Should all specimens taken during surgical treatment of patients with benign prostatic hyperplasia be assessed by a pathologist?

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Introduction In some patients submitted to transurethral resection of the prostatic (TURP) or prostatectomy (OAE) due to benign prostate hyperplasia (BPH), pathological evaluations (PE) revealed coexistence of prostate cancer (PCa) and BPH. The aim of the study is to evaluate the incidence of PCa diagnosed incidentally in prostate specimens taken during BPH surgery, to assess the need of routine PE and to define the group of patients in whom PE could be abandoned without the risk of omitting clinically significant PCa.
Material and methods 968 consecutive men were subjected to surgical treatment due to BPH in Jan. 2004–Sep. 2010.
Results 823 (85%) underwent TURP and 145 (15%) OAE. Incidental (Inc) PCa was diagnosed in 34(3.5%) pts. T1a and T1b stages were determined in 19 (2%) and 15 (1.5%) cases. Preoperative prostate biopsy due to abnormal prostate specific antigen (PSA) or digital rectal exam (DRE) was performed in 85 (8.8%) pts. Of PCa pts, 7 (20.58%) had undergone a cancer negative biopsy preoperatively. In BPH pts, 78 (8.35%) had undergone a prostate biopsy previously (p <0.01). Univariate and logit regression analyses had not revealed any correlations between age, Pv, serum PSA and frequency of IncPCa. The difference in rate of PCa diagnosed in patients with PSAD ≥0.15 and <0.15 was 8 pts (14.04%) and 20 pts (4.05%), respectively (p <0.001). Gls in those pts was >6 only in 4 cases.
Conclusions Despite the fact of low PCa detection rate observed in our study, this condition was clinically relevant in 15 (1.5%) subjects. It is difficult to establish any cut off values of pts' age, Pv, serum PSA level suggestive of negligible risk for prostate cancer.

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INTRODUCTION

Before it became standard practice to determine prostate specific antigen (PSA) levels in patients with benign prostatic hyperplasia (BPH) qualified for a transurethral resection of prostate (TURP) or open adenoma enucleation (OAE), the incidental prostate cancer (IncPCa) was the most common cancer limited to the organ of origin accidentally diagnosed during pathological evaluation (PE) [1]. The rate of such established InPCa diagnoses was approximately 35%.

Currently, the number of such diagnosed PCa cases is minimal and amounts to approximately 4–16% of all diagnoses [2].
The stage of cancer (pT) detected in the surgical specimens taken from patients during TURP and OAE procedures, determined in accordance with the WHO TNM 2004 classification as T1a and T1b, depends on the amount of neoplastic tissue present in the specimen (<5% and >5%, respectively), and on the neoplasm's grade defined by Gleason score (<7 and ≤7, respectively) [3].

The qualification of patients to TURP and OEA procedures is mainly based on clinical conditions, e.g. lower urinary tract symptoms (LUTS), IPSS questionnaire, result of the digital rectal examination (DRE) and evaluation of the prostate's volume in an ultrasound examination. The DRE completed by the serum PSA (sPSA) level determination is especially important and allows for the selection of patients with higher CaP risk occurrence. Concurrent BPH and CaP, as well as prostatitis and prostatic intraepithelial neoplasia (PIN), which affect the PSA level and prostate's morphology, make it difficult to diagnose accurately. Finally, when prostate cancer is diagnosed in patients with BPH symptoms, treatment appropriate for both conditions may be chosen. In other patients, BPH diagnosis is only presumptive and can only be confirmed by a PE. Currently, post–surgical PE is rather routine than standard management, especially since there are no uniform guidelines as for the amount of tissues examined and the method of their examination. The quantity and sites of collection of the specimen to be examined often depend on an individual decision of the urologist performing the procedure, especially with TURP. Moreover, the question stated in this paper's title is especially justified nowadays, when it is common to use vaporization techniques in the treatment of patients with BPH, making the collection of surgical specimens impossible.

This study was performed in order to evaluate the frequency and oncological characteristics of incidental prostate cancers (IncPCa) accidentally detected during TURP and OAE procedures performed in patients with BPH. In addition, we would like to establish whether it is possible to select a group of patients with BPH who need not undergo PE without increasing the risk of potentially overlooking concurrent prostate cancer.

MATERIAL AND METHODS

The data of all 968 males who underwent surgical treatment due to BPH in the period from January 2004 to September 2010 was analyzed. The data of patients undergoing TURP as part of PCa diagnostics conducted due to PSA level increase and several negative prostate biopsy results were excluded from the analysis. The data of patients with one previous prostate biopsy were not excluded from the analysis. The data obtained in the period from 2004 to 2008 were retrospectively analyzed; the data of patients treated from the beginning of 2009 to September 2010 were collected in the prospective manner. The following elements were analyzed: patients' age, prostate volume, PSA level determined during quali-

fication to surgical treatment, PSAD, and cancer's stage and grade (if neoplasm was detected). In some patients, some diagnostic procedures were not performed or the appropriate data were not recorded. Surgical specimens collected during TURP and OAE were all examined by one of two experienced pathologists.

A multivariate logistic regression model was used to investigate the association between independent covariates and the presence of CaP. A stepwise selection procedure was applied with a 10% level for staying in the model. All tests were two–sided and a 5% level of significance was used. In the case of a significant result, the odds ratio and 95% confidence intervals (CI) were presented for each predictor.

The univariate association between PIN, prostatitis and IncPCa was verified using chi2.

The calculation was done in Stata v. 12 Stata Statistical Software: Release 12, College Station, TX, Stata Corporation LP 2011.

RESULTS

The data obtained from 968 patients surgically treated due to BPH was analyzed; in that group, 823 (85%) patients underwent TURP, and 145 (15%) subjects underwent OAE. Mean (median) (range) age, PSA level, prostate volume and PSAD were as follows: 70 [71] (32–94), 5.07 [3.36] (0.14–105) ng/mL, 70.05 [60.4] (10–350) mL, 0.08 [0.05] (0.01–2.12) (Table 1).

Table 1. *The entire group characteristics*

	Median	Mean	Range
Age	71	70	32–94
Pvol (ml)	70	60.4	10–350
PSA (ng/ml)	3.36	5.07	0.14–105
PSAD	0.05	0.08	0.01–2.12

IncPCa		34	

		T1a – 19				T1b – 15		
Gleason	Score	2	3	4	5	6	7	9
	Pts no	2	5	4	5	12	4	2

Prostatitis	338 (35%)
PIN	45 (4.65%)
RUC	225 (23%)
TRUScoreBx	85 (8.8%)
TURP	823 (85%)
OAE	145 (15%)
Positive DRE	13 (1.34%)

Serum PSA was available in 572 cases. PSA value 0–4 ng/ml; 4.01–10 ng/ml; 10–20 ng/ml and ≥20 ng/ml was noticed in: 339 (59%); 171 (30%); 47 (8%); 15 (3%). Most of patients with high PSA values had other factors influencing PSA levels, including: transurethral catheter, prostatitis or bladder stone (Table 1).

The cancer was diagnosed in 34 patients (3.5%); 29 patients (85%) received TURP, and 5 subjects (15%) underwent OAE (p >0.05). T1a and T1b stages were determined in 19 (2%) and 15 (1.5%) cases, respectively. The IncPCa with a grade ≤6; = 7; ≥8 defined by Gleason score was diagnosed in: 28 (82.4%); 4 (11.7%); and 2 (5.9%), respectively. The mean (median) PSA and PSAD levels in BPH or PCa T1a and T1b groups were as follows: 4.2 [3]; 4.75 [3.09]; 13.51 [4] ng/mL and 0.07 [0.05]; 0.08 [0.06]; 0.39 [0.11]; and they are statistically higher in patients from the PCa

T1b group (p <0.001). Table 2 contains a detailed characteristic of patients with a cancer diagnosis. Detailed characteristic of patients with incidental prostate cancer (IncPCa) diagnosis.

Mean age, PSA level, prostate volume and PSAD level in patients with an incidental prostate cancer diagnosis were as follows: 75 years (49–84), 9.28 ng/mL (0.85–50), 59.31 mL (13.71–160), 0.24 (0.02–2.12). Table 3 contains the data of patients with BPH or prostate cancer diagnosis.

The mean PSA and PSAD levels are statistically higher in patients diagnosed with prostate cancer (p <0.001). Before the surgery, prostate biopsy (TRUScoreBX) was performed in 85 patients (8.8%) with abnormal PSA levels and/or DRE results. Indications for TRUScoreBX included an abnormal DRE result (7 patients), PSA level >4 ng/mL (68 patients), abnormal DRE and

Table 2. *Detailed characteristics of patients with incidental prostate cancer (IncPCa) diagnosis*

		IncPCa	T1a	T1b	p
No		34	19	15	>0.05
Age range (mean) [median]		49–84 (73.3) [75.5]	49–84 (74.4) [74]	50–81 (73) [77]	>0.05
PSA range (mean) [median]		0.85–50 (9.28) [3.64]	0.85–23.4 (5.05) [3.09]	1.68–50 (13.5) [4]	>0.05
Pvol range (mean) [median]		13.7–160 (59.4) [47.86]	17–150 (61.5) [42]	13.7–160 (60) [51]	>0.05
PSAD range (mean) [median]		0.02–2.12 (0.24) [0.07]	0.03–0.19 (0.08) [0.06]	0.02–2.12 (0.3) [0.1]	>0.05
Gleason	≤6	28	19	9	>0.05
	=7	4	0	4	>0.05
	≥8	2	0	2	>0.05
Previous Bx	7	2	5		>0.05
TURP		29 (85%)	15 (79%)	14 (93%)	>0.05
OAE		5 (15%)	4 (21%)	1 (7%)	>0.05

Table 3. *Comparison of patients with BPH and IncPCa*

Surgery type		PIN HG	IncPCa		BPH
			T1a	T1b	
TURP	Age range (mean) [median]	57 – 83 (70) [72]	74.4 [74]	77 [74]	41–94 (70) [71]
			73.1 [76]		
	sPSA range (mean) [median]	0.84–5.6 (3.06) [3.2]	0.85–6.4 (3.02) [2.5]	1.68 –45.61 (4.4) [14.3]	0.14–19.23 (3.36) [2.49]
			0.85–45,61 (9.34) [3.1]		
OAE	Age range (mean) [median]	52–78 (69) [73]	74.5 [73.5]	73 [73]	53–91 (71.3) [72]
			74.2 [73]		
	sPSA range (mean) [median]	2.2–14.04 (7.56) [6.45]	3.64–23.4 (11.1) [6.23]	2.48 (2.48) [2.48]	0.14–28 (7.8) [6.25]
			2.48–23.4 (8.94) [4.93]		
All	Age range (mean) [median]	52–83 (70) [72]	74.4 [74]	77 [73]	41–94 (70.2) [71]
			73.3 [75.5]		
	sPSA range (mean) [median]	0.84–14.04 (4.19) [3.45]	0.85–23.4 (4.75) [3.09]	1.68–45.61 (13.51) [4]	0.14–28 (4.2) [3]
			0.85–45.61 (9.28) [3.64]		

PSA level >4 ng/mL (2 patients). In 8 patients, no indications for prostate biopsy were established on the basis of available medical records. In patients diagnosed with prostate cancer postoperatively, previous biopsy was negative in 7 males (20.58%); in patients diagnosed with BPH, previous biopsy was negative in 78 subjects (8.35%); the aforementioned difference is statistically significant (p = 0.014).

In 338 (35%) patients with prostatitis diagnosed in a PE, 8 males (2.35%) were also diagnosed with PCa; in other patients, 26 cancer cases were diagnosed (4.1%), p = 0.195.

In 45 (4.65%) patients with PIN diagnosed in a PE, 2 males (4.44%) were also diagnosed with PCa; in other patients, 32 cancer cases were diagnosed (3.47%), p = 0.33.

In 225 (23%) patients with urine retention, 7 males (3.1%) were also diagnosed with PCa; in other patients, 31 cancer cases were diagnosed (3.57%), p = 0.9. In patients treated with TURP and OPSU, univariate and logistic regression analyses did not demonstrate any correlation between the patients' age, PSA level and Pv and PCa frequency.

In 57 patients with PSAD level ≥0.15, 8 cases of IncPCa (14.04%) were diagnosed; however, in 493 patients with PSAD level <0.15, 20 cases of IncPCa (4.05%) were established; this difference is statistically significant, p <0.01 (Table 5).

In the group of males with PSA level <4 ng/mL and PSAD level <0.15, 15 cases of prostate cancer were diagnosed. In 9 patients, the stage was T1a, and in 6 males it was determined as T1b. In 4 (0.41%) subjects, Gleason score was 7 or 9 (Tables 4 and 5).

Patients with PSAD ≥0.15 have significantly higher odds of developing PCa than patients with PSAD

Table 4. *Characteristics of patients with IncPCa diagnosis and PSA <4 ng/mL, and PSAD <0.15 values*

				Number (%)			
PSA (ng/ml)				2.06 (0.85–3.77)			
PSAD				0.05 (0.02–0.09)			
CaP		15		T1a – 9		T1b – 6	
Glea-son	Score	2	3	4	5	6	7	9
	Pts no	0	2	3	2	4	2	2
Prostatitis				2 (13.3%)			
PIN				2 (13.3%)			
RUC				0			
TRUScoreBx				0			
TURP				13 (86.7%)			
OAE				2 (13.3%)			
Abnormal DRE				0			

Table 5. *Association with IncCaP (multifactorial logit model)*

CaP	OR	95% CI for OR	P >z
Age ≥71 *vs.* <71			>0.1
PSA 4–10 *vs.* PSA <4			>0.1
PSA ≥10 *vs.* PSA <4			>0.1
PSAD ≥ 0.15	6.24	(1.6; 24.3)	0.01
DRE			>0.1
RUC			>0.1

<0.15. This is the only factor independently associated with PCa.

DISCUSSION

Despite the growing number of new PCa cases, the frequency of IncPCa in patients undergoing surgical treatment for BPH has significantly decreased in recent years [4].

This may result from a lower probability of cancer occurring in patients qualified for TURP and OAE as per current standards (PSA test, TRUS), as well as from a lower number of surgically treated BPH patients due to more efficient pharmacological methods [5].

When using the qualification protocol based on a preoperative assessment including a DRE, PSA level and Pvol, we still have to consider diagnosis of incidental PCa reaching 3–16%. However, in a subsequently published case series we can observe a decreasing tendency, which can be confirmed by a 3.5% rate of IncPCa diagnosis in our material [6, 7, 8].

This tendency is more pronounced after considering the IncPCa pT1b cases. Those patients are in a group of special interest due to their worse prognosis. Robinson et al. (2007) [9] showed that in a group of 196 patients diagnosed with IncPCa pT1a/b, cancer was the cause of death in 2.3% of patients with IncPCa pT1a and in 21.1% of patients with pT1b.

In 85 (8.8%) patients examined before BPH treatment, a TRUScoreBx was performed due to PCa suspicion. The PE of biopsy specimens did not reveal any case of cancer. In that group, IncPCa diagnosis was significantly more frequent after PE of surgical specimens collected during TURP or OAE. In the study period, a standard method used in our Clinic was a sextant prostate biopsy. However, this method is no longer recommended as per the 2012 European Association of Urology (EAU) Guidelines. In patients with prostate volume below 40 mL, the minimal number of recommended tissue cores collected during TRUScoreBX is 8. However, the collection of 12 tissue cores during TRUScoreBx significantly in-

creases the probability of PCa diagnosis (32.5% *vs.* 40.4%) (p 0.004). The collection of subsequent 9 tissue cores, i.e.: 21 in total, increases the rate of PCa diagnosis by 6.7% *vs.* 12–tissue core protocol [10].

A discrepancy between the site of the most common PCa localization (peripheral zone) and the purpose of intervention – adenoma (transition zone) is also significant. The low rate of PCa diagnosis in the surgical specimens collected during TURP performed in patients who previously had several biopsies caused that TURP is no longer a recommended tool in PCa diagnostic [11].

However, there are studies demonstrating that TURP significantly increases the sensitivity of prostate cancer detection by 12.5% in patients who underwent at least two previous negative Bx [12]. In patients with low PSA levels and normal DRE results, TURP enables detection of PCa in a higher percentage of subjects *vs.* biopsy. Undoubtedly, this phenomenon is mainly affected by the amount of tissue collected, which is significantly higher in case of TURP and OAE [8].

An argument in favour of not performing the PE is the presumption that a complete excision of neoplasm during TURP or OAE is possible; such a presumption would make those interventions therapeutic procedures [13]. However, the results of other studies deny this. It has been shown that in patients undergoing radical prostatectomy (RP) due to IncPCa, cancer was not detected in the postoperative specimen in approximately 20% of cases. In the same paper, there was also no difference in the patients' cancer specific survival between the pT1a and pT1b groups observed. The only prognostic factors were PSA levels determined before TURP or OAE, and Gleason score of incidentally diagnosed PCa [14]. In our paper, IncPCa pT1b was diagnosed in 15 (1.5%) patients. However, the use of the aforementioned criteria resulted in a diagnosis of only 6 (0.5%) clinically relevant cancer cases. Due to the retrospective character of a part of this study, we have obtained data from the follow–up of 18 patients (53%) with IncPCa diagnosis. In that group, the following events were reported: 1 patient died due to prostate cancer (3%) (he had previously been receiving hormonal therapy), 1 patient received treatment with radical prostatectomy (3%), 2 patients (6%) received hormonal therapy; 2 subsequent patients (6%) received radiotherapy with HTx, and 12 (35%) males underwent the watchful waiting (WW).

Despite the IncPCa diagnosis, the majority of patients underwent WW, which consists of routine patient examination and regular PSA level determination. We know that the risk of prostate cancer occurrence in patients hospitalized due to BPH is 8–fold higher than in healthy males [15]. Therefore, patients undergoing BPH treatment without IncPCa detection should be qualified for a further urological follow–up consisting of routinely performed DREs and PSA level determinations. Another group of patients consisting of subjects with abnormal DRE results and/or elevated PSA levels qualified for a prostate biopsy (Bx), which revealed no neoplastic lesions. For urologists performing minimally invasive prostate procedures, this is a sufficient argument to qualify the patient for a treatment method, which makes the collection of tissue material for PE impossible [16].

Undoubtedly, patients about to undergo TURP or OAE should be made aware of the possibility of accidentally diagnosing PCa during these procedures. It is especially important with patients qualified for surgical treatment with methods precluding collection of tissue specimens for PE (laser, microwave) [16].

In our study in MVA, PSAD was the only factor independently connected with higher frequency of IncPCa (p = 0.01). Our results confirm observations of other authors that PSAD can be useful in predicting PCa in patients submitted to surgical BPH therapy and not only for improving PCa detection in PSA "gray zone" patients submitted to TRUScoreBx [17]. The same study indicates that PSAD for transitional zone is more useful than PSAD and PSA alone [17].

Another aspect is the co–presence of prostate cancer, prostatitis, prostate enlargement and urine retention, which may render an accurate interpretation of the PSA and DRE results difficult. However, no association between the aforementioned conditions has been observed up to date [18]. In our results, we also did not observe a significant association between prostatitis, PIN or urine retention occurrence.

The main bias of the study is its partially retrospective nature. Prostate volume was assessed mainly based on transabdominal ultrasound (271 pts underwent TRUS). No statistical significance was noted in subanalysis for groups of men with Pvol assessed in TRUS compared to the overall cohort (data not shown). Therefore, we assume that this did not significantly affect our main results.

Postoperative specimens were assessed by one of two pathologists, which allows for an interobserver variability. In that time, we also did not use nomograms to predict IncPCa diagnosis and patients with previous negative TRUScoreBx did not have PCA3 test; both of which are considered to improve PCa diagnosis [19]. Finally, a small number of cases with IncPCa influenced the statistical results.

However, in cases when the PE was not performed in patients with normal DRE results, PSA level <4 ng/mL and PSAD level <0.15, the risk of overlooking the

IncPCa still exists. In our paper, 15 patients (1.5%) meeting this criteria were diagnosed with IncPCa. In that group, 4 patients were diagnosed with clinically relevant cancer.

CONCLUSIONS

Despite the fact of the low prostate cancer detection rate observed in our study, this condition was clinically relevant in 15 (1.5%) subjects.

It is difficult to select a group of patients with a specific age, Pv, and serum PSA level enabling the omission of pathological analysis of surgical material collected during BPH treatment. Patients who underwent previous prostate biopsy with abnormal PSAD levels are in the group of subjects with an increased risk of IncPCa occurrence; and it seems that PE should be performed in this group.

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