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CONTENT

underwent simple prostatectomy. The authors concluded that there was minimal risk of prostate cancer in patients with BPH compared to the general population (1% lower incidence and 2% excess mortality after the first five years).

Contradictory to these data, clinical studies have shown a minimal risk of only 1-3% for prostate cancer in patients undergoing BPH surgery over a follow-up period of 10 months to 27 years.

No clinical study indicates that BPH increases the risk of prostate cancer and that BPH is not a pre-malignant lesion.

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PROSTATE CANCER AFTER SURGERY FOR BENIGN PROSTATIC HYPERPLASIA

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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 it was 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 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 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 6.5 times increased (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 borderline significant predictors of prostate cancer after BPH surgery.

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

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. 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). The worldwide difference in incidence existed between developed countries in Europe and America and Asia and the African continent (4,5). Both conditions are associated to epidemiological, hormonal, anatomical factors as well as the impact of inflammation, metabolic syndrome and genetic alterations (6-9).

As anatomical connections, the 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 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 oestrogens to androgens increases by 40% in older men and this may affect the natural course of BPH and CaP (14). Asians in the diet use phytoestrogens, which impact the lower prevalence of BPH and CaP compared to the Western diet (15).

Inflammation is associated to a 7.7-fold higher incidence of BPH. Fast-growing prostate may be a risk factor for 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 from 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 for three months. Before surgery patients' PSA value were determined, as well as prostate volume, IPSS score and type and duration of previous drug treatment. At this point PSA value was controlled. Patients with elevated PSA above 4ng/ml had prostate biopsy and in case of 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 for a period of 5 years. Statistical analysis of all examined parameters was performed in patients with prostate cancer, as well as correlation with parameters in the period of BPH surgery was made.

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 Person 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. SPSS statistical software (version 22.0 IBM, Armonk, NY, USA) was used; 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 were undergone to BPH surgery. Transurethral resection of the prostate (TURP) was performed in 476 patients (89.5%) and open prostatectomy (OP) in 56 (10.5%) of the cases. In a period from 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 with suspicion digital-rectal examination and PSA values, a prostate biopsies were done. In three of them, prostatic carcinoma was a diagnosis 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 lower for 6.5 points 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 is 5.3 ccm greater volume 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 45.9ng/ml, a mean of 15.0ng/ml before the prostatic biopsy. The PSA level before BPH surgery was 2.3ng/ml (1.1 to 3.4), and three months after those values were from 0.3 to 1.6ng/ml, mean 0.94ng/ml. In the cancer group, the PSA levels were 6.5 times increased (p=0.001) compared to the ones 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. The longer duration of the medical therapy was associated to 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 the 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 of four patients with therapy with 5ARi had Gleason score ISUP1 and one had ISUP-2. Seven patients were in the T2N0M0 stage, 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 for 7.1 years than in 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 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.

Table3. *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 unadjusted analysis. In PCa group, PSA values decreased from 2.30±0.83 to 0.95±0.38ng/ml after three months and in BPH group from1.98±0.84 to 0.54±0.33ng/ml. PSA reduction rate was 58.4±11.6% for PCa group compared to70.7±0.58% in BPH group.

In the Age-adjusted analysis HR (CI), the PSA reduction rate was 0.050 (0.001-0.937) and 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 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. Swedish study by Chokkalingam et al. reported two times higher (2.96%) incidence of prostate cancer after BPH surgery in a group of 1,748 patients treated with TURP and 824 with open prostatectomy. They reported two times more patients with TURP than OP, but the most of them were undergone surgery before the 1980 s when TURP was routinely used (17).

Danish study by Ørsted et al. in 77,698 men who received surgical BPH treatment observed 3.48% of PCa patients and Kanno et al. from Japan presented a similar incidence of 3.2% patients with prostate cancer over 1 to 7 years in a cohort of 407 patients with TURP (18, 19). Carlson et al. in the cohort of 7,901 patients with previous TURP (1982-1997) reports increased standardized incidence ratio (SIR) for prostate cancer [1.26, CI 95% (1.17 – 1.35)], but not increased standardized mortality ratio (SMR), [0.59, CI 95% (0.47 – 0.73)](20). In contrast, Ørsted et al. found that clinical BPH was associated with a two-fold to three-fold increased risk of PCa incidence and a two-fold to eight-fold increased risk of PCa mortality. The authors emphasized that these data should not be used to infer causality. Kanno, Karlsson and Orsted in their studies presented two times higher incidence than ours. Armenian et al. also observed an increased risk of prostate cancer incidence after BPH surgery (21).

But, studies of 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 increase risk of prostate cancer (22, 23).

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

We reported the meantime 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 of 3 years (range: 0-27 years). In the Tanaka study, 7 out of 319 cases of prostatic cancer had previous BPH surgery 22 months to 15 years ago (25).

Hua L in a Chinese study from 2004 analyzed twelve cases of prostate cancer after BPH surgery that appeared after 10 months to 14 years, 5.6 years on average.

We did not find a significant difference in the time of occurrence of prostate cancer in TURP and OP subgroups (7.5 years versus 8.1years). In a study from Japan by Kanno et al. in the period 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. referred to mild to heavy symptoms according to IPSS (21).

We presented reduction values of PSA after three months on 0.94ng/ml which was a higher percentage of the reduction compared to the study of Wolff et al. where PSA was reduced from 6.8ng/ml to 2.2ng/ml after 48 months. We found that PSA levels were 6.5 times increased compared to the ones at the time of BPH surgery. In the Tanaka study, all prostate cancer presented a significant elevation of the PSA (6.4-399ng/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) which was similar to Wolff's findings (24).

According to TNM classification and Gleason score, our patients were in low stage and grade, but two had metastatic disease. Kanno's findings were that 6 of 13 patients were moderately differentiated, the other 6 were with poorly differentiated cancer, also one with ductal carcinoma of the prostate. Hua L described that out of twelve cases 3 were in the T2 stage, 3 in T3 and six were with metastasis (21).

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

The limits of our investigation were the small number of patients with prostate cancer, 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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