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INCIDENCE AND ASSOCIATED FACTORS FOR INCIDENTAL PROSTATE CANCER FOLLOWING ENDOSCOPIC ENUCLEATION FOR BENIGN PROSTATE HYPERPLASIA PERFORMED BY A SINGLE UROLOGIST

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Objective: to assess the incidence of incidental prostate cancer and associated factors after endoscopic enucleation of benign prostate hyperplasia performed by single urologist.

Materials and methods: a retrospective study included 753 patients after endoscopic enucleation of benign prostate hyperplasia performed by single urologist with more than 3000 enucleation experience. Bipolar enucleation was performed in 22,2% of cases and thulium fiber enucleation (ThuFLEP) was performed in 77,8% of cases.

Results: incidental prostate cancer after endoscopic enucleation of benign prostate hyperplasia performed by single urologist was detected in 6,7% cases (51 patients): in 8,4% – after bipolar enucleation, in 5.3% – after ThuFLEP (p=0,141). Patients with incidental prostate cancer were older (median age 71,5 years and 67,0 years, respectively, p<0.001), had smaller prostate volume (68,0 cm^3 and 83,0 cm^3, respectively, p=0,048), had higher PSA density (0,08 ng/ml/cm3 and 0,05 ng/ml/cm^3, respectively, p=0,006). Univariable logistic regression analysis revealed that additional factor increasing the chance of incidental prostate cancer after endoscopic enucleation is lower IPSS values (OR=0,948; 95%CI=0,897-0,999; p=0,045). During the ROC analysis for these parameters, it was shown that the quality of the parameters «age» and «PSA density» as predictors of incidental prostate cancer after endoscopic enucleation is average (AUC 0,662 and 0,624, respectively), while the parameters «prostate volume» and «IPSS» are unsatisfactory (AUC 0,584 and 0,555, respectively). The value of 68,5 years was chosen as the cut-off point for the age of patients: if the patient is older, it was predicted a high chance of incidental prostate cancer with sensitivity and specificity of 69,6% and 57,4%, respectively. The value of 0,0543 ng/ml/cm^3 was chosen as the cut-off point for PSA density: if the PSA density is higher, it was predicted a high chance of incidental prostate cancer with sensitivity and specificity of 68,2% and 56,1%, respectively.

Conclusions: in the present cohort of patients after endoscopic enucleation for benign prostate hyperplasia, there is a low incidence of incidental prostate cancer (6.7%), which, together with the absence of strong predictors, indicates a full competent examination before planning endoscopic enucleation. Nevertheless, before surgery, it is important to pay attention to such parameters as the older age and higher PSA density associated with a higher chance of incidental prostate cancer.

K e y w o r d s: *incidental prostate cancer, prostate hyperplasia, endoscopic enucleation of prostate hyperplasia, prostate-specific antigen density, thulium fiber enucleation of benign prostate hyperplasia, bipolar enucleation*

The authors declare no conflict of interest. For citation: Sorokin N.I., Strigunov A.A., Nesterova O.Yu., Pshikhachev A.M., Burlakov I.D., Oleynikova N.A., Varentsov M.G., Bondar I.V., Tereshina A.D., Veriaskina A.E., Kamalov A.A. Incidence and associated factors for incidental prostate cancer following endoscopic enucleation for benign prostate hyperplasia performed by a single urologist. Urologiia. 2025;3:59-67. Doi: https://dx.doi.org/10.18565/urology.2025.3.59-67

Introduction. The main method of surgical treatment for benign prostate hyperplasia (BPH) is various transurethral procedures, recommended for prostates of any volume [1]. For many years, transurethral resection of the prostate (TURP) remained the "gold standard" [2]. However, endoscopic enucleation of the prostate, which

has become firmly established in clinical practice, is now rightfully regarded as a worthy alternative, comparable to TURP in terms of efficacy and safety, and, according to some studies, even superior [3, 4].

Endoscopic enucleation can be performed using electroresection or various types of laser energy, however, according to leading experts, the functional outcomes do not depend on the energy source and equipment used [5]. Despite the technical differences in performing endoscopic enucleation and TURP, all types of surgical interventions for BPH aim to the removal of adenomatous tissue followed by histological examination in order to exclude incidental prostate cancer (PCa) [6]. It should be noted that benign prostatic hyperplasia (BPH) primarily results from the growth of the transition zone of the prostate, which is the target of surgical removal. In contrast, the peripheral zone, most commonly associated with PCa, remains unaffected by the procedure and thus outside the pathologist's field of view. Thus, a negative result of histological examination of the removed adenomatous tissue does not completely exclude the presence of PCa [7]. The routine implementation of prostate-specific antigen (PSA) testing has reduced the frequency of detecting incidental PCa by 65%, however, this problem is still relevant and new cases are regularly recorded [8, 9].

According to the meta-analysis by Zhenlang Guo et al. (2022), the frequency of detecting incidental cancer is on average 26.1%, however, it can vary widely depending on the type of surgical intervention [10]. Thus, the prevalence of incidental PCa varies from 4% to 26% after TURP, from 6% to 23% after holmium laser enucleation of the prostate (HoLEP), and from 4% to 30% after open simple prostatectomy [10]. Most studies show that incidental PCa is most often clinically insignificant (grade 1 according to the classification of the International Society of Uropathologists [ISUP]) [11, 12]. In this regard, international guidelines for the management of such patients tend to favor active surveillance. However, in some cases, when clinically significant incidental PCa is detected, patients require radical treatment, and its technical feasibility after transurethral procedures on the prostate is rather complicated [13]. Thus, it is advisable to identify patients with incidental PCa, especially in the case of normal PSA levels and/or negative results of prostate biopsy before performing transurethral interventions. According to Zhenlang Guo et al. (2022), the frequency of detecting incidental PCa after TURP in patients with negative prostate biopsy results is 4.7% [14].

Various studies have identified several risk factors for incidental PCa, including patient age, total PSA level, PSA density, prostate volume, absence of preoperative magnetic resonance imaging (MRI) of the pelvic organs and/or prostate biopsy [15–17], abnormalities detected during digital rectal examination, and the presence of metabolic syndrome [18]. Preoperative assessment of these parameters, according to researchers, allows to minimize the probability of detecting incidental PCa. Given the diversity of the literature data, we carried out our own study.

Aim. To assess the frequency of the prevalence of incidental PCa, as well as to assess potential risk factors in patients after endoscopic enucleation of BPH performed by one urologist.

Materials and methods. This was a retrospective study. Electronic medical records of 753 patients with BPH who underwent endoscopic enucleation at the University Clinic of the Medical Scientific and Educational Institute of Lomonosov Moscow State University from March 2019 to February 2024 by a single urologist with experience in more than 3,000 endoscopic enucleations. Bipolar enucleation of prostate hyperplasia was performed in 22.2% of patients (n=167), while 77.8% (n=586) underwent thulium fiber laser enucleation of prostate hyperplasia (ThuFLEP – Thulium Fiber Laser Enucleation of the Prostate).

The following parameters were evaluated: age, total PSA level, prostate volume according to the results of transrectal ultrasound examination of prostate (TRUS), and PSA density. In case of increased PSA and/or the presence of focal abnormalities in the prostate according to the results of TRUS or MRI, transrectal prostate biopsy was performed for morphological confirmation of BPH before performing endoscopic enucleation. Additionally, parameters such as the presence of a urethral catheter/cystostomy tube preoperatively, the total score on the International Prostate Symptom Score (IPSS) scale, Quality of Life (QoL) score, maximum urine flow rate (Qmax), postvoid residual volume (PVR) according to ultrasound were recorded.

Histological examination. In all cases, a standard histopathological examination was performed. The enucleated tissue was fixed in 10% buffered formalin and completely processed. Histological preparation included automated tissue processing, paraffin embedding, and sectioning with a microtome at a thickness of 3–4 microns. Standard hematoxylin and eosin (H&E) staining was applied. The specimen, which is small fragments of tissue of 5-10 mm, was evaluated by a pathologist under a Leica DM2500 microscope. Even with a single focus of atypical glands in one micropreparation, the diagnosis of PCa was made. In the presence of a focus of suspicious glands, an unclear border of glands, a "controversial" myoepithelial layer, an immunohistochemical study was carried out with antibodies to p63, alpha-methylacyl-CoA racemase (AMACR), high-molecular keratins (CK-H – Cytokeratin H). In the absence of p63/CK-H reaction and the presence of AMACR reaction, the diagnosis of PCa was confirmed.

Statistical data processing. Statistical analyze was carried out using RStudio software (version 4.3.3.). Quantitative variables were presented as medians with interquartile ranges (Q1–Q3), while nominal variables were expressed as absolute numbers (n) and percentages (%). The Mann-Whitney test was used to compare quantitative variables in two independent samples. To compare nominal variables, the Chi-square test and the Chi-square test with Yates' correction were done. To assess potential predictors of incidental PCa, a univariate logistic regression analysis was used. To assess potential risk factors, receiver operating characteristic (ROC) curves were constructed, and the area under the curve (AUC) was calculated. Statistical significance was defined as a p-value < 0.05.

Results. The median age of patients was 67 years (range: 44–93 years; interquartile range [Q1–Q3]: 62.0–73.0 years). An incidental PCa was detected in 6.7% of patients (51 people) after endoscopic enucleation of the prostate, while 93.3% of patients (708 people) had BPH. When assessing the prevalence of incidental PCa in relation to the type of energy used, it was found that the incidental

Table 1

Distribution of patients with incidental PCa according to ISUP classification

ISUP grade	% (*n*)
1	70.0% (35)
2	8.0% (4)
3	12.0% (6)
4	6.0% (3)
5	4.0% (2)

PCa was detected in 8.4% of patients who underwent bipolar enucleation of prostate hyperplasia, and in 5.3% of those who underwent ThuFLEP. At the same time, the differences between the groups were statistically insignificant (p=0.141). *Table 1* shows the distribution of patients with incidental PCa depending on ISUP grade.

A comparative analysis of patients with and without incidental PCa (*Table 2*) showed that patients with incidental PCa were older, with a median age of 71.5 years versus 67.0 years ($p < 0.001$), and had a smaller prostate volume, with a median of 68.0 cc compared to 83.0 cc ($p = 0.048$). Also, for patients with PCa, a higher PSA density was found, while the level of total PSA was comparable. The remaining parameters in the two groups did not differ statistically significantly (*Table 2*).

Figure 1 provides a graphical representation of the clinical, laboratory, and instrumental parameters that differed significantly between the groups. At the next stage of the study, we performed a univariate logistic regression analysis to assess potential risk factors for incidental PCa. The results of the analysis are in *Table 3*.

Based on our analysis, we showed that factors that increase the chance of having incidental PCa after endoscopic enucleation of the prostate are the patient's age and the total score on the IPSS scale. Thus, with an increase in age by 1 year, the chance of having incidental PCa increases by 1.061 times, or by 6.1%. With an increase in IPSS by 1 point, the chance of having incidental PCa decreased by 1.055 times, or by 5.2%. And, conversely, with a decrease in IPSS by 1 point, the chance of having incidental PCa increases by 1.055 times, or by 5.2%. For these parameters, a ROC analysis was performed (*Fig. 2, A* and *B*).

Prostate volume and PSA density were not associated with the presence of incidental PCa, however, given the differences in those with and without PCa, we also performed a ROC analysis for these parameters, the results of which are presented in *Figure 2 (B* and *D*). Based on the data shown in *Figure 2*, it was found that the best predictors of the presence of incidental PCa after endoscopic enucleation are the age of patients and PSA density (AUC 0.662 and 0.624, respectively), less sensitive are prostate volume and IPSS (AUC 0.584 and 0.555, respectively). According to the widely accepted AUC classification scale, the quality of the parameters "age" and "PSA density" as predictors of incidental PCa after endoscopic enucleation of the prostate is average, while the parameters "prostate volume" and "IPSS" are unsatisfactory.

Table 2

Comparative characteristics of patients with and without incidental PCa after endoscopic enucleation of prostate

Parameter	No PCa (*n*=708)	Incidental PCa (*n*=51)	*p*
Age, years, median (Q1–Q3)	67.0 (62.0–73.0)	71,5 (68,0–75,0)	<0,001
Type of enucleation:			0.193**
Bipolar enucleation, *n* (%)	21.6% (153)	31.1% (14)	
ThuFLEP, *n* (%)	78.4% (555)	68.9% (31)	
Enucleation technique:			0.653*
• 3-lobe, *n* (%)	54.8% (328)	62.2% (23)	
• 2-lobe, *n* (%)	40.9% (245)	35.1% (13)	
• En-bloc, *n* (%)	4.3% (26)	2.7% (1)	
Prostate volume, cc, median (Q1–Q3)	83.0 (59.4–114.0)	68.0 (54.4–96.0)	0.048
Preoperative urethral catheter, n (%)	20.9% (148)	21.7% (10)	0.954**
IPSS, points, median (Q1–Q3)	26.0 (23.0–29.0)	26.0 (18.0–26.0)	0.192
QoL, points, median (Q1–Q3)	5.0 (4.0–6.0)	5.0 (3.0–6.0)	0.808
Qmax, ml/s, median (Q1–Q3)	9.3 (7.1–12.0)	8.2 (6.0–12.0)	0.425
PVR, ml, median (Q1–Q3)	75.0 (44.0–113.0)	85.0 (56.0–127.0)	0.623
PSA density, ng/ml/cc, median (Q1–Q3)	0.05 (0.03–0.09)	0.08 (0.04–0.13)	0.006
PSA, ng/ml, median (Q1–Q3)	3.9 (2.2–7.0)	4.3 (3.0–9.4)	0.116
PSA, ng/ml, n (%):			0.341*
• < 4 ng/ml	53.7% (374)	40.9% (18)	
• 4–10 ng/ml	32.2% (224)	43.2% (19)	
• > 10 ng/ml	14.1% (98)	15.9% (7)	

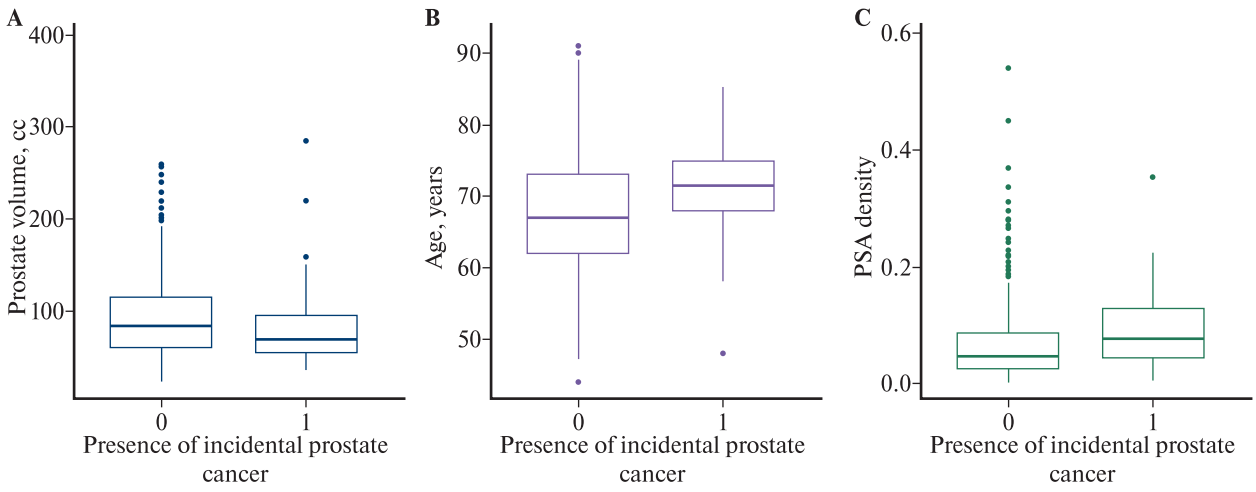


Fig. 1. Significantly different parameters between patients with and without incidental prostate cancer after endoscopic enucleation of the prostate

For predictors with average quality, cut-off points were selected. As a cut-off point for the age of patients, a value of 68.5 years was chosen. If the patient is older than 68.5 years, a high risk of having incidental PCa with a sensitivity and specificity of 69.6 and 57.4%, respectively, was predicted. A high risk of incidental PCa at this age value corresponds to a probability of 5.8%.

As a cut-off point for PSA density, a value of 0.0543 ng/ml/cc was chosen. If the PSA density is higher than this value, the patient is predicted to have a high risk of having incidental PCa with a sensitivity and specificity of 68.2 and 56.1%, respectively. A high risk of incidental PCa at this PSA density value corresponds to a probability of 6.049%. For predictors with unsatisfactory quality, analysis was not performed.

Discussion. In this study, incidental PCa was found in 6.7 % of cases after endoscopic enucleation of the prostate: in 8.4% of observations after bipolar enucleation and in 5.3% after ThuFLEP. The frequency of detection of incidental PCa according to different studies varies significantly. As shown in the study from Russia, incidental PCa after performing open simple prostatectomy is diagnosed in 7.6% of patients [19], after performing TURP in 4.2–11% [20, 21]. According to M. I. Kogan and colleagues (2011), incidental PCa was detected in 7.5 % of cases after open simple prostatectomy and TURP; specifically, it was found in 7.1 % of patients with a previously negative prostate biopsy and in 7.6 % of patients who had not undergone prior biopsy (p>0.05) [22]. Data on the prevalence of incidental PCa obtained by foreign colleagues also differ. According to Joao G. Porto et al. (2023), incidental PCa was found in 9.6% of cases (40 out of 417 patients) after HoLEP, and in 72.5% of men it was clinically insignificant [8], which

Table 3

Univariate logistic regression analysis of risk factors for incidental PCa

Parameter	OR (95 % CI)	*p*
Age, years	1.061 (1.020–1.100)	**0.001**
Enucleation type:		
• Bipolar enucleation	Reference	–
• ThuFLEP	0.610 (0.317–1.176)	0.140
Enucleation technique:		
• 3-lobe	Reference	–
• 2-lobe	0.757 (0.376–1.524)	0.435
• En-bloc	0.549 (0.071–4.221)	0.564
Prostate volume, cc	0.995 (0.987–1.002)	0.180
Preoperative urethral catheter	1.049 (0.509–2.163)	0.897
IPSS, points	0.948 (0.897–0.999)	**0.045**
QoL, points	0.964 (0.745–1.246)	0.777
Qmax, ml/s	0.959 (0.866–1.062)	0.423
PVR, ml	1.002 (0.997–1.001)	0.501
PSA density, ng/ml/cc	2.550 (0.432–15.039)	0.301
PSA, ng/ml	1.013 (0.969–1.059)	0.567
PSA:		
• > 4 ng/ml	Reference	–
• 4–10 ng/ml	1.635 (0.840-3.183)	0.148
• >10 ng/ml	1.377 (0.559-3.391)	0.487

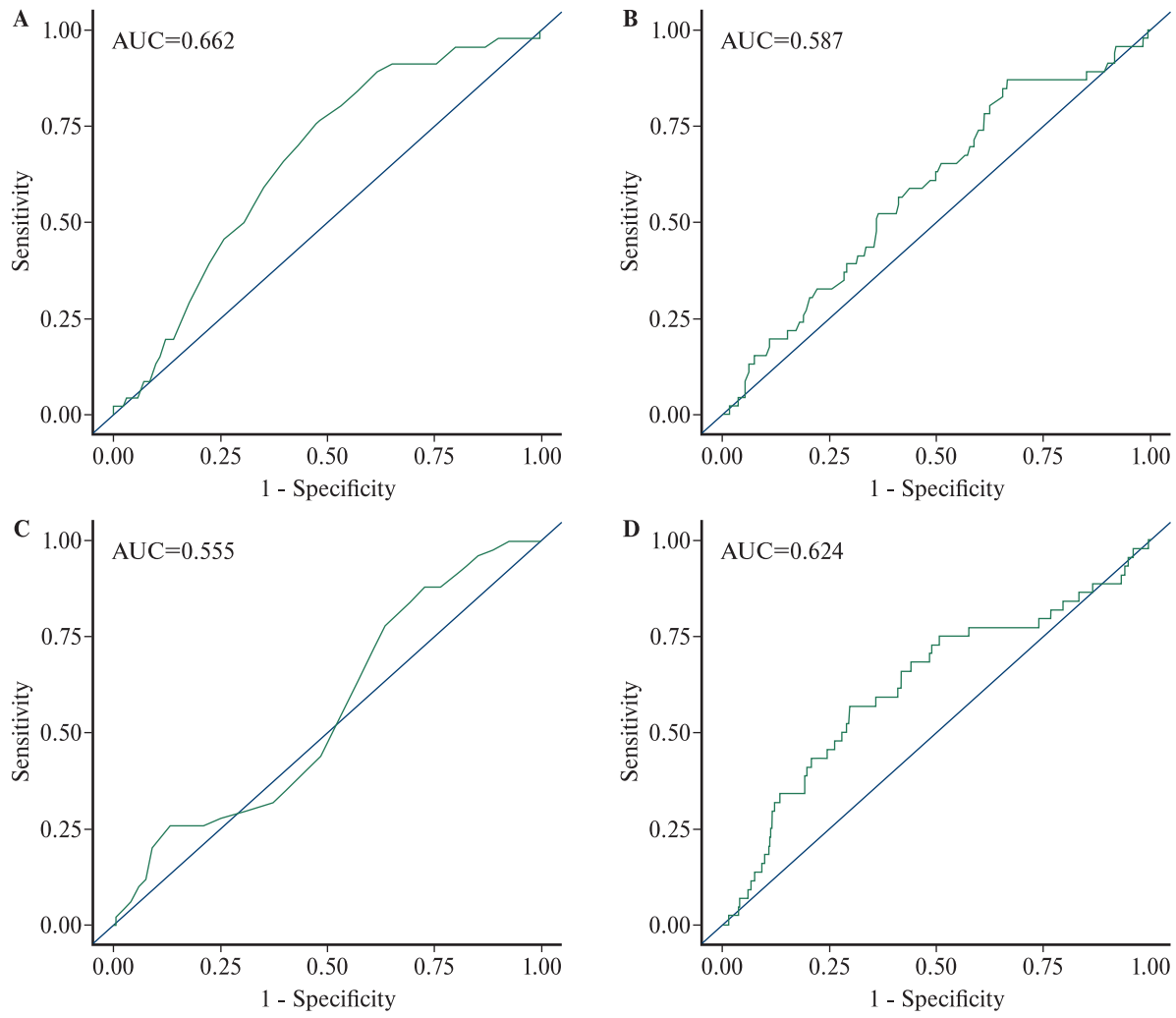


Fig. 2. ROC curves for potential risk factors of incidental prostate cancer
A – age, B – prostate volume, C – IPSS, D – PSA density

slightly differed from the data of Taro Banno et al. (2022) and Clément Klein et al. (2022), where incidences were 8.0% [15] and 10.7% [23], respectively. The prevalence of incidental PCa after HoLEP according to Jang Hee Han et al. (2023) was 2 times lower and amounted to 5.4% (141 patients out of 2630) [24]. Akihisa Sakai et al. (2024) found a higher prevalence of incidental PCa after HoLEP, which was 20% (183 out of 913 people), and a higher PSA density was indicated as a potential risk factor [25].

In 2022, Bryan Kwun-Chung Cheng et al. published a meta-analysis including 30,000 patients who underwent endoscopic enucleation of the prostate. According to the results of the meta-analysis, the prevalence of incidental PCa after endoscopic enucleation was 8%. When performing a subgroup analysis for HoLEP and thulium enucleation/vapoenucleation using a solid-state laser, these indicators were 8.1 and 7.3%, respectively [17], while there were no data for bipolar enucleation and ThuFLEP. Such an analysis was done for the first time in our study. We showed that incidental PCa was diagnosed in 8.4% of patients after bipolar enucleation of prostate hyperplasia and in 5.3% after ThuFLEP, and there was no significant difference between groups. Our results were consistent with the above data for other variants of endoscopic enucleation.

According to the national study from USA, in 48% of patients with incidental PCa the total PSA level did not exceed 4 ng/ml, in 31% it was in the range from 4 to 10 ng/ml and in 21% it was higher than 10 ng/ml [26]. Somewhat different data were obtained in our work. Thus, in the majority of patients with incidental PCa (43.2%), total PSA was in the gray zone from 4 to 10 ng/ml, while in 40.9% of patients it was below 4 ng/ml. In 15.9% of patients, the total PSA level was higher than 10 ng/ml.

The frequency of incidental PCa after TURP and open simple prostatectomy according to individual studies is somewhat higher than in our study, which included patients undergoing endoscopic enucleation. According to the results of Abdikarim Hussein Mohamed et al. (2023), incidental PCa was diagnosed in 18.3% of men after TURP and in 13.5% after open simple prostatectomy. Risk factors for incidental PCa were recognized as older age of patients, higher levels of total PSA, smaller prostate volume [27], which is partially consistent with our data, where incidental PCa was found in older patients with smaller prostate volumes.

According to the results of Francesco Esperto et al. (2024), the frequency of incidental PCa after TURP and open simple prostatectomy was 16.3% (74 out of 454 patients). As in our work, Francesco Esperto et al. (2024) showed that PSA density in patients with incidental PCa was significantly higher, while in regression analysis this relationship was not seen, and the only predictor was the fact of not performing MRI preoperatively [28]. Similar results were obtained in the study of Kanami Mori et al. from China (2024), where the absence of MRI increased the chance of having incidental PCa after HoLEP by 2.92 times [29]. This was also confirmed by the results of the largest national study by Eugenio Bologna et al. (2024), including 230,000 patients who underwent various operations for BPH. The overall prevalence of incidental PCa was 2.2%, and factors that reduced the likelihood of its detection included younger age and performing MRI and/or prostate biopsy at the preoperative stage [30]. In this study, we did not evaluate the fact of performing a prostate biopsy or MRI of the pelvic organs. Nevertheless, we, like foreign colleagues, showed that patients with incidental PCa have a higher PSA density.

According to Eric V. Li et al. (2024), the prevalence of incidental PCa after HoLEP is 12.8% (104 out of 811 people), while clinically significant PCa (ISUP grade 2 and above) is 4.4%. Our analysis revealed that an elevated Prostate Health Index (PHI) independently predicted incidental prostate cancer, whereas clinically significant disease was associated with both a higher PHI and an increased PSA density [31]. In the meta-analysis by Zhenlang Guo et al. (2022), each incremental rise in total PSA was linked to a 1.13-fold increase in the likelihood of incidental PCa after any surgical treatment for BPH, while patient age and prostate volume showed no predictive value [10].

A large study on the prevalence and risk factors of incidental PCa was published by Julien Anract et al. (2024) and included almost 2500 patients who underwent endoscopic enucleation of the prostate (68%), TURP (20%) or open simple prostatectomy (12%) [32]. Incidental PCa was detected in 10.0% of patients, and 20.2% of them had clinically significant PCa (ISUP grade ⩾2). Independent predictors of incidental PCa after surgical treatment of BPH were older age of patients (OR = 1.04, 95% CI: 1.02–1.06; $p<0.001$), PSA density (OR=2.3; 95% CI: 1.6–3.4; $p<0.001$) with AUC values of 0.605 and 0.600, respectively [32]. Similar results were obtained in our study. Thus, clinically significant PCa of ISUP grade ⩾2 was detected in 30% of all cases. Patient age and PSA density, with AUC values of 0.662 and 0.624 respectively, emerged as predictors associated with an increased likelihood of incidental PCa. Consistent with findings from international studies, these parameters demonstrated only moderate prognostic value.

Thus, the low frequency of detection of incidental PCa and the absence of strong predictors may be associated with a comprehensive preoperative examination, which allows at the preoperative stage to screen out all men with possible malignant tumors [33].

Our study has some limitations, including the retrospective nature, which could lead to distortion of results due to different strategies for preoperative examination of patients with BPH. Nevertheless, we tried to level these shortcomings by including patients treated by one specialist who independently prescribed preoperative examination. Another important point is the absence of follow-up data on patients diagnosed with incidental PCa and their clinical outcomes. However, since the last patient included in the study has been under follow-up for less than three years since diagnosis, this analysis is planned for a future study.

Conclusion. The prevalence of incidental prostate cancer after endoscopic enucleation of the prostate is 6.7 % overall, with 8.4 % observed following bipolar enucleation and 5.3 % after ThuFLEP. This should be taken into consideration when counseling patients prior to transurethral procedures on the prostate. In 70 % of cases, the detected incidental prostate cancer is clinically insignificant and classified as ISUP grade 1. Older age and elevated PSA density demonstrated moderate predictive power and were associated with a higher likelihood of incidental PCa. The absence of strong predictive factors suggests that patients with BPH are being appropriately and thoroughly evaluated before surgical intervention.

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Received 28.10.2024
Accepted 17.01.2025

Funding: The study was conducted under the state task force of the Medical Research and Educational Institute of Moscow State University.

Contribution of the authors. N.I. Sorokin – scientific guidance, critical review, data collection; A.A. Strigunov – literature review, data analysis, writing the text of the manuscript; O.Yu. Nesterova – literature review, data collection, data analysis, writing the text of the manuscript; A.M. Pshikhachev – data collection, data analysis; I.D.

Burlakov – data collection, data analysis; N.A. Oleynikova – data collection, data analysis; M.G. Varentsov – data analysis, writing the text of the manuscript; I.D. Bondar – data analysis, writing the text of the manuscript; A.D. Tereshina – data analysis, writing the text of the manuscript; A.E. Veriaskina – data analysis, writing the text the manuscripts; A.A. Kamalov – scientific guidance, data analysis, critical review.

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