Rates of incidental prostate cancer following HoLEP: Can it be predicted preoperatively?

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ABSTRACT

Introduction: This study aimed to identify preoperative predictors of incidental prostate cancer (iPCa) in patients undergoing holmium laser enucleation of the prostate (HoLEP) for benign prostatic hyperplasia (BPH) and to evaluate subsequent followup strategies.
Methods: We retrospectively analyzed 571 patients who underwent HoLEP by a single surgeon between 2020 and 2024 and who attended at least one postoperative followup visit at our tertiary center. Demographic features, preoperative clinical parameters, and pathologic findings were recorded. Treatment decisions following the diagnosis of iPCa were also analyzed. To reduce baseline imbalances and ensure analytical rigor, propensity score matching was performed.
Results: The incidence of iPCa was 7.81%. After propensity score matching, elevated preoperative prostate-specfic antigen (PSA) density was significantly associated with the presence of iPCa (odds ratio [OR] 1.095, 95% confidence interval [CI] 1.04–1.16, p=0.01). In a separate analysis, older age (OR 1.11, 95% CI 1.03–1.19, p=0.005), higher total PSA (OR 1.13, 95% CI 1.04–1.22, p= 0.03), and higher PSA density (0.24 vs. 0.04, p<0.001) were identified as clinically significant factors distinguishing the clinically significant prostate cancer group from the clinically insignificant prostate cancer plus benign group.
Conclusions: PSA density was identified as an independent preoperative predictor of incidental prostate cancer following HoLEP, whereas older age, higher total PSA, and elevated PSA density were found to be clinically significant factors associated with clinically

significant cases. In older patients with high PSA density, further evaluation for possible prostate cancer may be considered before HoLEP, particularly if the detection of clinically significant disease would alter the decision to proceed with surgery.

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed malignancy and a leading cause of cancer-related mortality among men worldwide.[1] Although diagnosis is typically established through clinical assessment, imaging, and prostate biopsy, some cases evade detection preoperatively despite comprehensive evaluation. Incidental prostate cancer (iPCa) refers to histologically confirmed malignancy detected in surgical specimens obtained during benign prostatic hyperplasia (BPH) surgery, despite negative preoperative findings on digital rectal examination (DRE), prostate-specific antigen (PSA), transrectal ultrasound (TRUS), multiparametric magnetic resonance imaging (mpMRI), and biopsy.

Transurethral resection of the prostate (TURP) remains the gold standard for BPH; laser enucleation of the prostate is recognized as an effective option and has gained popularity in recent years.[2-5] The prevalence of iPCa identified during TURP ranged from 1.4% to 16.7%.[6]. Compared to TURP, HoLEP provides a more anatomical excision of the transitional zone (TZ) and yields a larger tissue specimen for pathological evaluation.[7] While some studies report comparable rates of iPCa between TURP and enucleation techniques[8], others suggest that AEEP is associated with a higher incidence, ranging from 5.6% to 23.3%.[9,10] Additionally, in cases of incidentally diagnosed prostate cancer, there is no clear consensus regarding post-diagnostic treatment decisions due to the limited data on long-term outcomes. Even if International guidelines recommend conservative management with active surveillance for patients with low-risk prostate cancer after diagnosed with incidentally[11,12], with the increasing number of BPH surgeries and the consequent rise in incidental prostate cancer diagnoses, there is ongoing debate regarding whether current treatment recommendations adequately address this clinical scenario.

To address this clinical uncertainty, we sought to identify preoperative predictors of incidental prostate cancer, with particular emphasis on clinically significant cases.

METHODS

We conducted a retrospective cohort study of patients who underwent HoLEP at our tertiary referral center between 2020 and 2024. A total of 571 patients who had at least one postoperative follow-up visit were included. Eleven patients with a known diagnosis of prostate cancer who underwent HoLEP for palliative purposes were excluded from the study. All of those procedures were performed by a single surgeon (M.İ.G.). Surgical specimens were evaluated by pathologists with genitourinary expertise at our institution.

The following parameters were recorded for each patient: age, body mass index (BMI), comorbidities, smoking status, preoperative serum PSA level, prostate volume measured by TRUS, PSA density, and mpMRI findings. In patients diagnosed with iPCa,

additional pathological and follow-up data were also collected, including ISUP score, tumor stage and volume, PSA kinetics, and treatment modality.
All procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments. Institutional ethics committee approval was obtained (Application No: 2024000741-1; Decision No: i10-807-24).

HoLEP surgery procedure
Depending on the preoperative decision or intraoperative prostate anatomy, all procedures were carried out either as en-bloc or bilober enucleation.

All procedures were performed using a 140-Watt Holmium:YAG laser (Dornier Medilas® H 140, Dornier MedTech Systems GmbH, Wessling,Germany) with a 550-μm end-firing laser fiber. The laser settings were set to 105 W (3 J and 35 Hz). Morcellation was carried out using a mechanical morcellator (Dornier Medilas® H 140) under continuous saline irrigation.

Statistical analysis
Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Categorical variables were compared using the chi-square test, and continuous variables were analyzed using the Mann–Whitney U test, as most variables did not meet the assumption of normal distribution. Propensity score matching (2:1 ratio) was conducted based on age, BMI, diabetes, hypertension, smoking status, and hyperlipidemia to minimize baseline differences between the iPCa and non-iPCa groups. Continuous variables were summarized using mean, median, standard deviation (SD), and interquartile range (IQR 25-75), while categorical data were reported as frequencies and percentages. Logistic regression analysis was used to identify associations between PSA parameters and incidental cancer status. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS
iPCa was identified in 7.81% of the study population (45/571 patients). Demographic characteristics of patients with and without PCa are summarized in Table 1a, while perioperative features of patients diagnosed are shown in Table 1b. The mean age was 72.68 for the cancer group and 69.37 for the non-cancer group. The median preoperative total PSA level was 4.78 ng/mL in the cancer group and 3.5 ng/mL in the non-cancer group ($p = 0.058$). The median prostate volume was significantly lower in the cancer group compared to the non-cancer group (55 vs 76 mL, $p=0.010$). The median PSA density was significantly higher in the cancer group than in the non-cancer group (0.07 vs 0.04, $p=0.003$). Preoperative mpMRI was performed in 15.6% of cancer patients (7/45) and 14.5% of non-cancer patients (76/526). Mean lesion sizes were comparable between groups (11.20 ± 4.76 mm vs. 11.76 ± 5.2 mm, $p=0.770$). At the third postoperative month, median PSA levels were 0.97 ng/mL in the cancer group and 0.84 ng/mL in the non-cancer group ($p=0.016$). Total follow-up time was 31.61 ± 16.85 months for the cancer group and 27.68 ± 16.1 months for non-cancer group.

In logistic regression analysis, preoperative PSA level was not significantly associated with cancer status (OR: 1.048; 95% CI: 0.999–1.107; p=0.67). However, PSA density was a significant predictor of iPCa (OR: 1.095; 95% CI: 1.040–1.164; p=0.01), indicating a 9.5% increase in the odds of cancer per 0.1 unit increase in PSA density.

In another univariate logistic regression analysis comparing clinically significant prostate cancer (csPCa) with clinically insignificant prostate cancer (cisPCa) plus benign pathology, older age (77 ± 8.7 vs. 69.4 ± 8.1 years; OR: 1.12; 95% CI, 1.04–1.20; $p < 0.001$), higher total PSA (9.45 vs. 3.48 ng/mL; OR: 1.11; 95% CI, 1.06–1.16), higher free PSA (1.79 vs. 0.90 ng/mL; OR: 1.35; 95% CI, 1.11–1.62; $p = 0.002$). In multivariate analysis, only age and total PSA remained independently and clinically significant predictors of csPCa. Including PSA density in the multivariable model would cause model instability and dominate the effect estimates of other covariates. Therefore, PSA density was excluded from the multivariable model, and its effect was evaluated separately. The median PSA density was 0.24 in the csPCa group and 0.04 in the cisPCa + benign group, showing a statistically significant difference ($p < 0.001$) (Table 2).

Postoperative features of patients diagnosed with iPCa are shown in Table 3. Among patients with iPCa, 31 (68.9%) had ISUP grade 1 tumors, followed by 6 (13.3%) with grade 2, 1 (2.2%) with grade 3, 1 (2.2%) with grade 4, and 6 (13.3%) with grade 5. Most tumors were staged as T1a (n = 28), while the remaining 17 were classified as T1b. The median tumor involvement in HoLEP specimens was 5%. Of the patients diagnosed with prostate cancer, 36 were assigned to active surveillance, 2 to radical prostatectomy, 4 to radiation and androgen deprivation therapy (ADT), and 3 received ADT alone (Table 3).
Table 4 presents a comparison of the clinical characteristics between the active surveillance and active treatment groups in patients diagnosed with incidental prostate cancer following HoLEP surgery. During follow-up, five patients initially under active surveillance required definitive treatment due to PSA progression or clinical findings. One cancer-related mortality was observed.

DISCUSSION

Following the implementation of PSA testing as a screening tool for prostate cancer, the rate of iPCa in specimens obtained after BPH surgery decreased significantly, from approximately 31% to 5.4%.[6] However, although total PSA has been a valuable biomarker in PCa screening, its limitations in specificity and sensitivity have prompted the exploration of alternative biomarkers (e.g., PHI, PCA3, PSA density) to improve preoperative risk stratification.
In cases with clinical suspicion despite inconclusive findings, mpMRI and systematic or MRI-ultrasound fusion-guided prostate biopsies may be recommended by clinicians.[13,14] The addition of mpMRI prior to prostate biopsy in prostate cancer diagnostic pathways has resulted in the detection of more clinically significant prostate cancers, and has been shown to reduce the detection of clinically insignificant cases.[15,16] Another study demonstrated that a negative mpMRI does not entirely exclude the presence of PCa, as MRI-invisible tumors are detected in approximately 8–20% of patients.[17] Therefore, many patients with elevated PSA

and negative mpMRI findings may undergo BPE surgery without a prior biopsy, which could eventually lead to an increased proportion of iPCa detections.

In our cohort, iPCa was detected in 7.81% of patients with negative preoperative findings, and higher PSA density appeared to be associated with its presence. Importantly, while most cases were clinically insignificant, a subset required definitive treatment, highlighting the need for vigilant postoperative follow-up.

While TURP remains the gold standard treatment for BPH, the utilization of laser enucleation techniques has been steadily increasing. Capogrosso et al. compared these surgical techniques and reported that the HoLEP group demonstrated a higher likelihood of iPCa. Similarly, He et al. found that in cases with PSA levels <4 ng/mL or within the 4–10 ng/mL range, HoLEP was associated with a significantly higher iPCa detection rate compared to TURP. However, in patients with PSA levels >10 ng/mL, no statistically significant difference in iPCa detection was observed between the two techniques.[18] In addition, Herlemann et al. reported no statistically significant difference in iPCa detection rates between HoLEP and TURP.[8] While this study did not directly compare the two approaches, , the incidental prostate cancer rate in our study was found to be 7.81%.

Numerous studies have investigated various preoperative clinical factors to identify patients at higher risk of iPCa following BPH surgeries. Bhojani et al. investigated iPCa following HoLEP and identified several factors significantly associated with iPCa, including older age, increasing preoperative PSA levels, and lower surgical specimen weight.[19] Another study found that the detection rate of iPCa was associated with increased patient age and higher PSA density.[8] In contrast, Rosenhammer et al. and Elkoushy et al. reported that PSA density was the only independent risk factor for iPCa.[10,20] On the contrary, some studies reported that no specific risk factors were associated with iPCa.[21,22] In the current study, after dividing the patients into iPCa and benign groups using matched analysis, PSA density was the only independent predictive factor for iPCa.

In a separate analysis, age, total PSA, and PSA density were identified as clinically significant factors distinguishing the csPCa group from the cisPCa plus benign patient group. The median PSA density was 0.24 in patients with clinically significant incidental prostate cancer, while the PSA density of those with clinically insignificant incidental prostate cancer closely resembled that of benign cases. After propensity score matching, the median PSA density among 45 patients with incidental prostate cancer was 0.07. We attribute this apparent discrepancy to two main factors. First, the inclusion of clinically insignificant incidental prostate cancer cases—whose PSA densities are comparable to benign cases—likely lowered the overall median PSA density of the incidental prostate cancer group. Second, these patients underwent surgery for BPH and typically had larger prostate volumes compared with routine prostate cancer populations, which may result in lower PSA densities. This interpretation is consistent with the findings of Elkoushy et al., who reported a PSA density cut-off of 0.092, and it also aligns with other studies advocating the use of different PSA density reference values according to prostate volume.[20,23,24]

There is ongoing controversy over the optimal treatment approaches and follow-up strategies for patients with incidentally diagnosed cancer following BPH surgeries. In a

systematic review analyzing 19 studies on treatment approaches following BPH surgeries, Cheng et al. reported that active surveillance was the most frequently adopted management strategy (68.7%), followed by radiotherapy (12.2%), ADT (8%), radical prostatectomy (7.1%), and watchful waiting (4.1%).[25] All of these studies recommend active treatment such as radical prostatectomy, radiotherapy, or ADT for patients with high grade tumors. Additionally, watchful waiting may be considered for both low and high grade tumors, depending on the patient's age, comorbidities, and patients preferences.[26]

In this study, among patients diagnosed with iPCa, a substantial proportion had higher-grade disease, including ISUP Grade Groups 3 to 5. In our study, the relatively high proportion of patients with ISUP grade 3–5 disease may be attributed to the older age of this cohort compared with patients harboring clinically insignificant prostate cancer. In our institution, consistent with the PIVOT and ERSPC trials[27,28], further diagnostic evaluations are not routinely performed in asymptomatic patients with an estimated life expectancy of less than 15 years in order to minimize overdetection. If preoperative assessments such as prostate mpMRI or biopsy had been performed in these patients prior to BPH surgery, the number of cases diagnosed with incidental prostate cancer—particularly high-grade iPCa—might have been reduced. In these patients, a combination of radiotherapy and ADT was administered to 4 (8.9%), and 3 (6.7%) received only ADT. Notably, all but one patient with clinically significant cancer—who chose watchful waiting primarily due to advanced age and comorbidities—opted for active treatment modalities, underscoring the clinical relevance of pathological findings even in an incidental context.

Among our patients, two individuals with clinically insignificant cancer underwent radical prostatectomy, suggesting that factors beyond histopathological grading such as clinical findings and patient preference play a critical role in treatment decisions. Of the 37 patients diagnosed with clinically insignificant prostate cancer, 35 were managed with active surveillance. Nevertheless, a subset of patients initially managed conservatively transitioned to definitive treatment due to evolving clinical parameters, including rising PSA levels, suspicious MRI findings, or repeat biopsy results. As reported by Capitanio et al., patients with iPCa and PSA levels >1 ng/mL had worse outcomes than those with PSA levels <1 ng/mL. Tumor percentage in the pathological specimen, patient age, and other parameters also play important roles in risk stratification. In the same study, the dropout rate from active surveillance was 12.1% in T1a–T1b cases.[29] Based on both our findings and the current literature, we believe that individualized management strategies are more appropriate for managing iPCa than uniform procols for patients with iPCa. In our cohort, majority of patients (66.7%) in the iPCa group have remained on active surveillance without evidence of disease progression.

This study has several limitations. The retrospective design represents the main limitation, and the relatively short follow-up period may restrict the evaluation of transitions to active treatment. In addition, although the patient population is relatively large, this is a single-institution experience from an academic tertiary center, and the results should be interpreted within this context. Although the weight of the resected prostate tissue was measured in our clinic, it was not recorded routinely; therefore, this variable could not be

included in the regression analysis, which may have influenced the results. Nevertheless, all HoLEP procedures were performed by a single surgeon with experience in more than 2,000 enucleations, which strengthens the reliability and consistency of the findings.

Future prospective studies with larger, multi-institutional cohorts and longer follow-up are warranted to validate our findings and refine risk stratification in patients with iPCa following HoLEP.

CONCLUSIONS

PSA density was identified as an independent preoperative predictor of incidental prostate cancer following HoLEP, whereas older age, higher total PSA, and elevated PSA density were found to be clinically significant factors associated with clinically significant cases. In older patients with high PSA density, further evaluation for possible prostate cancer may be considered before HoLEP, particularly if the detection of clinically significant disease would alter the decision to proceed with surgery.

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FIGURES AND TABLES

Table 1A. Demographic characteristics					
	All patients			**After matching score analysis**	
	Group 1 (benign pathology) (n=526)	**Group 2 (incidental prostate cancer) (n=45)**	**p**	**Group 1 (benign pathology) (n=90)**	**p**
Age, years, mean ± SD	69.37 ± 8.17	72.68±8.3	0.03	70.94±7.10	0.16
BMI, median (IQR)	27.2 (24.8–29.4)	26.2 (24.5–28.2)	0.97	27 (24.8–28.5)	0.44
Hypertension			0.37		N/A
Yes	268	26		45	
No	258	19		45	
Diabetes mellitus			0.17		N/A
Yes	143	8		18	
No	383	37		72	
Hyperlipidemia			0.22		N/A
Yes	53	2		8	
No	473	43		82	
Smoking status			0.03		N/A
None	202	25		39	
<20 p/y	166	7		25	
>20 p/y	158	13		26	

BMI: body mass index; IQR: interquartile range; SD: standard deviation.

Table 1B. Perioperative parameters of patients					
	All patients			**After matching score analysis**	
	Group 1 (benign pathology) (n=526)	**Group 2 (incidental prostate cancer) (n=45)**	**p**	**Group 1 (benign pathology) (n=90)**	**p**
Preoperative MRI status			0.72		N/A
Yes	76	7		19	
No	420	38		71	
MRI PI-RADS score			0.09		N/A
PI-RADS 1	6	2		1	
PI-RADS 2	34	1		11	
PI-RADS 3	27	3		4	
PI-RADS 4	8	1		3	
PI-RADS 5	1	0		0	
MRI lesion location			0.25		N/A

Central Transitional Peripheral	8 25 43	2 3 2		2 10 7	
Biopsy status Yes No	 95 431	 7 38	0.6	 19 71	N/A
Type of biopsy Systematic Fusion	 59 36	 3 4	0.28	 12 7	N/A
Preoperative prostate size, g, median (IQR)	76 (51-109)	55 (41–74)	0.01	84 (60–110)	N/A
Total PSA, median (IQR)	3.5 (1.83–5.94)	4.78 (2.14–10.3)	0.058	4.34 (2.48–8.04)	0.67
Free PSA, median (IQR)	0.9 (0.45–1.45)	1.18 (0.52–1.82)	0.058	1.16 (0.63–1.87)	0.99
Prostate density, median (IQR)	0.04 (0.03–0.07)	0.07 (0.03–0.19)	0.003	0.05 (0.03–0.08)	<0.01
Postoperative 3-month PSA, median (IQR)	0.84 (0.41–1.37)	0.97 (0.5–3.0)	0.016	0.99 (0.5–1.53)	N/A
Followup time, months, mean ± SD	27.68±16.1	31.61±16.85	0.12	28.9±15.95	N/A

BMI: body mass index; IQR: interquartile range; MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting and Data System; PSA: prostate-spesific antigen; SD: standard deviation.

Table 2. Multivariate logistic regression analysis of predictors of clinically significant incidental prostate cancer

	Univariate					**Multivariate**		
	csPCa (n=14)	**cisPCa + benign (n=557)**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**
Age, years, mean ± SD	77±8.7	69.4±8.1	0.001	1.12	1.04–1.20	0.005	1.11	1.03–1.19
BMI, median (IQR)	26.65 (24.77–28.95)	27.1 (24.8–29.4)	0.84	1.01	0.87–1.17			
Preoperative prostat size, g, median (IQR)	51 (32.75–67.75)	75 (50–107)	0.61	0.98	0.96–1.00			
Total PSA, median (IQR)	9.45 (7.08–14.17)	3.48 (1.82–5.91)	<0.001	1.11	1.06–1.16	0.03	1.13	1.04–1.22
Free PSA, median (IQR)	1.79 (1.27–2.48)	0.90 (0.45–1.44)	0.002	1.35	1.11–1.62	0.421	0.84	0.57–1.26
Prostate density, median (IQR)	0.24 (0.06–0.33)	0.04 (0.03–0.07)	<0.001	*	*	*	*	*

*Including PSA density in the multivariable model would cause model instability and dominate the effect estimates of other covariates. Therefore, PSA density was excluded from the multivariable model, and its effect was evaluated separately using the Mann-Whitney U test. BMI: body mass index; CI: confidence interval; csPCA: clinically significante prostate cancer; cisPCA: clinically insignificant prostate cancer; IQR: interquartile range, OR: odds ratio; PSA: prostate-spesific antigen; SD: standard deviation.

Table 3. Postoperative clinical characteristics of insidental prostate cancer group	
Characteristics	**n (%)**
HoLEP ISUP score	
ISUP 1	31 (68.9)
ISUP 2	6 (13.3)
ISUP 3	1 (2.2)
ISUP 4	1 (2.2)
ISUP 5	6 (13.3)
HoLEP TNM Stage	
1a	28 (62.2)
1b	17 (37.8)
HoLEP tumor percentage, median (IQR)	5 (1–18.75)
Postoperative third month PSA, median (IQR)	0.97 (0.5–3.0)
PostHoLEP treatment choices	
Active surveillance	36 (80)
Radical Prostatectomy	2 (4.4)
RT + ADT	4 (8.9)
ADT	3 (6.7)
Additional treatment after Active surveillance	
Yes	5 (13.89)
No	31 (86.11)
Cancer related mortality	
Yes	1 (2.22)
No	44 (97.78)

ADT: androgen deprivation therapy; HoLEP: holmium laser enucleation of prostate; ISUP: International Society of Urological Pathology; IQR: interquartile range; PSA: prostate-specific antigen; RT: radiotherapy; SD: standard deviation; TNM: tumor nodes metastasis.

Table 4. Comparison of active surveillance group and active treatment group in patients diagnosed with incidental prostate cancer			
	Active treatment (mean ± SD)	**Active surveillance (mean ± SD)**	**p**
Age, years,	76.90±11.37	71.64±7.17	0.09
Preoperative PSA	17.43±16.74	6.0±6.80	0.078
Pathology percentage of PCa	30.90±23.45	6.75±7.22	0.015
Preoperative PSA density, median (IQR)	0.27 (0.17–0.60)	0.05 (0.02–0.13)	<0.001
Postoperative 3-month total PSA, median (IQR)	3.02 (1.38–9.79)	0.88 (0.46–2.21)	0.024
HoLEP ISUP score			<0.001
ISUP G1	2	29	
ISUP G2	0	6	
ISUP G3	1	0	
ISUP G4	0	1*	
ISUP G5	6	0	
TNM stage			<0.001
T1a	0	28	
T1b	9	8	

*Watchful waiting. HoLEP: holmium laser rnucleation of prostate; ISUP: International Society of Urological Pathology; PCa: prostate cancer; PSA: prostate-specific antigen; TNM: tumor nodes metastasis.