# Evaluation of Factors Associated with the Detection of Incidental Prostate Cancer after Open Prostatectomy for Benign Prostatic Hyperplasia

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#### Abstract

Aim: To evaluate the incidental prostate cancer (PCa) rate and predictive factors in patients who underwent open prostatectomy (OP) with a pre-diagnosis of benign prostatic hyperplasia (BPH). Methods: This cross-sectional, retrospective study included patients with a pre-diagnosis of BPH, who underwent OP due to symptomatic prostate enlargement. Our database included age, medications, prostate-specific antigen (PSA), free/total PSA ratio, PSA density, digital rectal examination (DRE), prostate volume, serum neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, presence of metabolic syndrome (MetS), and histopathological results after OP. Results: Of the 430 patients that underwent OP with a pre-diagnosis of BPH, 406 (94.4%) with a benign pathological diagnosis were evaluated as the benign group in and 24 (5.6%) detected to have PCa constituted the incidental PCa group. In the univariate analysis, age, AST/ALT ratio, MetS, and DRE significantly differed between the groups (p=0.008, p=0.005, p=0.004 and p<0.001, respectively). The rate of incidental PCa was much higher in the elderly patients. The cut-off value of age was 71.5 years in the PCa group according to the receiver operating characteristic curve analysis. According to the multivariate analysis, only DRE and presence of MetS were effective in predicting PCa. DRE was found 16 times more effective and MetS was 2.8 times more effective than the other parameters. Conclusion: Our results showed that DRE and presence of MetS can be useful predictive factors of incidental PCa in OP.

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**Conclusion:** Our results showed that DRE and presence of MetS can be useful predictive factors of incidental PCa in OP.

Keywords: Metabolic syndrome; Open prostatectomy; Prostate cancer

#### What is known?

Benign prostatic hyperplasia is one of the most common diseases that affect men. The incidental prostate cancer detection rates vary between 6.6 and 40.7% after open prostatectomy.

## What our study adds?

This is the first study in the literature which evaluated the presence of metabolic syndrome and inflammatory hematological parameters in the prediction of incidental prostate cancer after open prostatectomy.

Digital rectal examination findings and presence of metabolic syndrome can be useful predictive factors for incidental prostate cancer in open prostatectomy.

#### Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases that affect men.<sup>1</sup> The incidence of BPH in men aged 50-60 years is 50% and rises with increasing age.<sup>2</sup>According to the current European Association of Urology Guidelines, open prostatectomy (OP) or enucleation approaches of the prostate, such as holmium laser/bipolar are the first choice of surgical treatment in men with a substantially enlarged prostate (>80 mL).<sup>3</sup>

Prostate cancer (PCa) is the second most common type of cancer in men.<sup>4</sup> The diagnosis of PCa is made by biopsy under the guidance of transrectal or transperineal ultrasonography for the histological confirmation of clinical cancer suspicion after digital rectal examination (DRE) and/or a high serum prostate-specific antigen (PSA) level.<sup>5</sup> Incidental PCa (PCa), defined as a non-palpable tumor detected after BPH surgery, has been reported as a low-risk but unfavorable disease in most cases.<sup>6</sup> The incidental PCa detection rates vary between 6.6 and 40.7% after OP.<sup>7-9</sup> With the widespread use of PSA, more patients with BPH undergo a prostate biopsy and are offered treatments other than BPH surgery in case of a cancer diagnosis, which can reduce the risk of incidental tumors after treatment. Advances in reducing biopsy procedures may lead to an increase in incidental PCa detection after BPH surgery.<sup>7</sup>

There are many studies that have reported various factors, such as age, PSA and its derives, prostate volume, DRE, body mass index, and previous prostate biopsy results as predictors of incidental PCa after OP.<sup>7,10</sup> However, to our knowledge, no research has evaluated the presence of metabolic syndrome (MetS) and inflammatory hematological parameters in the prediction of incidental PCa after OP. In this study, we evaluated the incidental PCa rate and predictive factors in patients who underwent OP with a pre-diagnosis of BPH in our clinic.

## Materials and Methods

This study had a cross-sectional, retrospective design. Data were collected from between 2010 and 2019. The study was approved by the local ethics committee of our institution (approval number: E-19-2544). The inclusion criteria were the presence of indications for BPH surgery, such as symptomatic prostate enlargement, bladder stones, and contraindication of endoscopic treatment. The exclusion criteria were as

follows: not attending follow-up or data to be retrospectively evaluated not being available in the hospital database, and pathological evaluation of the biopsy specimen revealing PCa, high-grade prostate intraepithelial neoplasia, or atypical small acinar proliferation. Our database included age, medications (5-alpha reductase inhibitors and or alpha blockers), PSA, free/total PSA ratio, PSA density (PSA/prostate volume), DRE findings, prostate volume (assessed with a transrectal ultrasound), serum neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, presence of MetS, and histopathological results after OP. Indications for transrectal ultrasound biopsy (TRUS-Bx) were the suspicion of malignancy in DRE and/or a serum PSA value of >4 ng/mL. The total prostate volume was computed by measuring the length, height and width of the gland on ultrasonography and multiplying the product by a coefficient of  $\pi/6$  (0.52). The American Heart Association/National Heart Lung and Blood Institute criteria were used for the diagnosis of MetS.<sup>11</sup> The presence of at least three of the following criteria was accepted to indicate MetS.

Waist circumference [?] 102 cm

Triglyceride level [?] 150 mg/dL or taking medicine

High-density lipoprotein level ; 40 mg/dL or taking medicine

Increased blood pressure (systolic pressure [?] 130 mm Hg and diastolic blood pressure [?] 85 mm Hg) or taking medicine

Fasting blood glucose [?] 100 mg/dL or taking medicine

All procedures were performed using transvesical Freyer's procedure. All surgical specimens were assessed by dedicated pathologists, and all cancers were graded according to the Gleason score (GS) based on the International Society of Urological Pathology 2005 and 2014 consensus. The patients were divided into two groups: The first group consisted of patients with a pathologically confirmed BPH and the second group comprised those with a pathological PCa diagnosis after OP.

#### **Statistical Analysis**

Data were analyzed using SPSS v.22.0 (IBM Corp. Armonk, NY, USA). Variables were summarized using mean, standard deviation, median, minimum, maximum and percentages based on their characteristics. Student's t- test (two-tailed, independent) was used to compare normally distributed continuous variables as appropriate. The Mann–Whitney U test was used in discrete variables as appropriate. The chi-square and Fisher's exact test were used to evaluate parameters on categorical scale. The binary logistic regression model was created for multivariate analyses. To determine the cut-off value for cancer, the receiver operating characteristic (ROC) curve analysis was performed. p<0.05 was considered statistically significant.

#### Results

The mean age of all patients included in the study was  $69.47\pm7.97$  (range, 47-90) years. The median PSA level was 7.49 (range, 0.18-121.15). The demographic data of the patients are given in Table 1. Among the 430 patients that underwent OP with a pre-diagnosis of BPH, 406 (94.4%) with a benign diagnosis after OP were included in the BPH group and 24 (5.6%) detected to have PCa after OP constituted the incidental PCa group. In the incidental PCa group, 21 (87.5%) patients had GS 3+3, one patient had GS 3+4 (4.1%), one had GS 4+4 (4.1%), and one had GS 4+5 (4.1%) prostatic adenocarcinoma. The histopathological evaluation revealed 29 cases of low grade prostatic intraepithelial neoplasia (PIN), three high grade PIN, 19 squamous metaplasia, five prostatitis and three atypical small acinar proliferation accompanying BPH after OP. A preoperative prostate biopsy was performed in 128 (31.5%) patients in the BPH group and 19 (79.1%) in the incidental PCa group.

In the univariate analysis, age, AST/ALT ratio, MetS, and DRE significantly differed between the groups (p=0.008, p=0.005, p=0.004, and p<0.001, respectively). The rate of incidental PCa was much higher in the elderly patients. In the ROC analysis, the cut-off value of age was 71.5 years in the incidental PCa group [area under the curve (AUC): 0.672, confidence interval (CI) 95%:0.574-0.770, sensitivity: 75%, specificity:

36.9%, p=0.005). Preoperative drug use for lower urinary tract symptoms, serum PSA, PSA density, prostate volume, free/total PSA ratio, NLR, and PLR were not significantly different in the BPH and incidental PCa groups (p>0.05) (Table 2).

The multivariate analysis revealed that only DRE and presence of MetS were effective in predicting PCa among all the parameters that were significant in the univariate analysis. DRE was 16 times more effective [df (1)=29.585, odds ratio (OR): 16.215, 95% CI: 5.942-44.249, p<0.001) and MetS was 2.8 times more effective [df (1)=4.656, OR: 2.808, 95% CI: 1.099-7.172, p=0.031] than the remaining parameters (Table 2).

The median follow-up duration for the incidental PCa group was 41.5 (14-86) months. In two (8.3%) patients that were defined to be high-risk, hormonotherapy was initiated immediately after OP. In a further two patients (8.3%), increasing PSA levels were detected, and therefore hormonotherapy was started. No metastasis was detected in any of the patients even in the high-risk group (GS 8 and 9).

#### Discussion

In this study, the incidental PCa rate and predictive factors in patients who underwent OP with a prediagnosis of BPH were evaluated and significant findings emerged. The multivariate analysis showed that only pathological DRE findings and presence of MeTS were significantly associated with the incidental PCa risk after OP surgery. To our knowledge, this study evaluated the highest number of parameters in the prediction of incidental PCa detection after OP.

PCa can be detected by DRE when the prostate volume is [?]0.2 mL. PCa is detected by a suspicious DRE finding alone in 18% cases.<sup>12</sup> In a multicentric study (11 centers, 1613 patients) Yoo et al. reported that the DRE finding was an independent predictive factor for diagnosing incidental PCa in tissue-ablative surgery for BPH, such as transurethral resection of the prostate and OP. The rate of an abnormal DRE finding was 12.7% in the BPH group and 36.6% in the incidental PCa group, and the incidental PCa rate was 4.8% in all cases.<sup>13</sup> Similarly, another retrospective study including 218 patients showed that DRE and elderly age were predictive factors for incidental PCa after BPH surgery (TURP and OP) (14). In our study, we also found that the rate of an abnormal DRE finding was significantly higher in the incidental PCa group (3.6% vs 45.8%, respectively). In light of all these results, in case of an abnormal DRE finding prior to OP, the risk of PCa should always be considered, and additional diagnostic tests, such as multiparametric MRI and target biopsies can be added to the algorithm.

Although the association between MetS and PCa is not clear, there are many studies that have revealed the higher risk of PCa development in patients with MetS. In Finland, Laukkanen et al. followed up 1880 patients for 13 years and found that the risk of PCa development was 1.9-fold higher in patients with MetS.<sup>15</sup> Similarly, in a study evaluating the relationship between PCa and MetS and late-onset hypogonadism, Kayali et al. showed a higher risk of PCa in the MetS group compared to the patients without MetS (32.7% and 21.2%, respectively).<sup>16</sup> On the other hand, according to a meta-analysis including 19 studies, no correlation was found between MetS and PCa development; however, a significant correlation was present between MetS and aggressive PCa development. The authors determined that MetS increased the risk of high-grade (GS [?] 7) and advanced-stage ([?] T3) PCa at a rate of 36 and 37%, respectively.<sup>17</sup> In the current study, we showed that MetS was significantly higher in the incidental PCa group. This is the first study that evaluated the presence of MetS and incidental PCa after OP.

PSA is organ-specific but it is not specific to cancer. It may be elevated in BPH, prostatitis, and other non-malignant conditions. As an independent variable, PSA is a better predictor of cancer than DRE or TRUS.<sup>18</sup> In a multicentric study, the authors reported that the PSA level was significantly higher in the incidental PCa group than in the BPH group (6.9 ng/mL and 4.7 ng/mL, respectively). In the current study, the PSA levels were similar in the incidental PCa and BPH groups (7.63 ng/mL and 7.47 ng/mL, respectively). Similarly, Antunes et al. reported that the presence of a high PSA level was not associated with incidental PCa detection after BPH surgery. They referred to the possibility of other reasons, such as the use of urinary catheters and presence of urinary retention increasing PSA levels.<sup>14</sup>Abedi et al. reported that the cut-off value of PSA in incidental PCa detection was 3.8 ng/mL.<sup>7</sup> We consider that high prostate

volume can be another possible factor that can change the PSA level.

Many researchers have shown that PCa is associated with increasing age. In autopsy reports, the prevalence of PCa has been reported as 29% in men aged 30 to 40 years and 64% in those aged 60-70 years.<sup>7</sup> A previous study showed that advanced age was statistically significantly related to the findings of the surgical specimen analysis. The mean age of patients with incidental PCa was approximately six years greater than those with BPH.<sup>14</sup>In another study, Sakamoto et al. determined that at a cut-off value of 75 years, age was an independent predictive factor for incidental PCa in TURP.<sup>19</sup> Similarly, in the current study, the incidental PCa group was older than the BPH group (73.6 and 69.2 years, respectively), but age was not found to be a statistically significant variable in the multivariate analysis.

AST/ALT ratio can predict several malignant tumors, such as pancreatic cancer and breast cancer. Zhou et al. showed that the AST/ALT ratio was significantly higher in PCa than in BPH, but they noted that this ratio was not a good predictor of high-risk PCa detection.<sup>20</sup>In our study, we also evaluated the AST/ALT ratio and found it to be higher in the incidental PCa group. Although this parameter was statistically significant in the univariate analysis, it was not significant in the multivariate analysis. NLR is common predictor factor for many cancer types. Wang et al. evaluated this ratio in patients with PCa by dividing them into two GS groups as [?]6 and [?]7 and reported that NLR was significantly higher in the high GS group.<sup>21</sup>We also found that NLR was higher in the incidental PCa group (2.57 vs 3); however, the difference between the two groups was not statistically significant. To our knowledge, none of the studies in the literature evaluated inflammatory hematological parameters for incidental PCa after OP. Our study has certain limitations. It had a retrospective design and included the data of 430 patients. Some parameters that could be associated with incidental PCa, such as a family history of PCa and smoking and alcohol habits were not evaluated due to the retrospective design. Despite these limitations, we consider our study to be important because it included the evaluation of the highest number of parameters in the prediction of incidental PCa detection after OP.

#### Conclusion

In this study, the rate of incidental PCa was found to be 5.6% among the patients who underwent OP for BPH. DRE findings and presence of MetS can be useful predictive factors for incidental PCa in OP. Even if patients have negative TRUS-Bx for PCa, they should be well informed of the possibility of a PCa diagnosis after the operation.

## Conflict of interest

None of the authors received any type of financial or nonfinancial support that could be considered a potential conflict of interest regarding the manuscript or its submission.

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#### Author contribution

Dr YK had the primary responsibility for writing the manuscript. Dr SS, Dr CO, Dr MB, Dr UE, Dr MY, Dr ICA, Dr YA participated in protocol development, preliminary data analysis. Dr BKA, Dr SB, Dr OG, Dr CSG, Dr CO and Dr AT participated in the development of the protocol and analytical framework for the study and the revision of the manuscript.

## Data availability statement

The data that support the findings of this study are openly available in Figshare Repository at https://figshare.com/s/f57e8b889278af24f385.

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