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INCIDENTAL PROSTATE CANCER IN PATIENTS TREATED FOR BENIGN PROSTATE HYPERPLASIA IN THE PERIOD OF 21 YEARS

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SUMMARY – The aim of this study was to determine the incidence of incidental prostate cancer and its clinical significance among patients who underwent transurethral prostate resection or transvesical adenomectomy for benign prostate hyperplasia at the Department of Urology in Sestre milosrdnice University Hospital Center from January 1997 to December 2017. A total of 277/4,372 (6.34%) patients from our cohort were diagnosed with incidental prostate cancer (mean age 74.5 years). Due to incomplete data, 12 patents were excluded from further analysis. 44.91% (119/265 patents) of our cohort were stage T1a and 55.09% (146/265) were stage T1b. Clinically significant prostate cancer was found in 168/265 patients (63.40%). When divided into two groups, Gleason score ≤6 (mean age 73.58 years) and Gleason score ≥7 (mean age 75.77 years), the results showed that Gleason score ≥7 patients were significantly older (p=0.0104) and that the tumor extent among patients in this group (mean = 34.58%) was higher than that in Gleason score ≤6 group (mean = 11.11%) (p=0.0169). More than a half of patients in our cohort had T1b stage prostate cancer. We found that 63.4% of carcinomas were clinically significant, with 52/265 (19,62%) patients affected by ISUP grade 4 and 5 cancers. Based on our research, we cannot give any recommendations regarding incidental prostate cancer treatment due to lacking preoperative (PSA, DRE) and follow-up data.

Key words: *Benign prostate hyperplasia; BPH; Incidental prostate cancer; TURP*

Introduction

Incidental prostate cancer is detected in histopathologic samples of men undergoing transurethral prostate resection (TURP) or transvesical adenomectomy for bladder outlet obstruction symptoms and related conditions (such as bladder stones, urinary infections etc.) under clinical diagnosis of benign prostate hyperplasia (BPH). Nowadays, prostate cancer is suspected in patents with elevated age-adjusted PSA levels and suspicious digital rectal exam findings. The diagnosis is confirmed by performing transrectal ultrasound guided prostate biopsy and histopathological examination of biopsy specimens. Before the introduction of wide-scale PSA testing, incidental prostate cancer was found in 10-31% of histopathology samples of patients surgically treated for BPH[1-6]. In the PSA testing era, the incidence of incidental prostate cancer has decreased severely and is now at 16%, according to literature[6,7]. Clinical significance and further treatment of incidentally found prostate cancer is strongly debated in literature. The aim of this study was to determine the incidence of incidental prostate cancer and its clinical significance among patients who underwent TURP or transvesical adenomectomy for BPH at our Department from January 1997 to December 2017.

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Patients and Methods

We performed a retrospective analysis of patients treated by transurethral prostate resection and transvesical adenomectomy for benign prostate hyperplasia at the Department of Urology at Sestre milosrdnice University Hospital Center over a 21-year period from January 1997 to December 2017. Surgical data, patient age at the time of the surgery and histopathology findings were reviewed. Histopathological examination was performed by an experienced pathologist at our Hospital. Tumor extent and Gleason score were determined. Patients with detected incidental cancer were divided in two groups according to histopathology findings - T1a group (tumor found in less than 5 % of the resected material) and T1b group (tumor found in more than 5% of the resected material). Patients who had undergone surgery for bladder outlet obstruction with previously diagnosed prostate cancer were excluded from the study. This analysis did not include postoperative follow-up of newly diagnosed prostate cancer patients. In generating results, only basic statistics (descriptive statistics and t-test) was performed using Excel data analysis.

Results

From January 1997 to December 2017 a total of 4,797 patients were surgically treated for bladder outlet obstruction at the Department of Urology at Sestre milosrdnice University Hospital Center (Table 1). 425 patients who had previously been diagnosed with prostate cancer and had undergone surgery to relieve bladder obstruction were excluded from further analysis. Thus, 4,372 patients in the period of 21 years were treated by performing TURP or transvesical adenomectomy due to bladder obstruction presumably caused by BPH. A total of 277/4,372 (6.34%) patients from our cohort were diagnosed with prostate cancer following histopathologic examination of tissue specimens obtained at transurethral prostate resection (TURP) or transvesical adenomectomy. Mean age at the time of the surgery among incidental prostate cancer patients was 74.5 years, with the youngest patient aged 46 and the oldest aged 93. Due to inconclusive histopathology findings, either because the pathologist was unable to determine the Gleason score due to poor tumor differentiation, or because ductal carcinoma was found (1 patient), 12/277 patients (4.33%) were excluded from further analysis.

Table 1. Surgical procedures for the treatment of BPH performed over a 21-year period at the Department of Urology in Sestre milosrdnice University Hospital Center (N=4797)

	TURP	Transvesical adenomectomy
1997	245	63
1998	208	43
1999	236	41
2000	255	31
2001	264	29
2002	307	45
2003	287	27
2004	155	50
2005	165	49
2006	176	39
2007	169	43
2008	163	61
2009	168	44
2010	147	56
2011	146	33
2012	122	40
2013	240	70
2014	128	46
2015	73	52
2016	74	51
2017	98	58
TOTAL:	3826	971

A total of 119 patients (44.91% of incidental prostate cancers and 2.72% of all operated due to BPH) were characterized as T1a prostate cancer group (tumor found in ≤5% of the resected tissue). Mean age in T1a group was 73.66 years, with the youngest patient aged 53 and the oldest 93. The remaining 146 patients (55.09% of incidental prostate cancers and 3.34% of our cohort) were characterized as T1b group (tumor found in more than 5 % of tissue sample) (Fig. 1). Mean age in T1b group was 75.39 years (range: 46 - 91 years). Upon reviewing the clinical significance of our findings, we found that there were 22 patients (18.49%) in T1a group with histopathologically found prostate cancer of Gleason score 7 or higher, which cannot be considered clinically insignificant.

Based on the Gleason score and tumor percentage, we divided our cohort into two groups: clinically significant (former A2 stage; tumor size >5% or Gleason score ≥7) and clinically insignificant (former A1 stage; tumor size <5% and Gleason score ≤6)[1]. In the clinically insignificant group, there were 97/265 (36.60%) patients with the mean age of 73.19 years (the youngest patient aged 53 and the oldest 93). Clinically significant prostate cancer was found in 168/265 patients (63.40%) with the mean age of 75.43 years (the youngest patient aged 46 and the oldest 91). Looking at age distribution of patients in clinically significant and insignificant incidental prostate cancer groups, our hypothesis was that there was no significant age difference between the two groups. Statistical analysis of age distribution overruled our initial assumption and showed that the significant cancer group (mean age 75.43 years) was older than the insignificant cancer group (mean age 73.19 years) and the difference was statistically significant (p=0.0197). When divided into groups based on the Gleason score, and excluding tumor volume from the calculation, patients with incidental prostate cancer showed a slightly different distribution. There were 144 patients (54.34%) with ISUP grade 1, 22 (8.3%) with grade 2, 47 (17.74%) with grade 3, 32 (12.08%) with grade 4 and 20 patients (7.55%) with grade 5 prostate carcinoma (Table 2). Tumor size (expressed as the percentage of tumor observed in histopathology specimen) was, expectedly, the largest among grade groups 4 and 5 carcinomas, with the mean value of 40 and 56%, respectively. Also, when divided into two groups, Gleason score ≤6 (mean age 73.58 years) and Gleason score ≥7 (mean age 75.77 years), taking only the Gleason score into consideration, the results showed that Gleason score ≥7 patients were significantly older (p=0.0104) and the tumor extent (%) among patients in this group (mean = 34.58%) was higher than that in the Gleason score ≤6 group (mean = 11.11%) (p=0.0169) (Fig. 2).

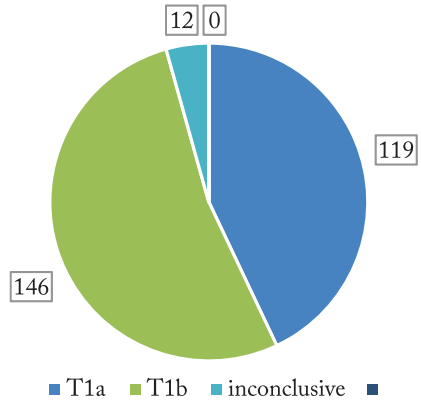

Fig. 1. Incidental prostate cancer patients distributed to groups according to histopathology findings (N=277).

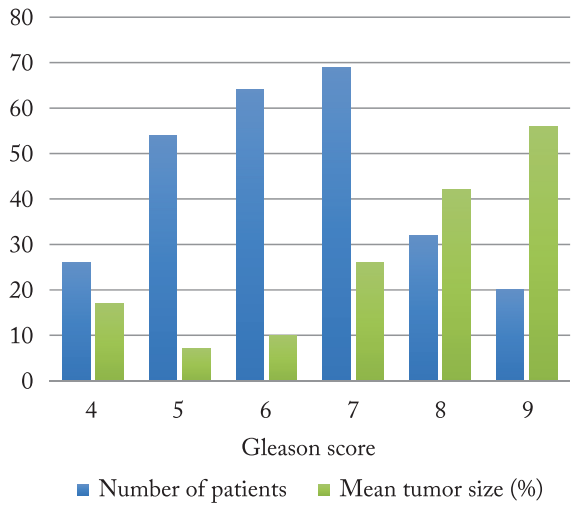

Fig. 2. Patient distribution according to Gleason score and tumor size (N=265).

Table 2. Patient distribution according to Gleason score, age and tumor extent (N=265)

Grade group	Gleason score	Number of patients	Mean age (Min-max)(y)	Mean tumor size (%)
1	4	26	77.13(66-93)	17
	5	54	72.37 (53-86)	7
	6	64	72.70 (46-89)	10
2	7(3+4)	22	75.82 (57-88)	16
3	7(4+3)	47	74.46 (53-87)	30
4	8	32	76.41 (59-89)	42
5	9	20	77.85 (65-91)	56
	10	0	0	0

Discussion

Incidental prostate cancer is defined as prostate cancer discovered during histopathological analysis of tissue samples obtained at TURP or transvesical adenomectomy performed due to bladder outlet obstruction in patients with negative digital rectal exam, age-adjusted PSA levels within normal range and no previous diagnosis of prostate cancer. It accounts for approximately 4-16% of all prostate cancers[1-8]. The incidence of incidental prostate cancer has dropped significantly in the era of routine PSA testing, as shown by retrospective studies performed worldwide in recent years[1-14]. Although it has been recorded that overall incidence of incidental prostate cancer has decreased by more than 50%, it has been highlighted in literature that, regardless of the significant decline in finding T1b incidental prostate cancer in TURP specimens, there is a significant increase in poorly differentiated prostate cancer[9,12]. Zigeuner *et al*. retrospectively reviewed medical and surgical histories of 445 patients who underwent TURP or open prostatectomy, but who had had at least one previous prostate biopsy due to elevated PSA levels or positive DRE findings. The results showed that cancer detection rate was 7.9%, and they found a positive correlation between positive DRE findings and incidental prostate cancer. During post-surgery follow-up of "cancer free" patients, biopsy was performed on 38 patients due to suspicion of prostate cancer. Consequently, 12 additional patents were diagnosed with prostate cancer[10]. Schwartz *et al*. recommend serial DREs in patients who underwent surgery due to BPH and have a negative histology for prostate cancer. Their study showed that approximately 5% of all newly diagnosed patients with prostate cancer have previously had surgery for benign disease and are presented in late stages of the disease and with bone metastases in 50% of cases[14]. Postoperative PSA values should be included in follow-up alongside DRE.

With the cancer detection rate during TUPR and transvesical adenomectomy at 6.34%, our results are comparable to the literature. The fault of our cohort is that PSA levels and preoperative DRE were not available for all the patients and were not considered. Also, postoperative follow-up was not reviewed, so cancer-specific mortality and recurrence rate is unknown. However, our findings diverge from those reported by most authors. In our cohort, 55.09% of patients were T1b stage and 63.4% (168 patients) had clinically significant prostate cancer (Gleason score ≥7 and ≥5% of tissue was tumor). A total of 52/165 (31,2%) patients had Gleason score 8 and 9 carcinoma. Our results showed an increase both in the incidence of poorly differentiated prostate cancer and in T1b stage prostate cancer. These findings could be explained by inadequate population education on the importance of PSA testing and urology exams. However, an increase in PSA testing, prostate biopsies, detection of early stages of prostate cancer and an increase in radical prostatectomy procedures has been recorded in recent years.

When observing treatment options, the general recommendation for T1a cancer is expectant management, and curative treatment for T1b cancer[16-20]. When discussing our data, we would like to point out that there were 22/119 (18.49%) patients with histopathologically detected prostate cancer of Gleason score 7 or higher in T1a stage. Recommending treatment options for these patients could be challenging. In their research, Capitanio *et al*. stated that T stage is not a good predictor for residual prostate cancer. Their analysis showed that pre- and postoperative PSA levels and Gleason score are significant predictors of residual cancer observed at histopathological specimens after radical prostatectomy[17]. Besides radical prostatectomy, active surveillance and watchful waiting, depending on patient age, are valid treatment options, according to literature[16-20].

Conclusion

Incidental prostate cancer was found in 6.34% (277/4,372) of patients operated at our Department for benign prostate disease. More than a half of patients had T1b stage prostate cancer. We found that 63.4% (168/265) of carcinomas were clinically significant, with 52 patients affected by ISUP grade 4 and 5 cancers. Patients with clinically significant prostate cancer were older than those with insignificant cancer. Patients with malignant carcinoma (Gleason score ≥7) were older and their tumors were larger in volume than those classified as Gleason score 6 or lower.

Based on our research, we cannot give any recommendations regarding incidental prostate treatment due to lacking preoperative (PSA, DRE) and follow-

up data. To understand the significance of incidental prostate cancer, further studies and long-term follow up will be required.

Abbreviations

TURP – transurethral prostate resection
DRE – digital rectal exam
PSA – prostate specific antigen

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Sažetak

INCIDENTALNI KARCINOM PROSTATE U PACIJENATA LIJEČENIH ZBOG BENIGNE HIPERPLAZIJE PROSTATE U PERIODU OD 21 GODINE

M. Pirša, I. Pezelj, M. Knežević, B. Spajić, I. Tomašković, A. Reljić i *B. Ružić*

Cilj ovog rada bio je utvrditi učestalost incidentalnog karcinoma prostate i klinički značaj istog u pacijenata podvrgnutih transuretralnoj resekciji prostate i transvezikalnoj prostatektomiji zbog benigne prostatične hiperplazije na Klinici za urologiju KBC-a „Sestre milosrdnice“ od siječnja 1997. do prosinca 2017. godine. Incidentalni karcinom prostate pronađen je kod 277/4,372 (6,34%) pacijenata iz naše studije (prosječna dob 74,5 godina). Zbog neadekvatnih podataka, 12 pacijentata isključeno je iz daljnje analize. 44,91% (119/265 pacijenata) nalazilo se u T1a stadiju, a 55,09% (145/265) u T1b stadiju bolesti. Klinički značajan karcinom pronađen je kod 168/246 pacijenata (60,40%). Kada se pacijenti podijele u dvije skupine, Gleason zbroj ≤6 (srednja dob 73,58 godina) i Gleason zbroj ≥7 (srednja dob 75,77 godina), rezultati pokazuju da su pacijenti s karcinomom prostate Gleason zbroja ≥7 statistički značajno stariji (p=0,0104) te da karcinom zahvaća veći dio pregledanog tkiva (prosjek= 34,58%) nego u bolesnika s karcinomom Gleason zbroja ≤6 (prosjek= 11,11%) (p=0,0169). U našoj studiji, više od polovice pacijenata s dijagnosticiranim karcinomom imalo je T1b stadij karcinoma prostate, 63,4% pacijenata imalo je klinički značajan karcinom, od čega je 52/265 (19,62%) pacijenata bolovalo od karcinoma ISUP stadija 4 i 5. Na temelju ovog istraživanja ne možemo dati preporuke o liječenju novodijagnosticiranog incidentalnog karcinoma prostate zbog insuficijentnih preoperativnih parametara (PSA, digitorektalni pregled) te nedostatnih podataka o postoperativnom praćenju tih pacijenata.

Ključne riječi: *Benigna hiperplazija prostate; BPH; Incidentalni karcinom prostate; TURP*