ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Frequency of Incidental Cancer in Transurethral Prostate Resection Materials and Our Clinical Approach to These Patients; a Retrospective File Scan

Transüretral Prostat Rezeksiyonu Materyallerindeki İnsidental Kanser Sıklığı ve Bu Hastalardaki Klinik Yaklaşımımız; Geriye Dönük Dosya Taraması

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ABSTRACT

Aim: *This study aims to determine the incidence of cancer in patients who underwent transurethral resection of the prostate (TUR-P) due to bladder outlet obstruction and to share our clinical approach to these patients at Niğde Ömer Halisdemir University Training and Research Hospital.*

Material and Method: *The pathology reports of 650 TUR-P specimens from January 1, 2012, to December 31, 2017, were retrospectively screened. In the pathology results of the prostatic adenocarcinoma patients, the age, tumor stage and Gleason score (GS) were evaluated. Physical examination data and the serum total Prostate Specific Antigen (PSA) levels, as well as the radiological findings, were analyzed according to the hospital records.*

Results: *After excluding nine patients with known prostate carcinoma there were 15 adenocarcinomas out of 641 patients (2.34%). The mean age was 72. Eleven patients were diagnosed as GS 6, and four patients were diagnosed with GS 7 prostate adenocarcinoma. Serum total PSA levels ranged from 1.56 to 9.22 ng/mL. T1a tumor was detected in 11 patients and T1b tumor in 4 patients.*

Conclusion: *Considering the studies that reported incidental prostate cancer (IPC) rates in the PSA era, our rate is close to the lower limit. The application of primary therapies should not be avoided in patients with IPC after TUR-P.*

Key words: *incidental prostate cancer; transurethral resection; PSA*

ÖZET

Amaç: *Çalışma, Niğde Ömer Halisdemir Üniversitesi Eğitim ve Araştırma Hastanesi (EAH)'nde mesane çıkış obstrüksiyonu nedeniyle transüretral prostat rezeksiyonu (TUR-P) uygulanan hastalardaki kanser sıklığını belirlemek ve bu hastalardaki klinik yaklaşımımızı paylaşmayı amaçlamaktadır.*

Materyal ve Metot: *1 Ocak 2012–31 Aralık 2017 tarihleri arasındaki 650 TUR-P materyaline ait patoloji sonuç raporu geriye dönük olarak tarandı. Patoloji sonuç raporlarında prostatik adenokarsinom tanılı hastaların yaşı, tümörün evresi ve Gleason skoru (GS), hastanemizin bilgi yönetim sisteminde serum total PSA düzeyleri, fizik muayene ve görüntüleme bulguları tarandı.*

Bulgular: *Bilinen prostat kanseri tanısı olan 9 hasta çıkarıldığında 641 hastadan 15'inde (%2,34) adenokarsinom saptandı. Ortalama yaş 72 olup 11 hasta GS 6, 4 hastada GS 7 prostat adenokarsinomu tanısı almıştı. Serum total PSA düzeyleri 1,56 ile 9,22 ng/mL arasında değişmekteydi. 11 hastada T1a, 4 hastada T1b tümör saptandı.*

Sonuç: *Serum PSA düzeyleri ölçümlerinin yaygın olarak kullanılmaya başlamasından sonra yapılan insidental prostat kanseri (İPK) oranlarını bildiren çalışmalar değerlendirildiğinde bizim oranımız alt sınıra yakındır. TUR-P sonrası İPK saptanan hastalarda birincil tedavilerin uygulanmasından kaçınılmamalıdır.*

Anahtar kelimeler: *insidental prostat kanseri; transüretral rezeksiyon; PSA*

Introduction

Prostate cancer is the second most common type of cancer in men. Autopsy series showed up to 80% latent prostate cancer over 80 years old[1]. Transurethral resection of prostate (TUR-P) is considered as standard surgical treatment modality for treating benign prostatic hyperplasia (BPH). Incidental prostate cancer (IPC) is defined as the prostate cancer, which is not evident clinically by digital rectal examination (DRE) or imaging methods. Today, with prostate-specific antigen (PSA) screening in serum, the incidence IPC in TUR-P specimens is low. In the pre-PSA era the rate of IPC was high up to 27%. Today the prevalence of IPC is reported to vary between 1.4–16.7% in different studies[2,3].

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It has been reported that radical prostatectomy is associated with low mortality compared to watchful waiting in early prostate cancer treatment and the benefit rate from oncologic surgical treatment was found to be higher in patients 65 years and younger[4].

Prostate carcinoma often arises from peripheral zone (PZ) while TUR-P targets the transitional zone (TZ) of the prostate. Studies emphasize that TZ originated prostate cancer has a better prognosis than prostate cancer located in the PZ[5].

Prostate adenocarcinoma is an important cause of morbidity and mortality. Incidental adenocarcinoma cases should be treated with appropriate methods after clinical staging. In some IPC cases clinical course can become unfavorable and further treatments can be costly. In the literature, the prevalence of IPC is reported at different rates in studies from different centers. This is often due to sampling differences by pathologists or due to differences in laboratory and radiological screening protocols for predicting carcinoma prior to TUR-P. In this study, we aimed to determine the incidence of cancer in patients who underwent TUR-P for BPH treatment, compare our rate with the literature and to share our clinical approach to these patients in our center.

Material and Method

Our study is planned as a descriptive retrospective research. The pathology result reports of 650 TUR-P specimens from January 1, 2012 to December 31, 2017 were retrospectively screened at Niğde Ömer Halisdemir University School of Medicine, Training and Research Hospital. In the pathology result reports with prostatic adenocarcinoma age, tumor stage and Gleason score (GS) were evaluated. Patients with known prostate cancer who underwent TUR-P for palliative purposes were excluded from the study.

The sample size calculation was not included due to the design of our study. The number of cases examined in our study was considered as tumor positive patients who were admitted to the urology clinic in our center for TUR-P and they were the whole population for incidental prostate carcinoma.

Regarding processing of TUR-P chips, guidelines of College of American Pathologists (CAP) were followed. All the specimens were weighed, then the specimens that weigh 12 g or less submitted in their entirety. For specimens that weigh more than 12 g, the initial 12 g were submitted and 1 cassette for every additional 5 g was submitted. In case of high grade prostatic intraepithelial neoplasia (H-PIN) or IPC, all remaining TUR material were submitted for histopathologic evaluation. Sections at a thickness of 4 μm were cut from formalin fixed paraffin embedded tissues and stained with hematoxylin-eosin.

For evaluating the GS, the primary and the secondary histologic patterns of tumor were scored ranging 1 to 5. Combined GS was determined by addition of scores of these two most common morphological patterns. If a tumor had only one histologic pattern, then score of that pattern was doubled to find the combined GS.

For determining the clinical stage of the tumor, the percentage of tissue involved by carcinoma was reported, with 5% the cutoff between T1a and T1b disease

In our hospital's information management system serum total PSA levels, physical examination and imaging findings were also screened for patients with adenocarcinoma.

Our study was conducted in accordance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki. Niğde Ömer Halisdemir University Ethics Committee has approved our study by the 2018/10–04 decision.

Results

After excluding 9 patients with known prostate carcinoma, who underwent palliative TUR-P for bladder outlet obstruction, there were 15 adenocarcinomas out of 641 patients (2.34%). The mean age was 72 (ranging from 59 to 81). 11 patients had GS 3+3=6, 3 patients had 3+4=7 and 1 patient had 4+3=7 prostatic adenocarcinoma (Figure 1, 2). T1a tumor was detected in 11 patients and T1b tumor in 4 patients. 3 (20%) of the patients with cancer were 65 years of age and younger while 12 patients (80%) were over 65 years of age. All patients under 65 years of age had T1a and combined GS 6 tumors. Serum total PSA levels ranged from 1.56 to 9.22 ng/mL among all 15 patients with carcinoma.

There are different approaches to the prostate needle biopsy decision in patients with no abnormal findings in DRE, with 2.5 ng/mL and 4ng/mL as the upper limit of PSA. In our practice we use PSA threshold of 4.0 ng/mL for men over 60 years of age and 2.5 ng/mL for men between 50–60 years of age. If there is no abnormality in DRE in patients with a PSA value below

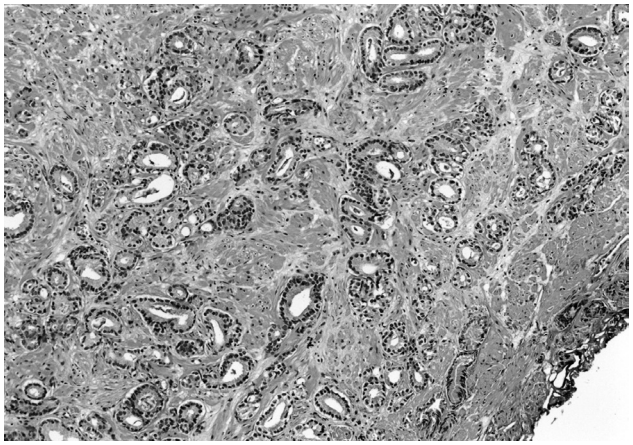

Figure 1. *Well-formed, individual glands of various sizes including branching glands with intervening stroma. Focus of Gleason pattern 3 prostatic adenocarcinoma. (HEx100)*

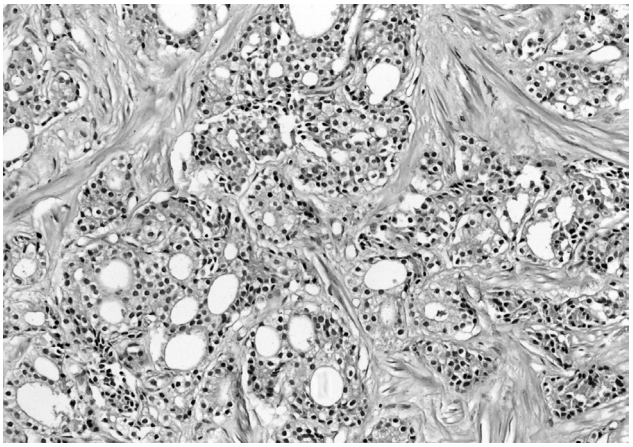

Figure 2. *Poorly-formed, fused, and cribriform glands. Focus of Gleason pattern 4 prostatic adenocarcinoma. (HEx200)*

2.5 ng/mL, no additional examination is performed. 5 patients with IPC had PSA values below 2.5 ng/mL (ranging from 1.56 to 2.2, mean 1.87) and no additional examination was performed prior to the operation due to the absence of abnormal findings in DRE. The mean age of these 5 patients was 69.2 (ranging from 59 to 79) and GS 6 prostatic adenocarcinoma was detected in all. The clinical stage of 4 patients was reported as T1a and the clinical stage of 1 patient was T1b (PSA 2.05 ng/mL, age 68). The biopsy results of these 5 patients were confirmed as GS 6 in the postoperative period. 4 patients with T1a is in active surveillance. 1 patient with T1b was informed about active surveillance, radical prostatectomy, radiotherapy and brachytherapy options. The patient chose the intensity modulated radiotherapy (IMRT). There is no biochemical recurrence in 3 years follow-up.

Screening for prostate carcinoma is recommended for patients who have a life expectancy of at least 10 years. Therefore, in patients over 80 years of age, there are approaches to avoid PSA screening if they are not symptomatic in terms of metastases that may be related to prostate carcinoma. In our study, two patients with IPC were above 80 years of age and PSA examination was performed due to surgical treatment planning (81 y, PSA 9.13 ng/mL, GS 3+3=6, T1a-80 y, PSA 7.09 ng/mL, GS 3+4=7, T1a). The patients were informed about the risk of prostate cancer due to elevated PSA levels but they did not want to perform the recommended prostate needle biopsy under guidance of transrectal ultrasonography. No metastases were detected in postoperative evaluation. One of the patients died at the 6th postoperative month due to chronic obstructive pulmonary disease. No additional treatment was given to the other patient due to the lack of PSA elevation.

The mean age of the other 8 patients was 71.6 (ranging from 59 to 76), and the mean PSA was 6.11 ng/mL (ranging from 4.41 to 9.22). 5 patients had T1a tumors with GS of 3+3=6 while 2 patients had T1b tumor with GS 3+4=7 and 1 patient had T1b tumor with GS 4+3=7.6 patients underwent TUR-P operation after benign preoperative TRUSG + prostate needle biopsy results. The mpMRI results of 2 patients were evaluated as PI-RADS 3 (intermediate risk, clinically significant cancer is equivocal). These patients showed symptoms of severe bladder outlet obstruction and they did not want to undergo additional examination but they requested surgical treatment (Table 1, 2).

Discussion

PSA is a serine protease secreted from prostate epithelial cells and serum PSA levels may also increase in benign pathologies such as BPH and prostatitis[6–8]. In T1a tumors and tumors with low GS it may not elevate enough to suggest cancer. In patients with serum total PSA levels above 4 ng/mL, it is recommended to exclude prostate cancer before TUR-P with prostate

Table 1. *Clinical and pathological data of PSA <4 patients*

Age	PSA (ng/mL)	DRE	Prostate volume	GS	Stage
79	1.56	Grade 1, Benign Consistency	46 cc	3+3=6	T1a
59	1.85	Grade 1, Benign Consistency	52 cc	3+3=6	T1a
68	2.05	Grade 1.5, Benign Consistency	68 cc	3+3=6	T1b
65	1.72	Grade 1, Benign Consistency	48 cc	3+3=6	T1a
75	2.2	Grade 1.5, Benign Consistency	73 cc	3+3=6	T1a

PSA, prostate specific antigen; DRE, digital rectal examination; GS, Gleason score.

Table 2. *Clinical and pathological data of PSA >4 patients*

Age	PSA (ng/mL)	DRE	Prostate volume	MpMRI	GS	Stage
76	6.3	Grade 1, Asymmetric Right Lobe	55 cc	-	4+3=7	T1a
59	5.04	Grade 1, Benign Consistency	41 cc	-	3+3=6	T1a
75	5.06	Grade 1.5, Benign Consistency	63 cc	PIRADS 3	3+3=6	T1a
76	8.86	Grade 1.5, Fibrotic Consistency	72 cc	-	3+3=6	T1a
70	4.41	Grade 1, Benign Consistency	45 cc	PIRADS 3	3+3=6	T1b
71	5.6	Grade 1, Asymmetric Left Lobe	58 cc	-	3+4=7	T1b
72	9.22	Grade 2, Benign Consistency	85 cc	-	3+3=6	T1a
74	4.44	Grade 1, Benign Consistency	57 cc	-	3+4=7	T1b
81	9.13	Grade 1.5, Fibrotic Consistency	69 cc	-	3+3=6	T1a
80	7.09	Grade 1, Benign Consistency	56 cc	-	3+3=6	T1a

PSA, prostate specific antigen; DRE, digital rectal examination; MpMRI, multiparametric magnetic resonance imaging; PIRADS, prostate imaging reporting and data system, GS, Gleason score.

needle biopsy. In recent years, this rate is recommended to withdraw to 2.5 ng/mL[9].

Many studies have compared IPC rates between the pre-PSA and the PSA era. Tombal et al. reported that the rate of IPC decreased from 27% to 9% comparing their pre-PSA era to PSA era IPC detection rates and the frequency of T1b tumors decreased from 15% to 2% in 1648 patients. In a similar study with 982 patients, Mai et al. reported that the rate of IPC decreased from 12.9% to 8% and the rate of T1b tumor from 10% to 5%. There were no significant changes in T1a tumor rates in both studies[10,11].

In a study with 120 TUR-P materials by Güvendi et al., the IPC rate was found to be 2.5%. The authors emphasize that the number of IPCs has decreased in recent years with the increase in clinical experience and the malignancy has begun to be diagnosed prior to TUR-P[12]. In a multicenter study by Yoo et al., the IPC rate was found to be 4.8%. The authors emphasize that, in addition to DRE findings, the PSA level and the evaluation of TZ volume together will provide more reliable information for IPC[13].

In five year period, Otto et al. and Khan et al., in two separate studies, reported the rate of IPC in TUR-P specimens 1.4% and 1.8%, respectively. For these low rates, researchers suggest that their pre-TUR needle biopsy rates might be higher than other centers' rates[2,14]. In the PSA era, Trpkov et al. reported a high IPC rate

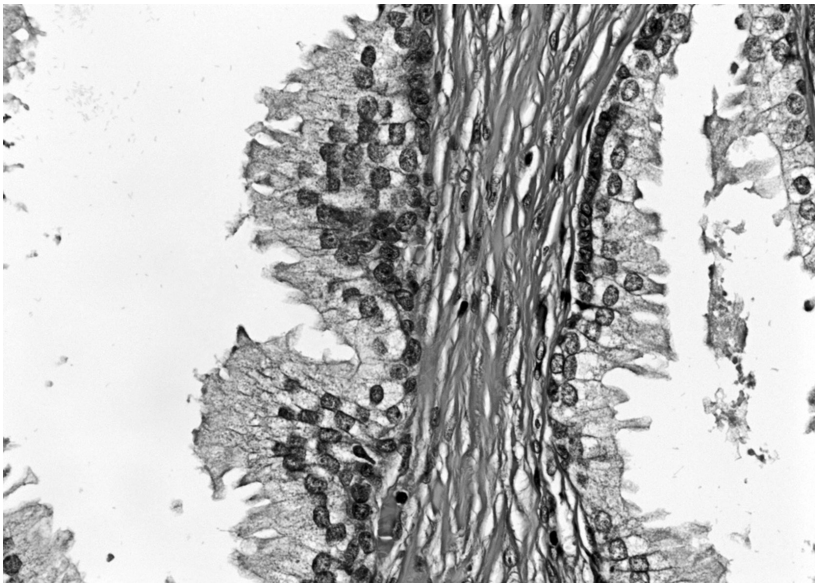

Figure 3. *Stratification of atypical epithelial cells with prominent nucleoli in a gland. High Grade Prostatic Intraepithelial Neoplasia (H-PIN). (HEx400)*

of 16.7%. However, the fact that patients with known prostate carcinoma are included in the study explains this high rate[15].

In our study, when known prostate carcinoma patients are excluded, the rate of IPC is 2.34%. Considering the studies reporting IPC rates in the PSA era, our rate is close to the lower limit (% 1.4–16.7)[2,13–17]. One of the reasons for this may be that prostate needle biopsy prior to TUR-P due to PSA elevation has become more widespread in recent years. In addition, as a limitation of our study, not all TUR-P specimens were sampled for microscopic examination. As in some T1a tumors, cancerous tissue is detected in a single block, we might have underdiagnosed malignancy cases due to not sampling all chips, which may be a cause of our low cancer rate.

This study has other limitations too. Retrospective study design, lack of sample size calculation, only one central's results are mainly limited the power of this study and the results are not generalizable to community settings.

The use of mpMRI in our clinic in some of the period covered by our study provides advantages over previous publications. We suggest that increased use of MR fusion prostate biopsy will lead to increase in detection of cancer in biopsies and therefore decrease in IPC, especially in clinically significant prostate cancer rates.

H-PIN is considered as a precursor lesion of prostate cancer and has similar genetic and molecular alterations as carcinoma. The presence of H-PIN in TUR-P material should alert the pathologist to process all TUR-P specimen for microscopic examination[18–19] (Figure 3).

For localized prostate cancer cases, in the low-risk group (T1 c-T2a, GS ≤6, PSA ≤10 ng/mL) active surveillance may be an option. Besides, curative treatment options such as radical prostatectomy, radiotherapy, brachytherapy, high intensity focused ultrasound can be offered[20].

In the cases with IPC, the understanding that radical prostatectomy cannot be performed due to the wound healing fibrosis in the postoperative period and complications such as incontinence or erectile dysfunction will be seen more frequently is being abandoned in recent years. Radical prostatectomy or localized treatment options can be performed following TUR-P[19–21].

We increased the number of cases by performing the archive scanning interval in the widest time interval allowed by the system thus, we aimed to reduce the potential confounding effects by increasing the total number of patients.

As a result, we demonstrated an IPC rate of 2.34%. Considering the studies that reported IPC rates in the PSA era, our rate is close to the lower limit. Despite the widespread use of biochemical markers and imaging modalities, IPC is detected in TUR-P materials even in a low rate. The application of primary therapies should not be avoided in patients with IPC after TUR-P.

Since the presence of cancer in prostate cannot be precisely excluded before the operation, we recommend sampling TUR-P specimens for their entirety for microscopy. Considering the patients who will lose their chances of treatment due to lack of sampling, we think such practice will be beneficial considering the cost implications.

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