Long term prostate-specific antigen trends following subcapsular prostatectomy

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Introduction: *The purpose of this study was to evaluate the utility of prostate-specific antigen (PSA) screening for prostate cancer after subcapsular prostatectomy.*
Materials and methods: *Data from 41 consecutive patients who underwent subcapsular prostatectomy at a single institution over a 15 year period were collected retrospectively. Patients were categorized into benign and malignant groups based on a diagnosis of prostate cancer identified in the surgical specimen or during subsequent follow up. Collected data included patient age, preoperative and postoperative PSA values, prostate volume determined by surgical specimen weight, and pathologic diagnosis. Preoperative and postoperative PSA velocities were calculated for patients with adequate data and average values were compared to determine factors that were predictive of a confirmed prostate cancer diagnosis.*
Results: *Thirty-one patients had adequate PSA values and follow up and were included in the analysis. Six (19%) were ultimately diagnosed with prostate cancer and 25 (81%) were never diagnosed with prostate cancer. Postoperative PSA velocity was found to be significantly higher for patients in the malignant group (1.22 ± 1.32 ng/mL/yr) as compared to patients in the benign group (0.06 ± 0.15 ng/mL/yr) (p = 0.003).*
Conclusions: *After subcapsular prostatectomy, patients with prostate cancer in the surgical specimen or who developed prostate cancer during long term follow up had elevated PSA velocity compared to patients who had no evidence of cancer in the surgical specimen or in follow up.*

Key Words: prostate-specific antigen, benign prostatic hyperplasia, prostatectomy

Introduction:

Despite the availability of minimally invasive surgery (MIS) techniques for the treatment of benign prostatic hyperplasia (BPH) and large prostate glands, simple (subcapsular) prostatectomy continues to be an effective treatment option. Although, transurethral resection of the prostate (TURP) remains the most commonly used surgical treatment for BPH[1] and the benchmark to which newer MIS techniques must be compared, there are still situations in which open removal of the benign prostate adenoma via simple prostatectomy is an acceptable treatment option. The most common indication for simple prostatectomy is large prostate size. Consideration for simple prostatectomy is warranted with an estimated gland weight of greater than 75 g or with estimated volumes greater than 100 cc. Other possible indications include concomitant bladder diverticuli, large calculi, or inability of the patient to tolerate positioning for TURP or MIS.

Simple prostatectomy can be performed via suprapubic, retropubic, or perineal approaches, and access to the prostate can be achieved using open laparotomy, laparoscopic, or robotic techniques. During the operation, the surgeon removes the hyperplastic adenoma, but the surgical capsule remains. This peripheral prostate tissue continues to secrete prostate-specific antigen (PSA) and remains susceptible to malignant transformation. The secretion of PSA is known to occur at a new reset level and has been observed in several types of surgical therapy for BPH.[2]

Postoperative PSA levels, even within the normal range, have been associated with malignancy,[2] as the reset PSA effectively creates new normal ranges for PSA and PSA velocity (PSAV). Although a few

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studies have examined trends for postoperative PSA and PSAV,[2-6] normative values have not been fully characterized long term in patients after subcapsular prostatectomy. Therefore, the purpose of this study was to investigate long term PSA and PSAV values following subcapsular prostatectomy in order to more accurately identify patients at risk for the development of prostate cancer.

Materials and methods

This is a retrospective review of PSA data on 41 men who underwent simple prostatectomy for treatment of BPH between 1991 and 2004. The study was approved by the institutional review board of the McGuire Veterans Affairs Hospital. All patients included in the study were screened for prostate cancer prior to simple prostatectomy and patients with elevated preoperative PSA values or abnormal digital rectal exams underwent transrectal guided prostate biopsy. Therefore, no patients had any evidence of prostate cancer at the time of simple prostatectomy. The following data were collected: patient age at time of surgery, preoperative and postoperative PSA, preoperative and postoperative TRUS prostate biopsy results, surgical specimen weight (g), and surgical specimen pathology. All PSA levels were measured by the laboratory at the McGuire Veterans Affairs Hospital in Richmond, Virginia and reported as ng/mL with values < 4.0 considered normal. PSA velocity was calculated by taking the difference in each two successive PSA values over time and taking the average of all 2-point PSA velocities for each patient. All patients included in this study had a minimum of two postoperative PSA values, and the time interval between the first and last postoperative PSA values was at least 16 months. No patients included in this study were on 5-alpha-reductase inhibitors postoperatively which eliminates a possible confounder as these drugs are known to decrease PSA levels in men with BPH or prostate cancer.[7] For patients found to have prostate cancer on surgical specimen or in postoperative follow up, PSA values were included up to the time point just prior to initiation of treatment for prostate cancer. Results were compared using Student's t-tests or Fisher's exact tests with $p < 0.05$ considered significant.

Results

There were a total of 41 men in this long term longitudinal study of which 31 had sufficient postoperative PSA data to allow calculation of velocity. Of 31 patients with available PSA velocity data, a total of 6 (19%) were ultimately diagnosed with prostate cancer either via prostatectomy specimen (2/31 or 6%) or in subsequent

TABLE 1. **Patient characteristics and PSA data**

	All patients	**Benign group**	**Benign group (n)**	**Malignant group**	**Malignant group (n)**	**Benign versus malignant (p value)**
Age	69 ± 1.19	68 ± 1.41	25	72 ± 1.09	6	0.146
Prostate size (g)	85 ± 4.67	83 ± 5.50	23	91 ± 8.07	6	0.499
Follow up (months)	73 ± 7.29	74 ± 7.96	25	72 ± 19.83	6	0.903
Preop PSA (ng/mL)	7.44 ± 0.82	7.21 ± 1.00	24	8.37 ± 1.06	6	0.590
PSA density (ng/mL/gm)	0.09 ± 0.01	0.09 ± 0.01	22	0.09 ± 0.01	6	0.844
Initial postop PSA (ng/mL)	1.46 ± 0.28	1.36 ± 0.29	25	1.88 ± 0.82	6	0.473
PSA Δ/g Resected (ng/mL)	0.07 ± 0.01	0.07 ± 0.01	22	0.07 ± 0.01	6	0.935
Postop PSA Velocity (ng/mL/yr)	0.46 ± 0.37	0.06 ± 0.15	25	1.22 ± 1.32	6	0.003

TABLE 2. **PSA and pathology for patients with prostate cancer**

Patient	Time of postop diagnosis (mos)	Gleason score	Preop PSA (ng/mL)	Initial postop PSA (ng/mL)	PSA velocity (ng/mL)
#1	0	2 + 5	9.30	0.47	0.27
#2	0	2 + 2	13.10	1.89	2.47
#3	42	3 + 4	7.40	5.80	4.86
#4	19	4 + 4	7.40	1.52	-1.24
#5	117	4 + 4	5.70	0.40	1.05
#6	98	4 + 5	7.30	1.18	1.20

postoperative follow up (4/31; 13%). These six patients will be referred to as the "malignant group." The patients with no detectable prostate cancer (25/31; 81%) will be referred to as the "benign group." Patient characteristics and PSA data are presented in Table 1. Preoperatively, there were no differences in age and preoperative PSA. Patients were followed for a mean of 73 months (range: 19-183), and the average number of postoperative PSA tests was 5 (range: 2-12). There were no differences in any parameters except for postoperative PSA velocity which was 0.06 ng/mL/yr for patients in the benign group and 1.19 ng/mL/yr in the malignant group ($p = 0.003$). There were 4/6 (67%) malignant group versus 12/25 (48%) benign group patients with initial postop PSA values ≥ 1 ng/mL ($p = 0.65$).

In addition, postoperative PSA velocity did not differ in patients with postoperative initial PSA ≥ 1 ng/mL (n = 17, 0.05 ng/mL/yr) versus patients with initial postoperative PSA velocities < 1 ng/mL (n = 14, 0.5 ng/mL/yr) ($p = 0.187$). Table 2 provides data on each of the six patients in the malignant group. Two of the six patients in the malignant group were diagnosed by surgical specimen, and the remaining four patients had cancer detected during follow up. Reanalysis of PSAV after removing the data from the one malignant group patient with clinically insignificant prostate cancer (patient #1, Gleason score: 2+2) did not change the results.

Discussion

In the current investigation, we found that postoperative PSAV was the only PSA parameter that was associated with the development or presence of prostate cancer. Previous studies have characterized postoperative PSA and PSAV following surgical therapies for BPH.[2-6] However, long term PSA trends after simple prostatectomy are still not well established. The findings in the current study are consistent with the few existing reports which evaluated long term PSA trends.[3-5]

Different surgical therapies for BPH result in varying degrees of decline in postoperative PSA, and this is thought to be directly related to the extent of prostate adenoma removed.[8] Furuya and colleagues[9] determined that size of prostate adenoma and specifically the transition zone are responsible for elevated PSA levels. To date, no study has analyzed long term PSA levels after simple prostatectomy, but our study observed the same phenomenon of a decreased, reset PSA level after prostate adenoma resection. For all patients in this study, the average preoperative PSA was 7.35, and the average initial postoperative PSA was 1.48. This represents an average 80% decrease in PSA after simple prostatectomy. For the benign and malignant groups, the average PSA decrease for each group was very similar (80% and 78%, respectively). This 80% decrease in PSA compares well to data collected in a study by Helfand et al[4] on patients who had undergone TURP or subcapsular prostatectomy for BPH. They reported an average PSA decrease of 93% for subcapsular prostatectomy and 60% for TURP.

The usefulness of PSAV for postoperative screening is well illustrated in a study by Berger et al[10] on 102 men who had undergone radical retropubic prostatectomy for prostate cancer. In their study that assessed risks of relapse after radical retropubic prostatectomy, PSAV was found to correlate significantly with tumor volume but not prostate volume which implies that PSAV has potential for detecting smaller, more curable cancers. The method for calculating PSAV is somewhat controversial. A study by Connolly et al[11] compared differences between three methods of calculating PSAV: arithmetic equation of change in PSA over time

(the method used in this study), linear regression, and rate of PSA change using first and last values only. The authors determined that linear regression had the best predictive value for accurately diagnosing prostate cancer. Another study by Yu et al[12] determined that a simple arithmetic method using two values from the year before diagnosis provides results that are adequate for clinical practice. Furthermore, a study by King et al[13] found only a 5% difference between the simple two point method and the linear regression method of calculating PSAV. Thus, we feel that the simple two point method used in this study, especially when taking the average of all two-point velocities, was an acceptable method for PSAV calculation.

In patient populations with no identifiable prostate cancer, studies have observed a correlation between elevated PSAV and risk of prostate cancer in patients who have undergone surgery for BPH. In a study by Helfand et al,[4] the authors observed a significant, direct association between PSAV and the detection of incidental prostate cancer upon surgery. This study suggested decreasing the PSAV biopsy threshold from 0.75 to 0.35 ng/mL/yr because the authors determined that a PSAV of 0.38 ng/mL/yr was 87% specific after TURP and 90% specific after subcapsular prostatectomy for the detection of prostate cancer. However, this study only evaluated PSAV in the first year after surgery. Furthermore, the "malignant" group in this study only included patients with prostate cancer found incidentally in the surgical specimen and placed on watchful waiting. The study did not attempt to follow patients to see if any of the patients subsequently developed prostate cancer. The only other study looking at PSA trends in patients who underwent simple prostatectomy[6] only looked at preoperative PSA variables in order to predict cancer based on the pathologic finding of cancer in the surgical specimen. In a study by Elmansy et al[3] which examined PSA trends flowing Holmium laser enucleation of the prostate, the authors did perform long term analysis of postoperative PSA trends but excluded all patients who had incidental prostate cancer detected in their pathologic specimens. This study found that PSAV was significantly higher for patients who developed prostate cancer at 1 and 3 years postoperatively.

Our study is limited by its retrospective nature and by a small sample size, reflecting practice trends for simple prostatectomy. As a consequence, we are not able to recommend a specific PSAV cut off that can accurately predict prostate cancer development after simple prostatectomy. However, despite these factors, a significant relationship between higher PSAV and development of prostate cancer was observed. In addition, the current study provides the only available data examining the risk of prostate cancer development after simple prostatectomy.

Conclusion

PSA screening is commonly practiced following surgical therapies for BPH. However, long term PSA trends following subcapsular prostatectomy have not been established. In this study, we found that patients with prostate cancer in the surgical specimen or who developed prostate cancer during long term follow up had elevated PSAV compared to patients who had no evidence of cancer in the surgical specimen or in follow up. Further, long term studies are necessary to confirm these findings and to establish more accurate guidelines for PSAV following subcapsular prostatectomy. □

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EDITORIAL COMMENT

Today, because of the general acceptance of medical management of BPH, we are finding by the time that this therapy has failed, that the patients' prostates can be very large. There are often associated bladder stones. The minimally invasive approaches to significant and symptomatic BPH, such as the Green Light Laser do not provide any tissue for analysis. If there are accompanying bladder stones, it usually means another traumatic and potentially morbid procedure. The open prostatectomy provides the tissue for a more complete analysis and immediate relief of the obstruction, with simultaneous removal of the bladderstones. Even if a patient had a transrectal prostate biopsy, the reality of obtaining complete and totally representative samples from a 100 gram prostate is minimal. This review gives the surgeon an accurate and excellent guideline as to when the suspicion for prostate cancer development is justified in the postoperative period after a subcapsular proastatectomy for the "huge benign" prostate.

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