# Is there a PSA cut-off value indicating incidental prostate cancer in patients undergoing surgery for benign prostatic hyperplasia?

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**Summary**
*Aim: To investigate incidental prostate cancer (IPCa) rate and to determine prostate specific antigen (PSA) cut-off value indicating PCa in patients who underwent surgery by being diagnosed with benign prostatic hyperplasia (BPH) clinically or by standard prostate biopsy.
Methods: Data of 317 patients, who underwent transurethral resection of the prostate (TURP) or open prostatectomy (OP) with pre-diagnosis of BPH, were evaluated retrospectively. The examined parameters included patients' demographics, preoperative serum PSA values, digital rectal examination (DRE) findings, surgical method, histopathological findings and Gleason Scores.
Results: A total of 317 patients were included the study. The median age of patients was 69 years (min: 51-max: 79) and the median PSA value was 3.24 ng/dl (min: 0.17-max: 34.9). In 21 patients (6.6%); DRE findings were in favor of malignancy, but prostate biopsy resulted as BPH. While 281 (88.6%) of the patients underwent TURP, 36 (11.4%) underwent open prostatectomy. PCa was detected in 21 (6.6%) patients.
PSA was statistically higher in patients who underwent OP compared to patient who underwent TUR-P, 5.9 (min: 1.2 - max: 27.6, IR: 8.7) vs. 2.8 (min: 0.1-max: 34.9, IR: 4.2) ng/dl, p < .001. The rate of IPCa among four PSA group was similar (p = 0.46). There was no difference between the rate of IPCa in patients younger and older than 70 years, (p = 0.11). Please change whole sentence as 'The median PSA level was slightly higher in patients diagnosed with BPH compared to patients diagnosed with IPCa, 3.2 (min: 0.1-max: 34.9) vs. 2.7 (min: 0.3-max: 26.5) ng/dL, p = 0.9.
Conclusions: IPCa still remains an important clinical problem. We were not able to find any correlation of PSA and age with incidental PCa.*

*KEY WORDS: Incidental; Prostate cancer; Open prostatectomy.*

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## INTRODUCTION

*Prostate cancer* (PCa) is the most commonly diagnosed cancer in men and the most common cause of cancer deaths following lung cancer. According to autopsy studies, the risk of PCa in men > 50-year-old is about 30% (1, 2).

Surgical treatment remains the most effective option in patients with lower urinary tract obstructive symptoms who did not respond to medical therapy and have moderate to severe symptoms. Evaluation of *prostate specific antigen* (PSA) and *digital rectal examination* (DRE) constitute the routine urological evaluations before surgery for *benign prostatic hyperplasia* (BPH) to exclude PCa; PSA density, PSA velocity, free/total PSA and PSA according to age could be utilized if required. A transrectal ultrasound-guided prostate biopsy is the gold standard to rule out PCa in these patients and have been used extensively. Neoplastic tissue may not be detected in sample when biopsy is performed with *transrectal ultrasound* (TRUS) guidance, even if the PSA levels are high or DRE findings are positive (11).
*Incidental prostate cancer* (IPCa) is the diagnosis of PCa with histopathological examination of resected prostate tissue, which was previously considered benign. IPCa rates after both *open prostatectomy* (OP) and *transurethral resection of prostate* (TURP) have been reported to be vary between 5% and 41% in the literature (3-8). Despite normal PSA values, DRE findings, and normal prostate biopsy results before surgery; IPCa is still a challenge for physicians and patients with high expectations. In this study, we aimed to evaluate rate of IPCa after benign prostate surgery and to determine if there is a PSA cut-off value indicating IPCa in Turkish population.

## MATERIALS AND METHODS

The study protocol was approved by the *Institutional Review Board of Turkiye Yuksek Ihtisas Training and Research Hospital* (Approval Number: 15.03.2018-29620911-929-E.2475).
The data of all consequent patients who underwent TURP or OP with the pre-diagnosis of BPH between 2008-2018 were evaluated retrospectively. Patients with normal DRE and PSA levels in preoperative evaluation as well as patients who underwent TRUS guided prostate needle biopsy prior to surgery due to abnormal DRE and/or high serum PSA values and were reported to have not PCa were included the study. Patients who had a history of PCa or patients who received any treatment

due to PCa were excluded from the study. The examined parameters included patients' demographics, preoperative serum PSA values, DRE findings, surgical method, histopathological findings and Gleason Scores.

The relationship between these parameters and IPCa was investigated. Tha patients were divided into 4 groups according to PSA values: Group 1: PSA < 2.5 ng/dL, Group 2: PSA = 2.5-4 ng/dL, Group 3: PSA = 4.10 ng/dL, Group 4: PSA > 10 ng/dL.

### Statistical analysis

Statistical analysis was performed using IBM SPSS statistical package program v 21.0. Continues variables were given in median (minimum-maximum) and categorical variables were given in numbers and percentage. ROC curve analysis was used to determine cut-off value for PSA. Spearman correlation test was performed for the relationship between PSA, age and IPCa. Chi-Square test was used to determine the differences between frequencies in two categorical variables. Mann-Whitney U test was used to compare the age and PSA of the patients with and without prostate cancer when there was not a normal distribution after Kolmogorov-Smirnov test.

### RESULTS

A total of 317 patients were included the study.

The median age of patients was 69 years (min: 51, max: 79) and the median PSA value was 3.24 ng/dl (min: 0.17, max: 34.9). In 21 patients (6.6%) DRE findings were in favor of malignancy, but prostate biopsy resulted as BPH. While 281 (88.6%) of the patients underwent TURP, 36 (11.4%) underwent open prostatectomy. PCa was detected in 21 (6.6%) patients (Table 1).

The Gleason scores of the patients with IPCa were as follow: G6 (n = 10), G7 (3 + 4) (n = 2), G7 (4 + 3) (n = 1), G8 (n = 2), G9 (n = 3) and G10 (n = 3). Four patients with Gleason scores > 6 underwent radical prostatectomy. A patient in high-risk group after this radical prostatectomy and a patient with low-surgical performance

who had a Gleason score > 9 were referred to the oncology clinic for adjuvant hormone therapy and radiotherapy. PSA was statistically higher in patients who underwent OP compared to patient who underwent TUR-P, 5.9 (min: 1.2- max: 27.6, IR: 8.7) vs. 2.8 (min: 0.1-max: 34.9, IR: 4.2) ng/dl, p < .001. The rate of IPCa among four PSA group was similar (p = 0.46). There was no difference between the rate of IPCa in patients younger and older than 70 years, (p = 0.11). The median PSA level was slightly higher in patients diagnosed with BPH compared to patients diagnosed with IPCa, 3.2 (min: 0.1-max: 34.9) vs. 2.7 (min: 0.3-max: 26.5) ng/dL, p = 0.9.

### DISCUSSION

Today, the rate of IPCa is still found to be high in patients diagnosed with BPH clinically or after prostate biopsy under the guidance of TRUS. The widespread use of new biopsy techniques such as multiparametric *magnetic resonance imaging* (MRI) - targeted biopsy may decrease the rate of IPCa. In our study, 6.6% IPCa was detected in patients who underwent open prostatectomy or TUR-P with the diagnosis of benign prostatic hyperplasia.

Prostate cancer incidence and cancer-related mortality are more common in European countries than in Asian countries (12, 13). The rate of diagnosis of IPCa reaches up to 16% in parallel with the increase in life expectancy and might not to be underestimated (5). The use of PSA and its derivatives in daily urology practice, the increase in the number of prostate needle biopsy cores and the improvement in technical methods have decreased the rate of IPCa cases over the years but it has not been minimized (5). *Rohr et al.* reported a rate of 15% IPCa in 457 TURP operations in 1987 and *Merril et al.*, reported in their study that the rate of IPCa determined by TURP gradually decreased between 1980 and 1999. They also reported that IPCa rates decreased from 39% to 7% from 1980s to 2000 (14, 15). In a study that emphasized the importance of age-specific PSA, IPCa was observed in 13% of patients who underwent TURP and open prostatectomy, whereas this rate was decreased to 6.3% with age-specific PSA assessment (16). In a study by *Zigeuner et al.*, it was reported that preoperative DRE and PSA test combination caused a 50% reduction in the detection rate of IPCa (16). In our study, we detected IPCa in 6.6% of patients that underwent TURP and open prostatectomy. Our rate is consistent with the literature and we think that the decrease in the rate of IPCa is related to early diagnosis with the advances in diagnostic tests and biopsy techniques we utilized in the light of the technological developments. On the other hand, with increase in life expectancy, it is obvious that IPCa that can be newly diagnosed is that was previously named as hidden prostate cancer. Perhaps the rate of 19.9% IPCa detected by *Abedi et al.* might be the best example of this. This demonstrates that IPCa diagnosis rate cannot be minimized and is not constantly reduced (4). The lack of

**Table 1.**

*Patient characteristics and comparison of patients with and without incidental prostate cancer.*

| | | Total (n = 317) | Benign prostate hyperplasia (n = 296) | Incidental prostate cancer (n = 21) | P value |
|---|---|---|---|---|---|
| **Median age** (years) | | 69 (51-79) | | | |
| | Age < 70 years | 178 | 170 | 8 | 0.11^ |
| | Age > 70 years | 139 | 126 | 13 | |
| **Median PSA** (ng/dL) | | 3.2 (0.1-34.9) | | | |
| | PSA < 2.5 | 118 (37.2%) | 109 | 9 | 0.46^ |
| | PSA: 2.5-4.0 | 73 (23%) | 71 | 2 | |
| | PSA: 4-10 | 93 (29.3%) | 85 | 8 | |
| | PSA > 10 | 33 (10.4%) | 31 | 2 | |
| **Gleason score** | Gleason 3+3 | 10 (3.15%) | | | |
| | Gleason 3+4 | 2 (0.63%) | | | |
| | Gleason 4+3 | 1 (0.31%) | | | |
| | Gleason 4+4 | 1 (0.31%) | | | |
| | Gleason 4+5 | 2 (0.63%) | | | |
| | Gleason 5+4 | 1 (0.31%) | | | |
| | Gleason 5+5 | 3 (0.94%) | | | |
| | Gleason 5+3 | 1 (0.31%) | | | |

homogeneous study cohorts and inter-racial differences might explain the wide range of this rate in literature.

*Zigeuner et al.*, reported an IPCa of 7.9% in 445 patients who underwent TURP or open prostatectomy after transrectal prostate biopsy due to high PSA level and/or abnormal DRE. The rate of IPCa reported in this study is similar to our results, however the inclusion of patients who underwent transrectal prostate biopsy prior to surgery might affect obtaining a low IPCa rate (17).

In a study conducted by *Otto et al.*, 771 patients who underwent TURP were retrospectively analyzed and IPCa was detected in 11 patients (1.4%). Among 11 patients, ten had a (91%) Gleason Score of 3+3 = 6 and one (9%) patient had a Gleason score of 3+4 = 7. Of 11 patients with IPCa, nine had T1a disease and two had T1b disease. (18). When compared with this study, the rate of IPCa was found to be higher in our study. However, in their study, *Otto et al.*, only included patients who underwent TURP and the mean resected tissue weight was 8.1 g.

The amount of prostate sample examined may affect the ratio of IPCa. In our study, 47.6% of IPCa cases had a Gleason Score of ≤ 6, which is lower than the rate reported by *Otto et al.*

In another study by *Abedi et al.*, authors reported higher IPCa rates detected via open prostatectomy compared to TURP (4). Although, IPCa ratios detected via open prostatectomy were higher compared to TURP in our study, it was not statistically significant. This might be due to the low number of patients in the open prostatectomy group. In PCa diagnosis, various methods have been developed to prevent unnecessary repeated biopsies and to detect PCa that need to be treated. Multiparametric *magnetic resonance imaging* (MRI) fusion biopsy is one of these methods gaining importance day by day (19). Several researchers reported that MRI-targeted biopsy is superior to standard *transrectal ultrasonography* (TRUS)-guided biopsy in detection of PCa (20, 21). *European Association of Urology* (EAU) guidelines favor MRI guided biopsy to systematic biopsy in detecting ISUP grade ≥ 2 PCa in the repeated-biopsy setting. However, in biopsy-naïve patients this difference was stated to be less significant (22). In their retrospective multicenter study, *Porreca et al.* investigated the utility of 'in-bore' MRI prostate biopsy to exclude significant PCa in patients with BPH scheduled for transurethral laser enucleation of prostate.

The authors concluded that including mpMRI and MRI guided biopsy prior to surgery for BPH might lead to low PCa and avoid unnecessary standard TRUS-guided biopsies (23). In our study, prostate biopsy was performed only with conventional TRUS which might be considered a limitation of our study.

Incidental PCa detection still remains as a troublesome problem for the patients, urologists and the pathologists. According to the *Collage of American Pathologists statement*, it was suggested to sample all prostate tissue left behind when T1a PCa was detected (8). In routine practice of pathologists, it is not possible to sample all of the TURP or open prostatectomy materials. This may cause IPCa cases to be overlooked. For this reason, the determination of preoperative clinical parameters that may predict IPCa may change the preoperative approach of the urologists, and may also help the pathologists to determine the required pathological sample amount for an accurate examination. However, this may also lead to over diagnosis and over treatment risk. Our study is not without limitations. The retrospective nature of our study and the inclusion of patients treated with different surgical methods are the main limitations of our study. In addition, the absence of patients to whom multiparametric MRI-targeted biopsy was applied might be another issue.

Prospective multicenter studies with large patient number comparing standard TRUS prostate biopsy and new biopsy techniques such as MRI-targeted prostate biopsy might improve our knowledge in this topic.

## CONCLUSIONS

Incidental PCa detection rate is considerably high in patients undergoing surgery for benign prostatic hyperplasia, which was diagnosed clinically or via standard TRUS-guided prostate needle biopsy. Thus, IPCa still remains an important clinical problem. We were not able to find any correlation of PSA and age with incidental PCa. Determination of new parameters that can predict IPCa detection and the widespread use of new biopsy techniques such as MRI-targeted biopsy may decrease the rate of IPCa.

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