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PROSTATE CANCER AFTER SURGERY FOR BENIGN PROSTATIC HYPERPLASIA

Abstract

Objective: To determine the incidence and characteristic of prostate cancer in patients with previous BPH surgery.

Materials and Method: In a retrospective study between 2002 and 2015, we analyzed patients who developed prostate cancer after surgery for BPH. Patients were examined by age, prostate volume, IPSS score, type and duration of the drug therapy, PSA values before and three months after surgery, and the type of BPH surgery. In patients with prostate cancer, we estimated the time between BPH surgery and the occurring of cancer, Gleason score, TNM stage, type of therapy and survival. Follow-up for BPH patients was 3 months and for the prostate cancer (PCa) group five years. Cox regression was used to determine the influence of various variables on the incidence of prostate cancer after BPH surgery.

Results: Incidence of prostate cancer was 1.69% (9 of 532 BPH surgeries) and was diagnosed significantly ($p<0.001$) more in patients who underwent open prostatectomy versus TURP. The mean time between BPH surgery and diagnosis of prostatic cancer was 7.2 years and did not correlate with the investigated parameters. The value of IPSS in the BPH group was significantly higher compared to before PCa surgery ($p=0.012$). In the PCa group, PSA values decreased from 2.30±0.83 to 0.95±0.38ng/ml after three months and in the BPH group from 1.98±0.84 to 0.54±0.33ng/ml. PSA

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reduction rate for the PCa group was 58.4±11.6% versus 70.7±0.58% in the BPH group. In the Age-adjusted analysis, the PSA reduction rate was 0.050 (0.001-0.937) HR (CI). In the PCa group, the serum PSA levels were increased by 6.5 times (mean 14.97ng/ml) (p=0.001) compared to the BPH group. Before BPH surgery, the mean prostate volume was 60, 4 ccm, 5.3 ccm greater than in the cancer group. Two PCa patients had bone metastases. Radical prostatectomy was performed in 5 cases and four were treated with LHRH agonists and antiandrogens. One died three years after PCa diagnosis. Conclusions: PSA reduction rate was a borderline significant predictor of prostate cancer after BPH surgery.

Keywords: benign prostate hyperplasia, prostate cancer, TURP, open prostatectomy, PSA reduction rate.

INTRODUCTION

There is controversy over whether benign prostatic hyperplasia or BPH surgery increases the risk of prostate cancer. Prostate cancer and benign prostatic hyperplasia are the two most common urological diseases in older men. Prostate cancer is the second most commonly diagnosed cancer in men, accounting for 15% of all cancers diagnosed (1). Otherwise, BPH is present in 70% of men over 70 years, and of all diagnosed prostate cancers, 80% of them had at the same time and BPH. Clinical BPH is present over 50% in men over 80 years old. The incidence of prostate cancer increases about 15 years later than with BPH. In both diseases, the incidence and mortality increase with age (1-3). There exists a worldwide difference in incidence between developed countries in Europe and America and Asia and the African continent (4,5). Both conditions are associated with epidemiological, hormonal, anatomical factors as well as the impact of inflammation, metabolic syndrome, and genetic alterations (6,7,8,9).

As anatomical connections, most cancers originate in the peripheral zone while BPH usually develops in the transition zone of the prostate (8,9). Well known 5ARI therapy for BPH reduced the relative risk of prostate cancer by detecting prostate cancer by 25% over 7 years and reducing prostate size as well as reducing the incidence of low-risk cancer (10-13). The ratio of estrogens to androgens increases by 40% in older men and this

may affect the natural course of BPH and CaP (14). Asians often have a diet containing phytoestrogens, which impact the lower prevalence of BPH and CaP compared to a Western diet (15).

Inflammation is associated with a 7.7-fold higher incidence of BPH. A fast-growing prostate may be a risk factor in developing prostate cancer. Several studies suggest an association between BPH and prostate cancer with certain genetic aberrations (16).

Large epidemiological and randomized controlled trials indicate a higher incidence of prostate cancer in patients who previously had BPH surgery. No causal link has been established between BPH surgery and the incidence of prostate cancer (17, 18).

MATERIALS AND METHODS

In a retrospective study in the period of 2002 to 2015, we analyzed the number and characteristics of prostate cancers that occurred in the group of 532 patients who had previous BPH surgery. Patients who underwent surgery for BPH had follow up meetings for three months. Before surgery, the patient's PSA values were determined, as well as prostate volume, IPSS score, and type and duration of previous drug treatment. At this point, the PSA value was controlled. Patients with an elevated PSA at above 4 ng/ml had a prostate biopsy, and in case of any positive findings, they were excluded from the study as well as all patients who presented T1a-b stage on histopathological finding.

Patients who developed prostate cancer were analyzed for PSA values, prostate volume, IPSS score, type of BPH surgery, period between BPH surgery and prostate cancer diagnosis, TNM stage, Gleason score, as well as the type of therapy and survival. Patients with PCa had follow-up meetings for a period of 5 years. A statistical analysis of all examined parameters was performed in patients with prostate cancer as well as determining any correlation with the parameters in the period of BPH surgery.

Statistical Analysis: Comparisons between the normally distributed variables were made with an independent Student t-test. If a non-normally distributed variable was involved in the comparison then non-parametric methods were used. For comparisons of non-numeric variables, the Chi-

squared test was used. To determine the relationship between numeric variables, Pearson's correlation was used. Cox regression was used to determine the influence of various variables on the incidence of prostatic cancer after BPH surgery. Hazard Ratios are given with 95% confidence intervals. We used SPSS statistical software (version 22.0 IBM, Armonk, NY, USA), and a two-tailed $p < 0.05$ was considered significant. Data are shown as mean ± standard deviation unless specified otherwise.

RESULTS

Between 2002 and 2015, 532 patients underwent BPH surgery. Transurethral resection of the prostate (TURP) was performed in 476 patients (89.5%) and open prostatectomy (OP) in 56 (10.5%) cases. In a period of 3.1 to 12.4 years after BPH surgery, nine patients (1.69%) were diagnosed with prostate cancer (PCa), six in the group with TURP (1.26%), and three (5.35%) in the group with open prostatectomy (p=0.001). Table 1.

Twenty-two patients with clinical BPH were excluded from the study because of a finding of incidental, T1a, T1b prostate carcinoma.

Table 1
Types of Benign Prostatic Hyperplasia Surgery done 2002-2015

	BPH surgery (%)	TURP(%)	OP(%)
BPH(n,%)	532 (100)	476 (89,5)	56 (10,5)
PCa(n,%)	9 (1.69)	6 (1.26)	3 (5.36) p=0.001

BPH- benign prostatic hyperplasia, TURP- transurethral resection of the prostate, OP- open prostatectomy,

In twenty-nine patients who had questionable digito-rectal examination results and PSA values, prostate biopsies were done. In three of them, prostatic carcinoma was diagnosed and they were excluded from the study.

The time from BPH surgery to the diagnosis of prostate cancer ranged from 37 to 149 months, with an average of 92.8 months (7.7 years).

The first two patients with prostate cancer were detected in 2011, followed by two in 2013, two in 2014, and three in 2015.

The average age in the PCa group was 74.4±1.68 (66-82) years, which is 7.2 years higher than the age in the BPH group. The age at the time of BPH operation correlates with the age at the time of prostatic cancer operation (R=0.770; p=0.015). The IPSS score before the BPH surgery was 29.4±0.74 (25-33) points. The IPSS score after cancer diagnosis was 22.9±2.1 (12-33) points, which is 6.5 points lower than in the BPH group (p=0.012). The mean prostate volume before BPH surgery was 60.4 ccm (26-92 ccm) and in the PCa group, 55.1 ccm (27-97), which greater in volume by 5.3 ccm than in the cancer group. Table 2.

Table 2
Prostate cancer group: clinical parameters

PCa N0	PCa age	PCa: year of diagnosis	Time from BPH surgery to PCa diagnosis months (years)	IPSS-BPH	IPSS before PCa diagnosis	Type of BPH surgery	PVol-BPH (ccm)	PVol-PCa (ccm)
1	74	2013	121 (10.1)	33	29	OP	59	45
2	82	2014	149 (12.4)	29	33	TURP	35	67
3	77	2015	91 (7.6)	30	23	OP	90	97
4	66	2015	87 (7.2)	28	23	TURP	37	32
5	76	2014	59 (4.9)	31	20	TURP	68	27
6	71	2011	80 (6.7)	29	12	OP	92	55
7	76	2015	85 (7.1)	25	22	TURP	26	60
8*	79	2011	126 (10.5)	29	17	TURP	85	35
9	69	2013	37 (3.1)	31	27	TURP	52	78
Mean +/-SD	74.4± 1.68		92.8±11.5 (7.7±0.95)	29.4± 0.74	22.9±2.10		60.4±8.32	55.1±7.71

PCa- prostate cancer, BPH- Benign prostatic hyperplasia, IPSS- The International Prostate Symptom Score, TURP- Transurethral resection of prostate, OP- open prostatectomy, PVol-prostate volume, * - death

The PSA value in the cancer group ranged from 6.9 to 45.9 ng/ml, a mean of 15.0 ng/ml before the prostatic biopsy. The PSA level before BPH surgery was 2.3 ng/ml (1.1 to 3.4), and after three months those values were at 0.3 to 1.6 ng/ml with a mean of 0.94 ng/ml. In the cancer group, the PSA levels were 6.5 times higher (p=0.001) compared to at the time of BPH surgery. PSA before BPH surgery correlated with PSA 3 months after BPH surgery (R=0.816; p=0.007). PSA before BPH surgery was significantly higher than 3 months postoperatively (p=0.001). PSA 3 months after BPH surgery was significantly lower than before prostatic biopsy (p=0.009).

All the patients in the cancer group had enlarged prostate volumes, significantly raised levels of PSA, and elevated IPSS score.

Five out of nine patients with prostatic cancer used alpha-blockers as monotherapy for BPH and 4 patients used combination therapy with alpha-blockers (AB) and 5 alpha-reductase inhibitors (5ARi). The mean duration of medical therapy before BPH surgery was 17.2 (3-35) months. A longer duration of medical therapy was associated with a lower IPSS before BPH surgery (R=0.757; p=0.018). There was no correlation found between alpha-blockers and combination therapy, duration of its usage, and the appearance of prostate cancer.

Regarding the Gleason score, six patients had 3+3 (International Society of Urological Pathology- (ISUP) 1), and three of them had a score of 3+4 (ISUP 2). Three out of four patients with 5ARi therapy had a Gleason score of ISUP1 and one of ISUP-2. Seven patients were in the T2N0M0 stage, and two with metastatic disease in the T2NXM1b, and T3NXM1b stage.

Radical prostatectomy was performed in four patients and the other five were treated with hormonal therapy (LHRH agonists and antiandrogens). The average age in the PCa group who underwent radical prostatectomy was 70.5 years (66-76), which is lower by 7.1 years in comparison to the PCa group treated with hormonal therapy, 77.6 years (74-82). One patient died 3 years after the diagnosis of prostate cancer was established, at the age of 82, after he was treated with LHRH antagonists.

The patients in the prostate cancer group had a significantly higher PSA 3 months after BPH surgery than patients in which cancer was not diagnosed (p= 0.014). PSA reduction rate was significantly lower in patients in which prostatic cancer was diagnosed after BPH surgery than in those in the BPH group (p=0.032). Table 3.

Table 3

Prostate cancer group: clinical parameters PSA, MT, BPH surgery. Gleason score, PCa therapy TM stage

PCa No	PSA before BPH surgery	PSA 3 months after BPH surgery	PSA before prostate biopsy	Type of MT before BPH surgery	Type of BPH surgery	Gleason score)	Treatment of PCa	TNM stage
1	2.1	0.6	9.1	AB+5ARi	OP	3+3	HT	T2NxMx
2	2.7	1.1	19.4	AB	TURP	3+3	HT	T2N0M0
3	1.3	0.8	45.9	AB	OP	3+4	HT	T3NxM1b
4	1.8	0.9	7.8	AB	TURP	3+4	RP	T2N0M0
5	3.1	1.3	13.7	AB+5ARi	TURP	3+4	RP	T2 NoM0
6	2.1	1.0	10.2	AB+5ARi	OP	3+3	RP	NoM0
7	1.1	0.3	7.4	AB	TURP	3+3	HT	T2NxMx
8	3.4	1.6	6.9	AB	TURP	3+3	HT	T2NxM1b
9	3.1	0.9	14.3	AB+5ARi	TURP	3+3	RP	T2NxMo
Mean±SD	2.3±0.27	0.9±0.13	15.0±4.1					

PCa –Prostate cancer, BPH-Benign Prostatic Hyperplasia, IPSS-The International Prostate Symptom Score, PSA-Prostate Specific Antigen AB-alpha blocker, OP-Open Prostatectomy; TURP- Transurethral Resection of Prostate, MT-Medical Therapy, AB- alfa blocker, 5ARi- 5 alfa reductase inhibitor, HT- hormonal therapy, RP- radical prostatectomy

In the Cox regression analysis of the predictors of cancer incidence in patients after BPH surgery, only the PSA reduction rate was a borderline predictor in the unadjusted analysis. In the PCa group, PSA values decreased from 2.30±0.83 to 0.95±0.38 ng/ml after three months and in BPH group from 1.98±0.84 to 0.54±0.33 ng/ml. PSA reduction rate was 58.4±11.6% for the PCa group compared with 70.7±0.58% in the BPH group.

In the Age-adjusted analysis for HR (CI), the PSA reduction rate was 0.050 (0.001-0.937) and this was the sole predictor of prostate cancer incidence after benign prostate surgery (p=0.048). Table 4.

Table 4
Cox regression analysis of predictors of prostatic cancer after benign prostatic surgery

Variable	**Unadjusted Analysis HR (CI)**	**p-value**	**Age Adjusted Analysis HR (CI)**	**p-value**
BPH Surgery Age	0.980 (0.851-1.129)	0.777	0.980 (0.851-1.129)	0.777
BPH-IPSS	0.924 (0.987-1.301)	0.924	0.908 (0.744-1.300)	0.908
Prostate Volume (ccm)	1.011 (0.980-1.044)	0.484	1.013 (0.979-1.048)	0.452
PSA prior to BPH surgery (ng/ml)	1.045 (0.419-2.607)	0.925	1.123 (0.406-3.111)	0.823
PSA 3months postop (ng/ml)	3.842 (0.632-23.35)	0.144	4.797 (0.736-31.25)	*0.101*
PSA reduction rate (%)	0.055(0.002-1.697)	*0.097*	0.050 (0.001-0.937)	0.048
AB+5ARi	4.432 (0.532-36.91)	0.169	4.435 (0.533-36.93)	0.168
AB	0.226 (0.027-1.879)	0.169	0.225 (0.027-1.877)	0.168
BPH surgery:TURP	0.540 (0.121-2.417)	0.420	0.524 (0.116-2.373)	0.401
BPH surgery: OP	1.851 (0.414-8.284)	0.420	1.901 (0.421-8.658)	0.401

BPH-Benign Prostatic Hyperplasia; IPSS- International Prostatic Symptom Score; PSA-Prostatic Specific Antigen; AB-Alpha blocker, 5ARi-5 alpha reductase inhibitors, TURP-Transurethral Resection of Prostate; OP-Open Prostatectomy;

DISCUSSION

The main finding in our study was a low incidence and low mortality of prostate cancer after BPH surgery. We also found that a PSA reduction rate, three months after BPH surgery, could be a predictor of prostate cancer.

Only 1.69% of patients with previous BPH surgery developed prostate cancer. Patients with prostate cancer who were treated with TURP compared to open prostatectomy (OP) had a 4.2-fold lower incidence. A Swedish study by Chokkalingam et al. reported an incidence rate twice as high (2.96%) for prostate cancer after BPH surgery in a group of 1748 patients who were treated with TURP and 824 treated with open prostatectomy. They reported two times more patients with TURP than OP but most of them underwent surgery before the 1980s, when TURP was routinely used (17).

A Danish study by Ørsted et al. observed an incidence rate 3.48% in PCa patients with 77,698 men who received surgical BPH treatment, and Kanno et al., from Japan, presented a similar incidence rate of 3.2% of patients with prostate cancer over 1 to 7 years in a cohort of 407 patients with TURP (18, 19). Carlson et al., with a cohort of 7,901 patients with previous TURP (1982-1997), reports an increased standardized incidence ratio (SIR) for prostate cancer [1.26, CI 95% (1.17–1.35)] but no increased standardized mortality ratio (SMR), [0.59, CI 95% (0.47–0.73)](20). By contrast, Ørsted et al. found that clinical BPH was associated with a two- to three-fold increased risk of PCa incidence and a two- to eight-fold increased risk of PCa mortality. The authors emphasized that this data should not be used to infer causality. The studies of Kanno, Karlsson, and Ørsted presented an incidence rate twice as high of ours. Armenian et al. also observed an increased risk of prostate cancer incidence after BPH surgery (21).

But studies by Greenwald et al. on 800 men with BPH and Simons et al. on sample size on 4,800 men with BPH, did not find an association between BPH and an increase risk of prostate cancer (22, 23).

Ørsted et al. reported the median age at PCa diagnosis was 72 yr. for PCa patients and 75 yr. for BPH patients. This was 2.2 years and eight years higher than in our study, respectively.

We reported a period of 7.7 years from BPH surgery to the diagnosis of prostate cancer. In Wolff, study time of appearance of all cancer cases was up to 7 years (24). Chokkalingam et al. found that patients with TURP developed prostate cancer after 6.5 years and patients with open prostatectomy, one year later. Ørsted et al. presented the median time to diagnosis of PCa after surgery for clinical BPH at 3 years (range: 0-27yr). In Tanaka, 7 of 319 cases of prostatic cancer had previous BPH surgery 22 months to 15 years prior (25).

Hua L, in a Chinese study from 2004, analyzed twelve cases of prostate cancer after BPH surgery which appeared after 10 months to 14 years, with the average at 5-6 years.

We did not find a significant difference in the time of occurrence of prostate cancer in TURP and OP subgroups (7.5 years versus 8.1 years). In a study from Japan by Kanno et al., from 1995 to 2003, 13 (3.2%) of 407 patients, all with TURP, developed prostate cancer over 1 to 7 years. Kato et al. presented case of prostate cancer fourteen months after open prostatectomy in 1996 (26).

All studies showed a period of diagnosis of prostate cancer after BPH surgery from 10 months to 27 years.

Regarding the IPSS score, our PCa patients were severely symptomatic before the diagnosis of prostate cancer. Hua L et al. reported mild to heavy symptoms according to IPSS (21).

We presented reduction values of PSA after three months at 0.94 ng/ml, which was a higher percentage of the reduction compared with the study by Wolff et al., where PSA was reduced from 6.8 ng/ml to 2.2 ng/ml after 48 months. We found that PSA levels were 6.5 times higher compared to the time of BPH surgery. In the Tanaka study all prostate cancer cases presented a significant elevation of the PSA (6.4-399 ng/ml) at the time of cancer diagnosis.

An important finding was a PSA reduction rate of 58.4% 3 months after BPH surgery compared to 70.7% in patients with BPH surgery who did not develop prostate cancer ($p = 0032$). This was similar to Wolff's findings (24).

According to TNM classification and Gleason score, our patients were at a low stage and grade but two had a metastatic disease. Kanno's findings show that 6 of 13 patients were moderately differentiated. The other 6 had poorly differentiated cancer and one had a ductal carcinoma of

the prostate. Hua L described that of twelve cases, 3 were at the T2 stage, 3 at T3, and six had metastasis (21).

In our study, one patient died of prostate cancer with bone metastases. In Hua L's study, 3 of 12 patients died with a metastatic disease.

The limits of our investigation include the small number of patients with prostate cancer and the short follow-up period of patients with BPH surgery. Our study was done in the PSA era, while large epidemiological studies were from the pre-PSA era.

CONCLUSION

BPH surgery did not increase risk of prostate cancer. PSA reduction rate was the sole predictor of prostate cancer incidence after benign prostate surgery.

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