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Incidental Prostate Cancer in Patients Undergoing Surgery for Benign Prostatic Hyperplasia: A Predictive Model

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Abstract

Background and objective: Histopathological examination of surgical specimens for benign prostatic hyperplasia (BPH) can detect incidental prostate cancer (iPCa). The aim of our study was to develop a predictive model for iPCa diagnosis for patients for whom BPH surgery is being considered.

Methods: We conducted a retrospective analysis of medical files for patients who underwent BPH surgery in three academic centers between 2012 and 2022. Patients diagnosed with PCa before surgery were excluded. We calculated the global iPCa rate, and the clinically significant iPCa rate (grade group $\geq$2). Univariate and multivariable regression models were used to assess factors predictive of iPCa. The area under the receiver operating characteristic curve (AUC) was compared for each risk factor and for the global model. We used χ^2 automated interaction detection (CHAID) for decision tree analysis.

Key findings and limitations: We included 2452 patients in the analysis, of whom 247 (10.0%) had iPCa, which was clinically significant in 49/247 cases (20.2%). Multivariable analysis revealed that age and prostate-specific antigen density (PSAD) were independent predictive factors for iPCa diagnosis. The AUC for a model including age and PSAD was 0.65. CHAID analysis revealed that patients with PSAD >0.1 ng/ml/cm^3 had an iPCa risk of 23.4% (χ^2 = 52.6; p < 0.001). For those patients, age >72 yr increased the iPCa risk to 35.4% (χ^2 = 11.1, p = 0.008). Our study is mainly limited by its retrospective design.

Conclusions and clinical implications: Age and PSAD were independent risk factors for iPCa diagnosis. The combination of age >72 yr and PSAD >0.1 ng/ml/cm^3 was associated with an iPCa rate of 35.4%.

Patient summary: We performed a study to find predictors of prostate cancer for patients undergoing surgery for benign enlargement of the prostate. Our model can

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identify patients at risk, and diagnose their cancer before surgery. This could avoid unnecessary or harmful procedures.

1. Introduction

Surgery for bladder outlet obstruction related to benign prostatic hyperplasia (BPH) is one of the most common procedures in urology [1]. Described in the early 1930s, simple prostatectomy and transurethral resection of the prostate (TURP) were considered the gold standards for 70 yr [2,3]. Endoscopic laser enucleation of the prostate was described more than 20 yr ago [4] and is now considered a standard of care [5,6]. All of these techniques involve removing the hyperplasic tissue and allow histological analysis of the tissue removed. The main objective of histological analysis is to rule out incidental prostate cancer (iPCa).

The emergence of minimally invasive surgical therapies (MISTs) has improved safety and the ability to preserve sexual function [7]. MISTs are based on various principles and use various energies, but none of them allow any tissue retrieval for histology. Thus, MIST procedures preclude the possibility of screening of surgical specimens for iPCa. Although MIST techniques are currently offered to a specific selected population of mostly young men, we are facing an expansion of these procedures and their indications. Thus, the development of these MIST techniques might lead to an increase in the rate of undiagnosed iPCa and raise the issue of management for these patients.

Several studies investigating iPCa rates revealed that most incidental diagnoses were clinically insignificant PCa (eg, International Society of Urological Pathology grade group [GG] <2 and <5% of tissue involved with PCa) [8–10]. Accordingly, most international guidelines recommend active surveillance for these patients [11–13]. By contrast, significant iPCa may warrant radical treatment instead or in addition to BPH surgery.

The aim of our study was to assess the iPCa rate in a large cohort of patients and to identify risk factors for iPCa for development of a predictive model.

2. Patients and methods

We conducted a retrospective analysis of all patients who underwent BPH surgery in three academic centers between 2012 and 2022. All patients who underwent TURP, simple prostatectomy, or laser enucleation and who did not express opposition to participation in clinical studies were included. The study was approved by the local ethics committee.

Medical charts were reviewed to collect relevant clinical data including age, prostate-specific antigen (PSA), prostate volume, 5α-reductase inhibitor (5ARI) use, surgical technique, and resected tissue weight. PSA density (PSAD) was calculated using the preoperative prostate volume estimated with any imaging modality (ultrasound and/or magnetic resonance imaging [MRI]). Patients with no evaluation of the preoperative prostate volume were excluded.

Histological analysis was conducted in each center by a senior uropathologist. Standard hematoxylin and eosin staining was used to screen the tissue, and p63 and racemase immunostaining was used in cases of unclear diagnosis to confirm the presence of iPCa. pT stage was assigned using the standard definition of the percentage of the specimen involved with prostate cancer (pT1a < 5%; pT1b >5%). Thus, assessment of pT stage was based only on the cancer volume.

Clinically significant iPCa (CS-iPCa) was defined as the presence of any tumoral gland with GG >1 in the specimen. Clinically nonsignificant iPCa was defined as GG 1 PCa in the specimen.

2.1. Statistical analysis

Results are presented as the median and interquartile range (IQR) for continuous variables, and as the absolute number and percentage for categorical variables. Student *t* test was used to compare median values. A two-tailed Fisher's exact test was used to compare proportions. Univariate and multivariable regression models were constructed to assess independent predictive factors for iPCa. Clinically and statistically significant variables were included in the multivariable model. Receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was calculated and compared for each risk factor, and for the global model combining multiple risk factors. For continuous variables, median values were used as thresholds to conduct subgroup analyses and calculate the variable-specific iPCa risk. A two-sided p value <0.05 was considered statistically significant. We also used the χ^2 automatic interaction detection (CHAID) algorithm for decision tree analysis in which iPCa presence or absence was the dependent variable. The independent variables were patient age, PSA, PSAD, prostate volume, and 5ARI use. The decision tree was set to have a maximum of three levels and a minimum of 100 cases for each parent node, and any given split should not generate a child node with fewer than 50 cases; the significance level (α_{merge}, α_{split}, and p value) was set at $\leq$0.05. All statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). CHAID decision tree analysis was performed using SPSS statistical software (SPSS Inc., Chicago, IL, USA).

3. Results

We included 2452 patients in the final analysis. The median age was 70 yr (IQR 65–76) and median preoperative PSA was 4.3 ng/ml (IQR 2.5–7.8). The majority of the patients underwent laser enucleation of the prostate (n = 1664,

68%). Patient characteristics and surgical data are summarized in Table 1.

In our cohort, 247 patients (10.1%) had iPCa and 52 (2.1%) had CS-iPCa. Stage pT1b disease was found in 40/52 (76.9%) of the CS-iPCa cases and 27/195 (14%) of the clinically nonsignificant iPCa cases (p < 0.001). Histological results for the iPCa cases are summarized in Table 2.

Univariate analysis revealed that elevated total PSA, PSAD, age, and the absence of long-term 5ARI use were significantly associated with iPCa detection. On multivariable analysis, age and PSAD were the only independent factors associated with iPCa detection, while long-term 5ARI use was identified as an independent protective factor against iPCa (Table 3).

To evaluate the accuracy of these factors in predicting iPCa, ROC curves for PSAD, age, and long-term 5ARI use were constructed (Fig. 1). The AUC was 0.60 for PSAD, 0.605 for age, and 0.60 for 5ARI use.

Table 1 – Patient characteristics (n = 2452)

Parameter	Result
Median age, yr (IQR)	70 (65–76)
Median total PSA, ng/ml (IQR)	4.3 (2.5–7.8)
Median prostate volume, cm^3 (IQR)	80 (56–107)
Median PSA density, ng/ml/cm^3 (IQR)	0.05 (0.03–0.08)
Long-term 5ARI use, n (%)	416 (17)
Surgical technique, n (%)	
Endoscopic enucleation	1664 (68)
Simple prostatectomy	309 (12)
Transurethral resection of the prostate	478 (20)
Median resected prostate weight, g (IQR)	44 (24–69)
Median percentage tissue resected, % (IQR)	52 (32–70)

5ARI = 5α-reductase inhibitor; IQR = interquartile range; PSA = prostate-specific antigen.

Table 2 – Histological results for the incidental PCa cases diagnosed in the cohort

Parameter	Patients, N = 247, n (%)
pT stage	
pT1a	185 (75)
pT1b	62 (25)
ISUP grade group	
1	195 (79)
2	33 (13)
3	9 (3.6)
4	4 (1.6)
5	6 (2.4)
Clinically significant PCa	52 (21)

ISUP = International Society of Urological Pathology; PCa = prostate cancer.

To ensure its clinical relevance and applicability, we included only PSAD and age in the final multivariable model. The ROC curve is shown in Figure 2; the AUC was 0.64.

We conducted CHAID decision tree analysis to identify the best cutoff point for iPCa (Fig. 3). iPCa was included as a dependent variable, and age, total PSA, PSAD and prostate volume were used as independent variables. The classification accuracy was 89.9%. The tree included five terminal nodes and two depth levels. This analysis showed that PSAD and age were the most decisive variables for classification, and two risk levels were created for iPCa. iPCa accounted for 23.4% of the patients with PSAD >0.1 ng/ml/cm^3 (χ^2 = 52.6; p < 0.001). For these patients, the probability of iPCa increased to 35.4% if they were older than 72 yr (χ^2 = 11.1; p = 0.008). For patients with PSAD of 0.1 ng/ml/cm^3 who were older than 63 yr, the iPCa probability was 13.5% (χ^2 = 10; p = 0.013).

4. Discussion

To the best of our knowledge, this is the largest multicenter study reporting iPCa detection in patients treated with simple prostatectomy, TURP, or endoscopic enucleation for BPH. iPCa detection rates reported in the literature are highly variable. In a study by Elkoushy et al [14] the rate of iPCa was only 5% in a cohort of 1242 patients, whereas others have reported much higher detection rates. Perera et al [8] reported an incidence rate of 23% in their series of 923 patients. In our work, the iPCa rate was at the lower end of the range, at 10.1%. Even though this variability may be explained by different factors, including the amount of tissue removed, we believe that the major factor may be the population itself. Thus, the actual PCa prevalence and the screening policy may affect results for the iPCa rate. Our study cohort comprised 2452 patients treated in three French academic centers over a period of 10 yr. During this time period, the three centers conducted PSA screening before BPH surgery and performed MRI, followed by targeted prostate biopsies in patients with any suspicious imaging results. This strategy is in agreement with the European Association of Urology guidelines [11]. We thus believe that the detection rates for iPCa and CS-iPCa in our centers are representative of what we should expect in contemporary practice in European countries.

Among the iPCa cases diagnosed during our study period, CS-iPCa accounted for 20%. The median age for the study cohort was 70 yr (IQR 65–76), so radical treatment was a

Table 3 – Univariate and multivariable results for factors associated with diagnosis of incidental prostate cancer

Variable	Univariate analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (per 1-yr increment)	1.03 (1.02–1.05)	<0.001	1.04 (1.02–1.06)	<0.001
Total PSA (per 1 ng/dL increment)	1.05 (1.03–1.07)	<0.001	1.0 (0.9–1.02)	0.31
Prostate volume (per 1 cm^3 increment)	0.99 (0.99–1.1)	0.49	–	–
PSA density (per 0.1 ng/ml/cm^3 increment)	1.7 (1.4–2.0)	<0.001	2.3 (1.6–3.4)	<0.001
5α-reductase inhibitor use	0.4 (0.3–0.6)	<0.001	0.4 (0.2–0.6)	<0.001
Resected prostate weight (per 1 g increment)	0.99 (0.99–1.1)	0.29	–	–
Prostate tissue resected (per 1% increment)	0.99 (0.98–1.01)	0.64	–	–

CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen.

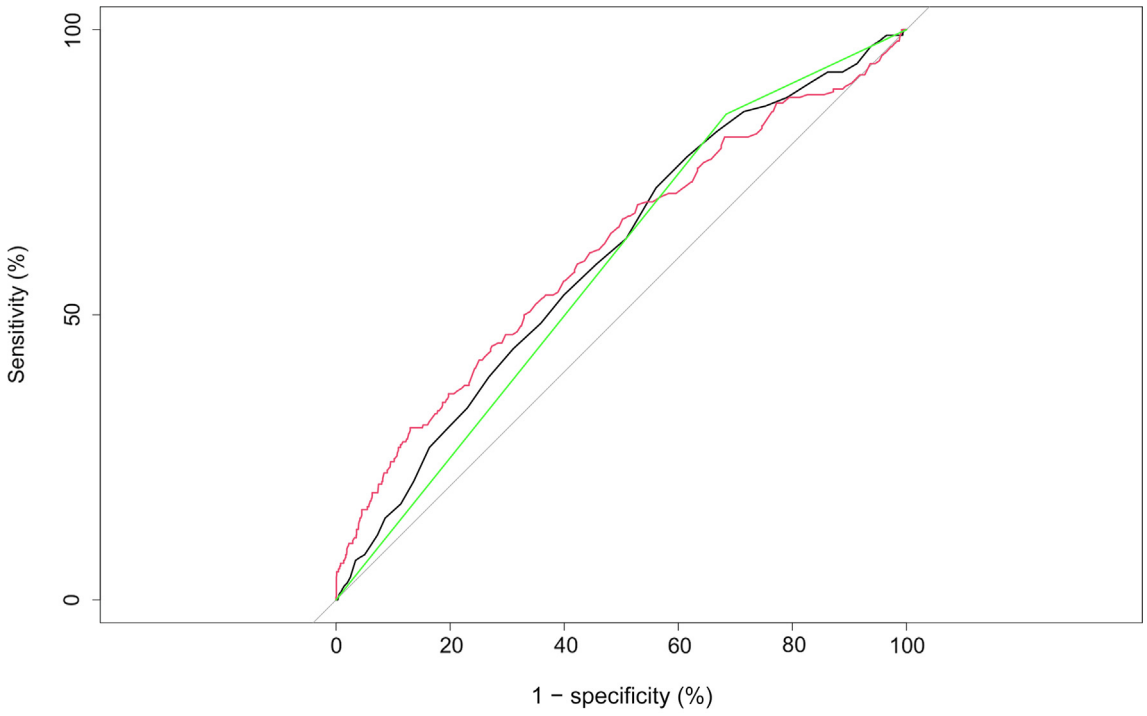

Fig. 1 – Receiver operating characteristic curves for prediction of incidental prostate cancer by age (black), prostate-specific antigen density (red), and 5α-reductase inhibitor use (green).

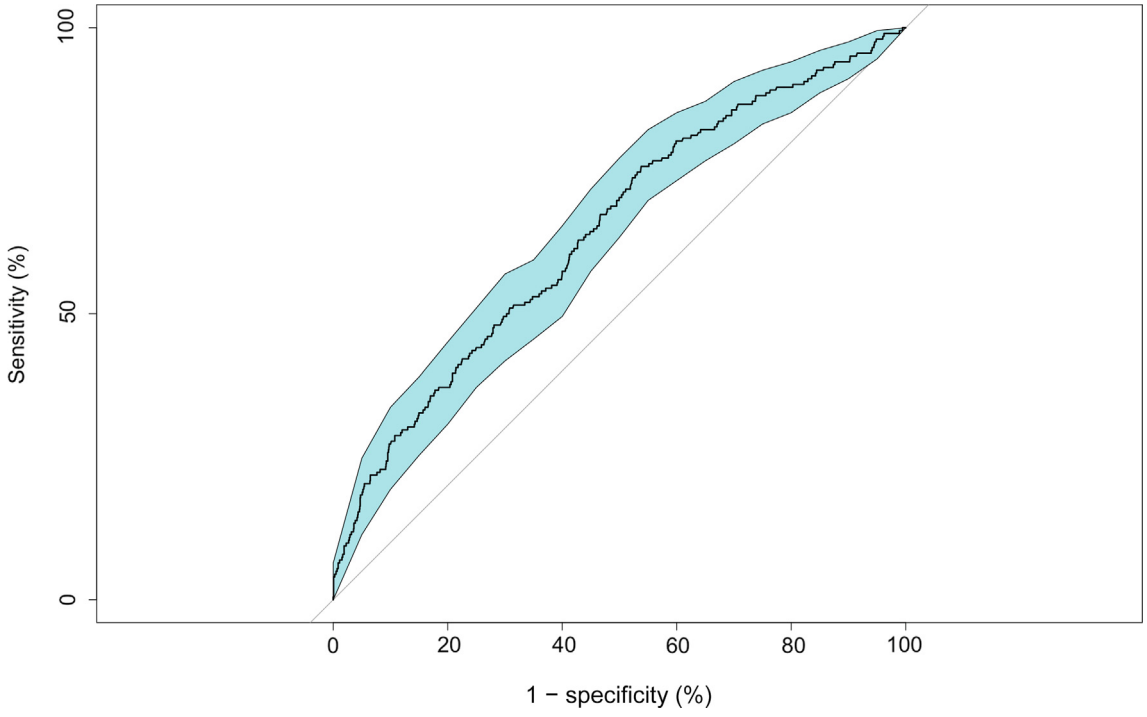

Fig. 2 – Receiver operating characteristic curve for prediction of incidental prostate cancer by the model including age and prostate-specific antigen density.

relevant option for the majority of our patients. However, the choice of radical treatment may differ from that for patients without prior BPH surgery because of significant differences in morbidity profiles [15–17]. Although radical prostatectomy (RP) is still considered feasible after endoscopic enucleation in high-volume centers, it has been reported that the 1-yr continence rate is significantly worse than for surgery-naïve patients [18]. Dissection difficulties may also impact the rate of postoperative erectile dysfunction and the risk of intraoperative complications. Nevertheless, recent data did not show any association between prior BPH surgery and rectal injury during RP [15]. It has been

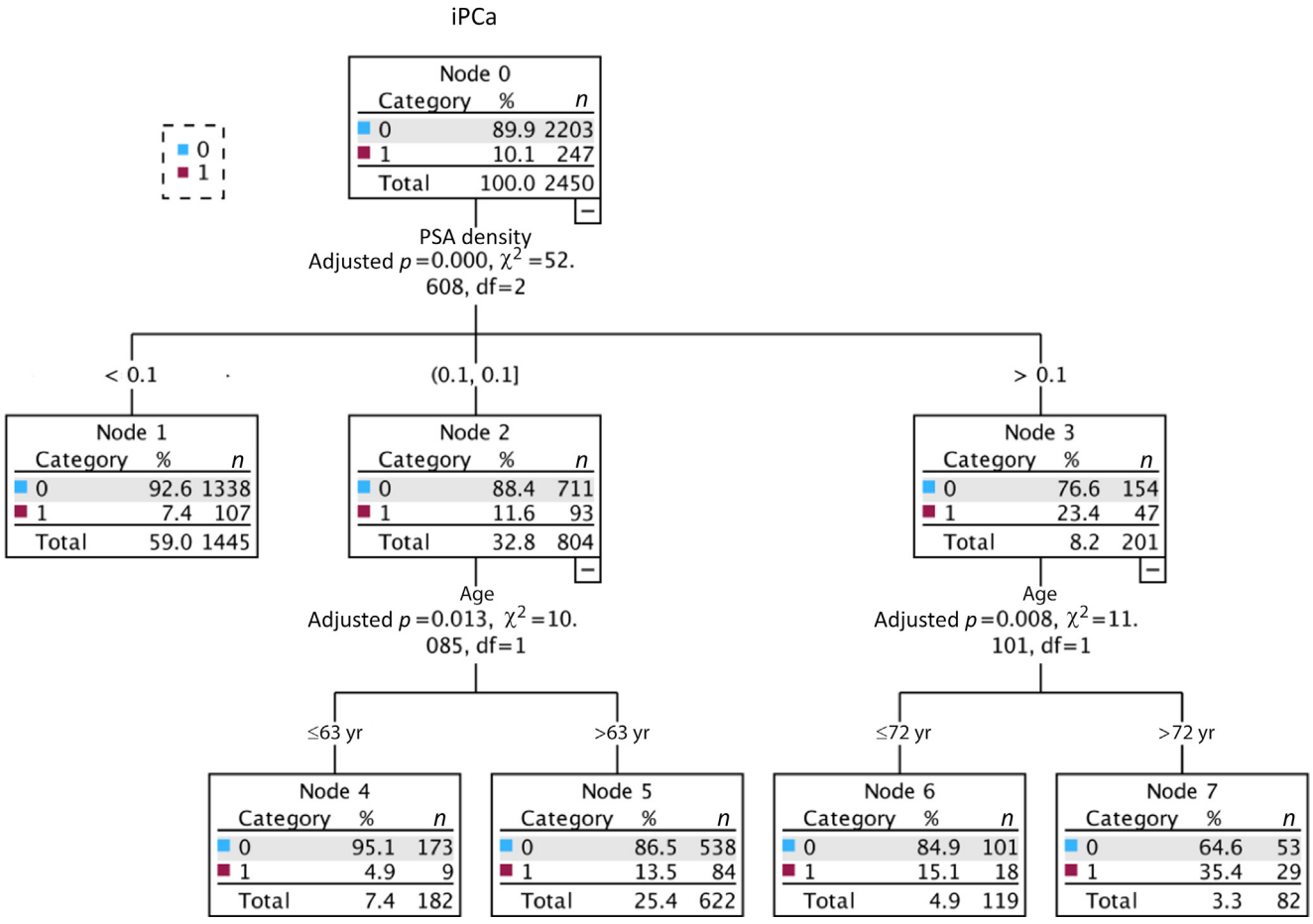

Fig. 3 – Decision tree for iPCa probability according to the χ^2 automated interaction detection algorithm. iPCa = incidental prostate cancer; df = degrees of freedom; PSA = prostate-specific antigen.

shown that external beam radiation therapy has a low risk of complications in this specific population [16]. Other patients may have been good candidates for focal therapy. However, there are no data on oncological and functional results of focal therapy after BPH surgery. To the best of our knowledge, focal therapy protocols usually exclude patients with prior BPH surgery because of difficulty in targeting lesions in the remaining peripheral zone [17,19]. These data suggest that a CS-iPCa diagnosis will affect patient management, and that the treatment option chosen for cancer control may not be the one that would have been considered as the optimal choice if PCa had been diagnosed before BPH surgery. For this reason, we think that an algorithm for prediction of CS-iPCa is relevant, especially one that is based on clinical and biological data that are readily available.

The high CS-iPCa incidence in our series also raises concerns regarding BPH management using MIST procedures. These alternatives to standard surgical techniques are burgeoning and their use in standard care is steadily increasing [7]. Prostatic artery embolization is associated with lower morbidity and preservation of ejaculation in most cases [20,21]. Water vapor thermal therapy and intraprostatic implants are considered feasible and safe as in-office procedures under local anesthesia, and improve lower urinary tract symptoms in patients with a prostate volume <100 cm^3 while preserving sexual function [22,23]. However, in addition to the lack of specimen retrieval for histological analysis with these MIST techniques, there is a sparsity of data regarding the feasibility of RP or focal therapy after any of these procedures.

Analysis using a CHAID algorithm confirmed the two independent factors predictive for iPCa, which we then prioritized in a decision tree. The strength of this tree is its applicability in daily practice, as it uses readily available preoperative data. The first parameter to consider is PSAD, which can be quickly estimated by the clinician from preoperative imaging data in most cases. Once PSAD is calculated, an age cutoff is used to stratify patients into two iPCa risk categories. Hence, the model appears to be applicable in daily practice, and could be a useful aid in managing preoperative PCa screening by estimating the iPCa probability for patient subgroups.

The decision tree revealed that the risk of any iPCa was low for patients with PSAD < 0.1 ng/ml/cm^3 (7.4%). Interestingly, the CS-iPCa risk was also low in this population (0.4%). For patients with PSAD >0.1 ng/ml/cm^3, the iPCa risk was 23.4% and the CS-iPCa risk was 12.4%. Among those

patients, the iPCa risk was 15.1% for patients younger than 72 yr, and 35.4% for patients older than 72 yr. Using the same age cutoff for this population, the CS-iPCa risk increased from 8.4% to 18.2% ($p = 0.06$). Although our model was not able to show statistical significance for CS-iPCa detection, probably because of the small number of events, the same trend as for iPCa was observed. Furthermore, we believe that any iPCa should be diagnosed before surgery, because such a diagnosis may change patient management in a way that is more clinically relevant.

On the basis of these results, the decision tree could assist urologists considering further PCa screening before BPH surgery for patients with high iPCa risk, including those for whom a MIST procedure is being planned.

Other studies identified PSA as a predictive factor for iPCa [24,25]. According to our results, PSA was only predictive for iPCa and CS-iPCa in univariate analyses. In multivariable models that included prostate volume, PSA, and PSAD, only PSAD appeared to be an independent predictive factor for iPCa. However, single-center studies [9,26] and one meta-analysis [27] found that PSAD and age were predictive for iPCa. We propose a predictive model that is based on thresholds for risk factors. This means that the model is applicable in daily practice to assist in decisions on PCa screening before BPH surgery, especially for techniques that do not allow retrieval of resected tissue for histological analysis.

Interestingly, we found that long-term 5ARI use was associated with lower iPCa risk. Large series have revealed a lower risk of PCa and a lower risk of PCa-specific mortality for patients treated with dutasteride [28,29]. The REDUCE trial evaluated dutasteride for chemoprevention of PCa [30]. The results confirmed a lower rate of PCa among men treated with dustasteride, but a greater number of high-GG cancers. As the number of high-GG iPCa cases was low in our study, we were unable to analyze the impact of 5ARI in this population. The association between 5ARI use and aggressive PCa remains unclear, and we chose not to include 5ARI use in our predictive model. Moreover, we believe that the applicability of this model in daily practice is much higher, as data on age and PSAD are widely available.

Our study has some limitations, including its retrospective design. This may have led to bias related to individual PCa screening strategies before BPH surgery. The lack of follow-up data for patients diagnosed with iPCa is also an issue. Regarding the cluster of patients with GG 1 iPCa, data on PSA follow-up and the time to progression would be crucial to analyze specific outcomes after iPCa detection. However, as the last patient included was treated <5 yr ago, this analysis will be performed in a separate study.

5. Conclusions

Age and PSAD were independent risk factors for iPCa diagnosis among patients who underwent BPH surgery. For patients with PSAD < 0.1 ng/ml/cm^3, the risk of iPCa was low (7.4%). For patients with PSAD >0.1 ng/ml/cm^3, age >72 yr doubled the risk of iPCa from 15.1% to 35.4%. Our results suggest that the risk of iPCa should be discussed before BPH surgery for patients with these risk factors.

Author contributions: Julien Anract had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Anract, Klein, Pinar
Acquisition of data: All auhtors
Analysis and interpretation of data: Anract, Pinar, Klein
Drafting of the manuscript: Anract, Pinar, Klein
Critical revision of the manuscript for important intellectual content: Robert, Barry Delongchamps.
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