametric tests were used because of the non-normal distribution of the PSAV estimates and the low number of patients in the malignant group. The incremental risk for malignant disease associated with increased PSAV was assessed by logistic regression analysis.

RESULTS

A total of 335 patients diagnosed with BPH were included in the study. The 35 patients discovered to have prostate cancer on pathologic assessment were excluded from the analysis. A total of 9 patients were newly discovered having prostate cancer in the follow-up period, whom we refer to in our results as a malignant group. This group represents approximately 2.68% of the total number of patients in the study. Of the 9 patients, 7 developed malignancy after 3 years and 2 after 4 years. The demographic and baseline characteristics of the study sample are described in Table 1. There was no

Table 1. Demographic and baseline characteristics of the study sample

Parameter	Benign	Malignant	<i>P</i>
No. patients	326	9	
Age (y)	73.95 ± (7.19)	75.33 ± (9.67)	.574
Preoperative TRUS	81.976 ± (43.81)	91.98 ± (81.72)	.512
Preoperative PSA ng/mL	5.44 ± (5.15)	9.46 ± (7.94)	.032
Postoperative—reset PSA ng/mL	0.91 ± (1.05)	5.83 ± (8.20)	<.001
PSA reduction %	75.39 ± (21.7)	47.49 ± (31.2)	<.001
Weight of resected tissue (g)	44.46 ± (32.51)	51.40 ± (77.37)	.795
<i>P</i> (pre vs reset PSA; within groups)	<.001	.009	

Table 2. Pretreatment and post-treatment clinical outcome parameters

Clinical Variable (Mean ± SD)	Preoperative N = 335	1 Year N = 335	3 Year N = 327	7 Year N = 52
Q _{max}	7.7 ± 2.7	25.2 ± 10.8	26.3 ± 10.5	28.3 ± 9.1
PVR	457.7 ± 250.2	34.3 ± 56.9	26.9 ± 43.8	25.5 ± 53.4
IPSS	18.4 ± 6.9	4.4 ± 3.6	4.3 ± 3.9	3.6 ± 3.1
QoL	3.6 ± 1.4	0.9 ± 1.1	0.9 ± 1.1	0.8 ± 0.9

Q_{max} indicates maximum flow rate; PVR = postvoid residual; IPSS = International Prostate Symptom Score; QoL = quality of life.

Table 3. PSA velocity calculated by the 3 different methods in patients with benign and malignant pathology

Method	Follow-Up (y)	Total		Benign		Malignant		<i>P</i> Malignant vs Benign		
		Mean	SD	N	Mean	SD	N		Mean	SD
Arithmetic mean	1	0.16	0.75	326	0.13	0.68	9	1.28	1.69	.022
	3	0.16	0.73	318	0.09	0.23	9	2.40	3.74	<.001
	7	0.14	0.25	52	0.14	0.25	0	NA	NA	NC
Slope	3	0.15	0.68	318	0.09	0.22	9	2.31	3.44	<.001
	7	0.09	0.20	52	0.09	0.20	0	NA	NA	NC
Rate	1	0.16	0.75	326	0.13	0.68	326	1.28	1.69	.022
	3	0.16	0.73	318	0.09	0.23	9	2.40	3.74	<.001
	7	0.14	0.25	52	0.14	0.25	0	NA	NA	NC
<i>P</i> mean vs slope	3	0.170		0.155		0.953				
	7	0.016		0.016		NC				
<i>P</i> mean vs rate	1	NC		NC		NC				
	3	NC		NC		NC				
	7	NC		0.830		NC				
<i>P</i> slope vs rate	3	0.170		0.155		0.953				
	7	0.016		0.016		NC				

NC indicates noncomparable; NA = not applicable; slope = regression analysis method.

significant difference in age, preoperative transrectal ultrasound (TRUS) volume, or the amount of tissue resected in both the groups. In the benign group, the mean PSA (ng/mL) dropped from 5.44 to 0.91 ($P < .001$) and the mean PSA reduction was 75.39%. In the malignant group, the mean PSA dropped from 9.46 to 5.83 ($P = .009$). These results show that the patients with malignant disease had significantly higher baseline PSA ($P = .032$) and significantly lower PSA reduction after treatment (75.39% vs 47.49%, $P < .001$) in comparison with the benign group.

The subjective and objective parameters were significantly improved immediately after surgery and continued to do so during subsequent follow-up as shown in Table 2. The mean Q_{max} increased from 7.7 ± 2.7 to 25.2 ± 10.8 at 1-year follow-up ($P < .0001$) and continued to be 26.3 ± 10.5 and 28.3 ± 9.1 at 3 and 7 years, respectively. The mean postvoid residual urine decreased from 457.7 ±

250.2 to 34.3 ± 56.9 at 1-year follow-up ($P = .002$) and continued to be 26.9 ± 43.8 and 25.5 ± 53.4 at 3 and 7 years, respectively. The IPSS decreased from 18.4 ± 6.9 to 4.4 ± 3.6 ($P < .0001$) and continued to be 4.3 ± 3.9 and 3.6 ± 3.1 at 3 and 7 years, respectively. The mean quality of life score improved from 3.6 ± 1.4 to 0.9 ± 1.1 ($P < .0001$) and continued to be 0.9 ± 1.1 and 0.8 ± 0.9 at 3 and 7 years, respectively. Bladder neck contracture and urethral stricture developed in 0.9% and 1.5% of patients, respectively. The reoperation rate as a result of recurrent obstruction because of residual adenoma was 0.9% of patients.

The results in Table 3 show that the PSAV calculated by the arithmetic mean and the rate methods produced identical results. However, the PSAV produced by the linear regression slope was similar to the arithmetic mean and rate methods at 3 years, whereas it produced significantly lower estimates at 7 years. In the malignant group,

Table 4. Relationship between PSAV and risk for malignancy

Method	Follow-Up (y)	Odds Ratio		P
		Estimate	95% CI	
Arithmetic mean	1	1.9	1.16-3.03	.010
	3	31.4	6.33-155.71	<.001
	7	NC	NC	NC
Slope	3	46.9	8.16-269.09	<.001
	7	NC	NC	NC
Rate	1	1.9	1.16-3.03	.010
	3	31.4	6.33-155.71	<.001
	7	NC	NC	NC

the mean PSAV (ng/mL) at 1 and 3 years was 1.28 and 2.4, respectively, which is higher than that in the benign group ($P < .022$, 0.001, respectively). The Gleason score was 6 (4 cases), 7 (3 cases), and 8 (2 cases). They received treatment in the form of watchful waiting (2 cases), radiotherapy (5 cases), radiotherapy with concomitant and adjuvant hormonal therapy (1 case), and hormonal therapy alone (1 case). The results in Table 4 show that although there is a significant relationship between the risk for having malignant disease and PSAV measured with all 3 methods, the linear regression slope produced the highest association. These results indicate that the linear regression method for estimating PSAV has the highest construct validity with respect to detection of malignant disease.

COMMENT

It has been reported that serum PSA level is markedly declined after open prostatectomy or transurethral surgery, as the transition zone is the major source of PSA production. Stamey et al¹⁹ reported the changes in PSA after open prostatectomy or transurethral procedures for treatment of BPH. There was a mean decrease in PSA of 95% in open prostatectomy group and 84% in transurethral resection of the prostate (TURP) group (73 men). Others reported mean percentage PSA reduction after TURP of 70%-75%.²⁰ Hai and Malek²¹ demonstrated a mean PSA decrease of 41.7%, with a decrease in TRUS volume of 27% at 1-year follow-up after KTP vaporization of the prostate. Te et al²² showed that there was an overall 29% reduction in TRUS-estimated prostate volume, a 17% reduction in serum PSA at 3 years after PVP, and the reoperation rate was 4.3%. Zlotta et al²³ found no change in PSA after 5-year follow-up period in patients who underwent transurethral needle ablation of the prostate.

Tinmouth et al⁵ found that HoLEP produces a significant diminution in PSA that correlates well with the weight of adenoma resected in a study at 2 institutions—Methodist Hospital, Indiana, and McGill University Health Centre. The mean decrease in PSA was 81.7% in the McGill group and 86% in the Methodist Hospital group. Marks et al²⁴ demonstrated long-term PSA levels in men after TURP, with a mean follow-up of 37 months.

The mean PSA level after TURP was 0.85 ng/mL. The mean PSAV was 0.01 ng/mL and was maintained throughout the follow-up of patients over a mean of 36 months. Shingleton et al⁶ reported that the resetting of PSA does occur after different surgical procedures, such as TURP, electrovaporization TVP, and laser ablation of the prostate, performed with KTP: Nd YAG laser system (Laserscope, San Jose, CA) with an ADDStat laser fiber. At 1-year follow-up, the mean PSA decreases to 46%, 8% and 32%, respectively, and it remains reset during the follow-up period (2 years). In the present study, patients with high preoperative PSA received antibiotics for 1 month and if it was still high, they were further investigated in the form of free and/or total PSA and prostatic biopsies. In the benign group, the mean PSA dropped from 5.44 to 0.91 ng/mL and the mean PSA reduction was 75.4%. Resetting of PSA and the percentage of PSA reduction are indicators that HoLEP is an effective technique in nearly complete adenoma resection. Additionally, there was a significant difference between preoperative PSA in benign group and patients who developed malignancy during follow-up period (malignant group) ($P = .032$) and another significant difference between PSA reset in both groups ($P < .001$). In the malignant group, PSA dropped from 9.46 to 5.83 ($P < .009$); however, the mean percentage reduction was <50% (47.49%). Kuntz et al² found that after 5-year follow-up, the improvement in micturition obtained with HoLEP and open prostatectomy for prostate >100 g was equally good. The mean American Urological Association symptom scores was 3 ($P = .8$) and mean Q_{max} was 24.4 mL in both the groups ($P = .97$), and postvoid residual urine was 11 mL in the HoLEP group and 5 mL in the open prostatectomy group ($P = .25$). The reoperation rate was 5% in HoLEP and 6.7% in open prostatectomy group. In the current study, our results confirm the immediate and durable effect of HoLEP. The preoperative mean Q_{max} increased from 7.7 to 25, 26.3, and 28.3 at 1, 3, and 7 years, respectively. The preoperative mean postvoid residual urine decreased from 457.7 to 34.3, 26.9, and 25.5 at 1, 3, and 7 years, respectively. The preoperative mean IPSS decreased from 18.4 to 4.4, 4.3, and 3.6 at 1, 3, and 7 years, respectively. The preoperative mean quality of life score improved from 3.6 to 0.9, 0.9, and 0.8 at 1, 3, and 7 years, respectively. Additionally, the late complication and reoperation rates were very low.

Shingleton et al showed that during follow-up period (2 years), the largest decrease in PSAV was -1.5 ng/mL in first year for TURP and it was maintained during the 2 years as -0.6 ng/mL. In the present data, the mean PSAV at 1-year follow-up (after the PSA reset) using the mean arithmetic method was 0.13 and as expected, it continued to be 0.09 and 0.14 at 3 and 7 years follow-up, respectively, confirming the durability of the size reduction of the prostate using HoLEP technique after 7-year follow-up period. The mean PSAV is clearly different in men with prostatic carcinoma as compared to those with

benign disease. In the present study, patients who were diagnosed with prostatic carcinoma during follow-up had PSAV of 1.28 ng/mL at 1-year follow-up, which became 2.4 ng/mL at 3-year follow-up. Additionally, it showed a significant difference between benign and malignant group ($P < .022$ and $< .001$, respectively). These changes have indicated the need for the biopsy and diagnosis of prostatic carcinoma. If the patient had been monitored according to their new absolute PSA levels without regard to PSAV, the diagnosis of prostatic carcinoma would have been delayed. Different methods of calculating PSAV are used and have the potential to produce different results from the same PSA data. Connally et al¹⁵ found that linear regression should be the method of choice for calculating PSAV, and linear regression and rate methods had similar predictive values, which were higher than arithmetic method. However, Yu et al¹⁶ showed that using simple arithmetic PSAV calculation yields results comparable to those of the more complicated regression analysis when restricted to PSA values starting 1-year before diagnosis in patients with clinically localized prostatic carcinoma. In the present data, mean arithmetic and rate methods produced identical results. However, the results of the linear regression slope were similar with arithmetic mean and rate methods at 3 years, whereas it produced significantly lower estimates at 7 years, making the simpler arithmetic method more practical.

The strength of this study is that HoLEP and the follow-up were done by the same surgeon, and therefore, the decision to proceed to prostate biopsy and the biopsy technique would be the same. PSA levels were obtained by the same method at the same laboratory. Additionally, significant number of patients and long follow-up periods were used. Finally, longer time interval between PSA tests was used, which was 1-year after the PSA reset. These time intervals are more likely to represent true change in PSA. The study has limitations worthy of note. First, it was a nonrandomized retrospective study. Second, the number of patients included in the malignant group is small as compared with the benign group; however, the differences observed between patients with malignant and benign disease were significant.

CONCLUSIONS

HoLEP technique results in a significant reduction in PSA, and this reduction remained at lower levels during follow-up period, suggesting that the glandular size reduction after HoLEP is durable. Using arithmetic method in calculating PSAV yields results that are comparable with those of the more complicated regression analysis and rate methods, making it a suitable method in daily clinical practice. As PSA remains the best marker for detection of prostatic carcinoma, recognition of PSA parameters such as PSAV is important in long-term follow-up of patients for prostatic carcinoma detection. We propose that if the reduction of PSA after HoLEP is $< 50\%$, these patients should be followed up more closely with PSA

measurements every 3-6 months for the first 2-3 years to allow earlier detection of prostate cancer.

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