

Prognostic Impact of Index Density of the Percentage of Positive Biopsy Cores in Clinical Prostate Cancer: Results in 1047 Patients Treated with Robot-Assisted Radical Prostatectomy in a Single Tertiary Referral Center

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Article

Prognostic Impact of Index Density of the Percentage of Positive Biopsy Cores in Clinical Prostate Cancer: Results in 1047 Patients Treated with Robot-Assisted Radical Prostatectomy in a Single Tertiary Referral Center

Running title: The prognostic impact of index density of the percentage of positive biopsy cores in operated prostate cancer patients

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Abstract: Objectives: To evaluate the index density (Id) of the percentage of biopsy positive cores (BPC), Id-BPC, as a prognostic factor of prostate cancer (PCa) progression after predicting unfavorable pathology in patients treated with robot-assisted radical prostatectomy (RARP) eventually associated with extended pelvic lymph node dissection. **Design:** Data from 1047 patients undergoing RARP were collected between January 2013 and December 2021. **Methods:** Id-BPC was defined as the ratio of BPC (%) to prostate volume (mL). Unfavorable pathology in the surgical specimen was defined as tumor grade group greater than 1 and/or non-organ confined disease. Disease progression was defined as biochemical recurrence and/or loco-regional recurrence and/or metastatic occurrence. Associations with the risk of unfavorable pathology and disease progression were evaluated by logistic regression and Cox proportional hazards model (univariate and multivariate analysis), respectively. **Results:** Unfavorable pathology was detected in 930 (88.8%) cases. Disease progression occurred in 160 (15.3%) patients after a mean (95% CI) follow-up of 89.0 (86.6-91.3) months. After adjusting for all clinical variables, patients with higher Id-BCR were more likely to have unfavorable pathology in the surgical specimen (odds ratio = 1.566; 95% CI: 1.029 – 2.383; $p < 0.001$). As Id-BCR increased, patients were more likely to experience disease progression, even when adjusting for clinical variables (hazard ratio = 1.587; 95% CI: 1.306 – 1.929; $p < 0.0001$), as well as unfavorable pathology (hazard ratio = 1.365; 95% CI: 1.166 – 1.597; $p < 0.0001$). The impact of Id-BPC on PCa progression was stronger than that of BPC, particularly after predicting unfavorable pathology. **Conclusions:** Id-BCR is an independent prognostic factor of unfavorable pathology and disease progression in PCa patients undergoing surgical treatment with curative intent. As Id-BPC increases, patients have a higher probability of experiencing unfavorable pathology in the surgical specimen and disease progression. Id-BCR is a clinical marker of PCa biology.

Keywords: prostate cancer; robot-assisted radical prostatectomy; extended pelvic lymph node dissection; pelvic lymph node invasion; biochemical recurrence; prostate cancer progression; prostate biopsy; percentage of biopsy positive cores; prostate volume; tumor density

1. Introduction

Prostate cancer (PCa) is a growing concern among aging men [1,2]. To address the most common form of presentation, clinical non-metastatic PCa, the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) have developed guidelines that offer valuable options for management. Depending on the clinical risk class, options may include monitoring strategies such as active surveillance (AS) or watchful waiting (WW), or active treatment like surgery, most frequently performed with robot-assisted radical prostatectomy (RARP) approach eventually associated with extended pelvic lymph node dissection (ePLND), and radiation therapy (RT) [1–3]. Although clinical risk classes provide valuable information about a disease's prognosis, it's essential to understand that risk groups are not homogeneous. As such, it's crucial to make further efforts within each class to detect patient subsets that may have indolent or aggressive disease, avoiding over-treatment, which patients may come to regret in the future [1,2,4,5]. Although molecular biology holds significant potential in identifying prognostic subgroups, it has yet to become commonly utilized in routine clinical practice. Conversely, multiparametric resonance imaging (mpMRI) is useful in diagnosing diseases, but its reproducibility is lacking and its ability to accurately stage diseases remains uncertain [6,7]. Therefore, the applications of validated nomograms remain an essential tool for stratifying low- and intermediate-risk patients and predicting the risk of unfavorable disease and pelvic lymph node invasion (PLNI) [1,2]. These nomograms rely on standard clinical parameters that are widely available in urological centers during PCa diagnosis [1,2]. Briganti's 2012 nomogram, which employs basic standard parameters, has proven highly effective in predicting unfavorable disease. Although the updated nomogram incorporates mpMRI parameters, its accuracy is heavily operator-dependent and varies across multicenter studies [1,2,6,8,9]. One of the most powerful parameters is the percentage of biopsy-positive cores (BPC), which is particularly useful for determining the risk of PLNI [1,2,8]. BPC provides valuable information on PCa biology, including tumor load after prostate biopsy, along with basal PSA, tumor grade, and stage [1,2,10]. However, the potential of tumor density within the organ being investigated as a parameter for defining cancer biology has yet to be explored. This study endeavors to investigate the index density of BPC (Id-BPC), defined as the ratio of BPC to prostate volume (PV), as a potential clinical marker of PCa biology. Id-BPC was evaluated as a predictor of the likelihood of unfavorable pathology in the surgical specimen, as well as a prognostic factor of disease progression following RARP for clinical PCa with curative intent.

2. Materials and Methods

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement (Supplementary Material 1).

2.1. Selection of the Investigated Patient Population

Between January 2013 and December 2021, a total of 1047 operated PCa patients who had follow-up data available were selected. Data were collected prospectively and evaluated retrospectively. All patients provided informed consent that was approved by the Institutional Review Board. Inclusion criteria consisted of at least 12 systematic prostate biopsy cores; 3 to 5 target biopsy cores for each PI-RADS > 3 lesions detected in Patients undergoing mpMRI before prostate biopsy; the measurement of prostate volume through transrectal ultrasound (TRUS) methods at the time of PCa diagnosis. Patients who had undergone androgen deprivation or previous active treatment were excluded. Following recommendations, RARP was eventually performed alongside ePLND, which followed a standard anatomical template that included external iliac, obturator, Cloquet's, and Marcille's regions [11]. The choice to perform ePLND was made considering the EAU risk class and nomograms to estimate the risk of lymph node extension of the disease. Surgical procedures were performed by five experienced urologists.

2.2. Evaluation of Clinical, Pathological, and Follow-Up Factors

During clinical assessments, patient age (years), body mass index (BMI; kg/m²), physical status, PSA (ng/mL), PV (mL), BPC (%), tumor grade, and stage were all evaluated. For each case, the ratios of BPC and PSA to PV, measured by TRUS methods, were calculated, and the resulting relative

densities were reported as Id-BPCD (%/mL) and PSA density (PSAD, ng/mL²), respectively. The surgical specimens were assessed by a dedicated pathologist for tumor grade, stage, and surgical margins status, while pelvic lymph nodes were counted and assessed for PLNI. The RARP and ePLND procedures have been previously described [11,12]. Tumors were graded according to the International Society of Urological Pathology (ISUP) system and staged using the TNM system [1,2]. Physical status was evaluated preoperatively using the American Association of Anesthesiologists (ASA) score system [11,12]. Patients were followed by recommendations [1,2]. In case of persistence/recurrence of PSA, imaging modalities were considered to restage the disease and plan further treatments, performed in a multidisciplinary setting involving urologists, radiation oncologists, and oncologists, to optimize recommendations while taking the patient's issues into account [1,2].

2.3. Model Description and Assumptions, Study Design, and Evaluation of Endpoints

The clinical factor investigated was the Id-BPC. The clinical model, depicted in Figure 1, was based on the following assumptions. Firstly, variations in PV are associated with tumor variations. Secondly, a constant BPC that correlates with variation in PV resulted in different tumor densities. Therefore, as PV increases, tumor densities decrease. For instance, tumors with a BPC of 10% could occur in a PV of 30 mL (Id-BPC = 0.33), 60 mL (Id-BPC = 0.16), or 90 mL (Id-BPC = 0.11). However, tumor load density is higher in the former case, where aggressive tumor biology should be expected when evaluating the surgical specimen. Thirdly, high tumor load densities should predict unfavorable pathology in the surgical specimen and PCa progression. We evaluated the Id-BPCD as a continuous variable and related it to unfavorable pathology in the surgical specimen and disease progression. Unfavorable pathology in the surgical specimen was defined as including unfavorable tumor grade (ISUP > 1) and/or non-organ confined disease (extracapsular extension (ECE) or seminal vesicle invasion (SVI)) and/or PLNI. Thus, PCa progression was defined as the occurrence of biochemical recurrence/persistence and/or local recurrence and/or distant metastasis.

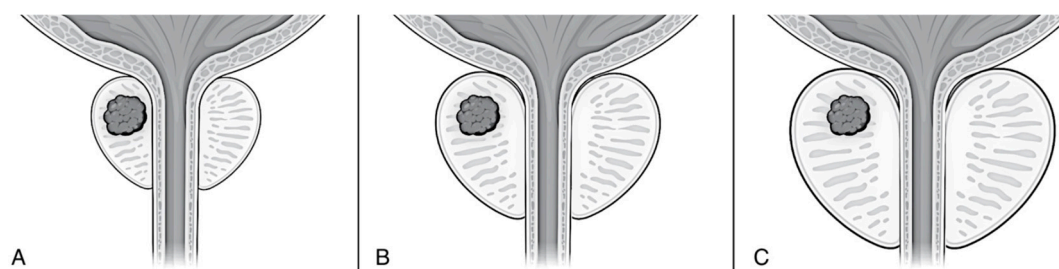


Figure 1. Model description and assumptions of index density of percentage of biopsy positive cores (Id-tumor densities decrease. For instance, tumors with a BPC of 10% could occur in a PV of 30 mL (Id-BPC = 0.33, (A)), 60 mL (Id-BPC = 0.16, (B)), or 90 mL (Id-BPC = 0.11, (C)). However, tumor load density is higher in the former case, where unfavorable pathology in the surgical specimen and an increased risk of disease progression are expected.

2.4. Statistical Methods

Continuous variables were measured by medians with interquartile ranges (IQR). Categorical factors were assessed by frequencies (%). Differences in the distributions of clinical factors between favorable and unfavorable pathology were assessed by chi-squared and Mann-Whitney tests. The association of clinical variables with the risk of unfavorable pathology was evaluated by a logistic regression model (univariate and multivariate analysis). Time elapsed between surgery and the clinical outcome of interest (disease progression) or last follow-up was measured as time to event occurrence. The Cox proportional hazards method (univariate and multivariate analysis) was used to estimate the association of clinical factors with the risk of PCa progression. In multivariable model analysis, the Wald forward method was computed to select significant predictive models. Finally, unadjusted Kaplan-Meier estimator curves of factors associated with the risk of disease progression were eventually displayed. The software used to perform the analysis was IBM-SPSS version 26. All tests were two-sided, and $p < 0.05$ was considered an index of statistical significance.

3. Results

3.1. Patient Population Demographics and Risk of Unfavorable Pathology in the Surgical Specimen

The study population included 1047 patients who underwent RARP with associated ePLND in 666 subjects. The median (IQR) count of lymph nodes was 25 (19 – 31). Clinical demographics of the PCa population stratified by unfavorable versus favorable pathology are described in Table 1. Among the surgical specimens with unfavorable pathology, detected in 930 cases (88.8%), extra-prostatic extension (pT3) occurred in 224 cases (24.1%) of which 122 (13.1%) with SVI and PLNI in 56 (6%). Only one case (0.1%) exhibited ISUP grade group 1. Unfavorable pathology resulted in a higher rate of positive surgical margins (27.1%) than in controls (10.3%). The distributions of pathology ISUP grade groups were as follows: grade 1 in 118 (11.3%), grade 2 in 409 (39.1%), grade 3 in 295 (28.2%), and grade 4/5 in 264 (25.2%) cases. Patients with unfavorable pathology were older, had smaller prostates, higher PSA levels, and unfavorable tumor features related to grade and stage. They were also associated with higher BPC and Id-BPC. The population was distributed according to the EAU risk classes: 297 (28.4%) at low risk, 527 (50.3%) at intermediate risk, and 223 (21.3%) at high risk. Table 2 illustrates the association of clinical factors with the risk of unfavorable pathology, indicating that patients with higher Id-BPC had a greater likelihood of unfavorable pathology in the surgical specimen, regardless of unfavorable tumor grade and stage.

Table 1. Distributions of clinical prostate cancer (PCa) factors according to pathological findings in 1047 patients treated with robot-assisted radical prostatectomy (RARP).

Factors	Population	Favorable pathology	Unfavorable pathology	
N (%)	1047	117 (11.2)	930 (88.8)	P-value
Age (years)	65 (60 - 70)	63 (58 - 68)	65 (60 - 70)	0.013
BMI (kg/m ²)	25.7 (23.9 - 28.1)	25.6 (23.7 - 28.1)	25.7 (23.9 - 28.1)	0.939
ASA 1	88 (8.4)	13 (11.1)	75 (8.1)	0.136
ASA 2	858 (82.0)	98 (83.8)	760 (81.7)	
ASA 3	101 (9.6)	6 (5.1)	95 (10.2)	
PV (mL)	40 (30 - 50)	42 (31.7-53)	39 (30 - 50)	0.020
PSA (ng/mL)	6.6 (5.0 - 9.1)	6.1 (4.6 - 7.8)	6.7 (5.0 - 9.3)	0.013
PSAD (ng/mL ²)	0.17 (0.11 - 0.25)	0.13 (0.09 - 0.21)	0.17 (0.12 - 0.26)	<0.0001
BPC (%)	31.2 (20 - 50)	21.4 (14.2 - 35.7)	33.3 (20 - 50)	<0.0001
Id-BPC (%/mL)	0.81 (0.43 - 1.37)	0.48 (0.28 - 1.05)	0.83 (0.47 - 1.42)	<0.0001
ISUP 1	361 (34.5)	98 (83.8)	263 (28.3)	<0.0001
ISUP 2/3	554 (52.9)	19 (16.2)	535 (57.5)	
ISUP 4/5	132 (12.6)	0 (0.0)	132 (14.2)	
cT1	600 (57.3)	92 (78.6)	508 (54.6)	<0.0001
cT2/3	447 (42.7)	25 (21.4)	422 (45.4)	
cN0	990 (94.6)	116 (99.1)	874 (94)	0.020
cN1	57 (5.4)	1 (0.9)	56 (6)	

Legend: OR, odds ratio; CI: confidence interval; continuous variables are reported as medians (interquartile ranges) while categorical factors are described as frequencies (%); BPC, percentage of biopsy positive cores; Id-BPC: index density of BPC; for other abbreviations see materials and methods.

Table 2. Clinical factors associated with the risk of unfavorable prostate cancer (PCa) pathology in 1047 patients treated with robot-assisted radical prostatectomy (RARP).

	Univariate analysis		Multivariate analysis	
Statistics	OR (95% CI)	P-value	OR (95% CI)	P-value

Age (years)	1.031 (1.005 - 1.059)	0.021		
BMI (kg/m ²)	1.004 (0.946 - 1.065)	0.907		
ASA 1	Ref			
ASA 2	1.344 (0.719 - 2.512)	0.354		
ASA 3	2.744 (0.996 - 7.562)	0.051		
PV (mL)	0.989 (0.980 - 0.998)	0.023		
PSA (ng/mL)	1.091 (1.031 - 1.154)	0.002		
PSAD (ng/mL ²)	40.796 (5.760 - 288.950)	<0.0001	9.004 (1.120 - 72.385)	0.039
Id-BPC (%/mL)	2.187 (1.541 - 3.103)	<0.0001	1.512 (1.029 - 2.221)	0.035
ISUP 1	Ref		Ref	
ISUP > 1	13.081 (7.482 - 21.819)	<0.0001	10.596 (6.306 - 17.806)	<0.0001
cT1	Ref		Ref	
cT2/3	3.057 (1.929 - 4.845)		1.904 (1.160 - 3.127)	0.011
cN0	Ref			
cN1	7.432 (1.019 - 54.202)	0.048		

Legend: OR, odds ratio; CI: confidence interval; Id-BPC: index density of percentage of biopsy positive cores; for other abbreviations see materials and methods.

3.2. Clinical Risk Factors of Prostate Cancer Progression after Robotic Surgery

The mean (95% CI) follow-up was 89.0 (86.6-91.3) months. Overall, PCa recurrence occurred in 160 (15.3%) cases, as reported in Table 3. Recurrent patients tended to have higher Id-BPC and PSA levels and undifferentiated cancers eventually associated with locally advanced stage. Deaths occurred in 14 (1.3%) patients, including 6 (0.6%) due to PCa. Radiation therapy was administered to 172 (16.5%) patients, with salvage intent in 73 (7.0%). Additionally, 172 (16.4%) follow-up patients were under androgen blockade.

Table 3. Clinical factors associated with the risk of prostate cancer (PCa) progression in 1047 patients after robot-assisted radical prostatectomy.

	No progression	PCaPca progression	Univariate analysis	Multivariate analysis
N (%)	810 (77.4)	237 (22.6)	HR (95% CI) P-value	HR (95% CI) P-value
Age (years)	65 (59.7 - 70.0)	65 (61 - 70)	1.032 (1.011 - 1.052) 0.002	
BMI (kg/m ²)	25.8 (23.9 - 28.1)	25.6 (23.8 - 28.1)	0.986 (0.947 - 1.027) 0.502	
ASA 1	66 (8.1)	22 (9.3)	Ref	
ASA 2	668 (82.5)	190 (80.2)	0.876 (0.563 - 1.365) 0.559	
ASA 3	76 (9.4)	25 (10.5)	1.336 (0.753 - 2.370) 0.322	
PV (mL)	40 (30 - 50)	39 (30 - 50)	1.005 (0.998 - 1.013) 0.178	

PSA (ng/mL)	6.3 (4.9 - 8.5)	8 (5.4 - 12.5)	1.038 (1.031 - 1.045)	<0.0001	1.027 (1.019 - 1.035)	<0.0001
PSAD (ng/mL ²)	0.16 (0.11 - 0.23)	0.21 (0.13 - 0.35)	4.314 (3.198 - 5.820)	<0.0001		
Id-BPC (%/mL)	0.74 (0.39 - 1.25)	1.07 (0.57 - 1.81)	1.468 (1.294 - 1.666)	<0.0001	1.561 (1.336 - 1.824)	<0.0001
ISUP 1	308 (38)	53 (22.3)	Ref		Ref	
ISUP 2/3	432 (53.3)	122 (51.5)	2.785 (2.010 - 3.857)	<0.0001	2.618 (1.880 - 3.646)	<0.0001
ISUP 4/5	70 (8.7)	62 (26.2)	6.658 (4.589 - 9.659)	<0.0001	4.709 (3.206 - 6.915)	<0.0001
cT1	477 (58.9)	123 (51.9)	Ref		Ref	
cT2/3	333 (41.1)	114 (48.1)	2.131 (1.647 - 2.758)	<0.0001	1.549 (1.181 - 2.031)	0.002
cN0	775 (95.7)	215 (90.7)	Ref		Ref	
cN1	35 (4.3)	22 (9.3)	2.840 (1.824 - 4.421)	<0.0001		

Legend: OR, odds ratio; CI, confidence interval; see also material and methods for explanations.

3.3. The Prognostic Impact of Id-BPC on PCa Progression after Predicting Unfavorable Pathology in the Surgical Specimen

The prognostic impact of Id-BPC on PCa progression after predicting the risk of unfavorable pathology in the surgical specimen is reported in Table 4. The results indicate that patients with higher Id-BPC have a higher likelihood of unfavorable pathology in the surgical specimen (odds ratio = 1.566; 95% CI: 1.029 – 2.383; p < 0.001) even after adjusting for other clinical variables. Therefore, patients with increasing Id-BPC are more likely to experience disease progression, accounting for both clinical variables (hazard ratio = 1.587; 95% CI: 1.306 – 1.929; p < 0.0001) and unfavorable pathology (hazard ratio = 1.365; 95% CI: 1.166 – 1.597; p < 0.0001). Interestingly, BPC showed a lower impact on predicting unfavorable pathology and PCa progression compared to Id-BPC, as shown in the reference table. Figure 2 displays the Kaplan-Meier risk curves of PCa progression stratified by unfavorable versus favorable pathology in the surgical specimen. Figures 3 and 4 present the distribution of Id-BPC for unfavorable versus favorable pathology and PCa progression versus non-progression, respectively.

Table 4. Multivariate analysis comparing the percentage of biopsy positive cores (BPC) and index density of BPC (Id-BPC) with the risk of unfavorable tumor pathology and prostate cancer (PCa) progression in 1047 patients treated with robot-assisted radical prostatectomy (RARP).

Event occurrence	Id-BPC (%/mL)	BPC (%)
UNFAVOURABLE TUMOR PATHOLOGY		
a) after adjusting for all clinical factors		
OR (95% CI)	1.566 (1.029 - 2.383)	1.018 (1.006 - 1.031)
p-value	<0.0001	<0.0001
PROSTATE CANCER PROGRESSION		
a) after adjusting for all clinical factors		
HR (95% CI)	1.587 (1.306 - 1.929)	1.015 (1.008 - 1.021)

<i>p-value</i>	<0.0001	<0.0001
a) after adjusting for unfavorable pathology		
HR (95% CI)	1.365 (1.166 - 1.597)	1.016 (1.010 - 1.022)
<i>p-value</i>	<0.0001	<0.0001

Legend: OR, odds ratio; HR, hazard ratio; CI: confidence interval.

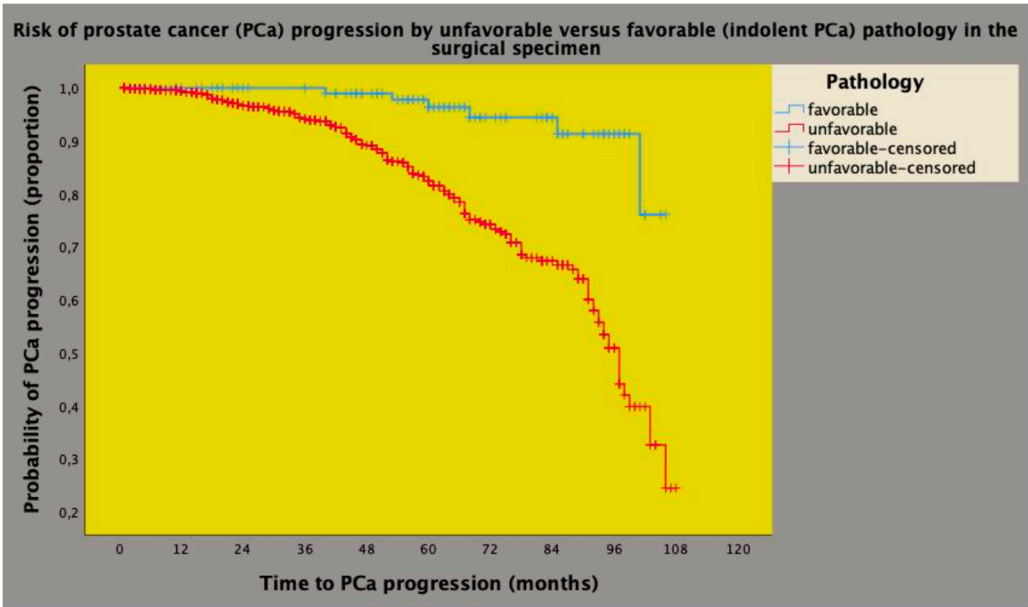


Figure 2. Kaplan-Meier survival risk curves of prostate cancer (PCa) progression stratified by unfavorable versus favorable pathology in the surgical specimen of 1047 patients treated with robot-assisted radical prostatectomy (RARP) eventually associated with extended pelvic lymph node dissection (ePLND). Mean survival time of PCa progression was longer for favorable pathology (101.8 months; 95% CI: 98.7 – 104.9 months) than unfavorable pathology (86.3 months; 95% CI: 83.7 – 88.9 months (Mantel-Cox log-rank test: $p < 0.0001$).

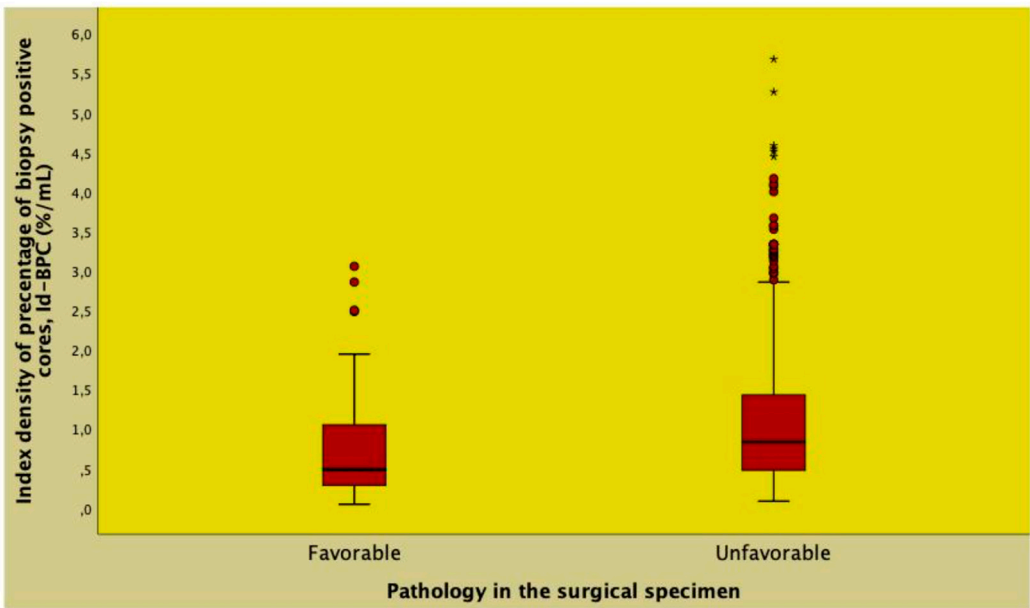


Figure 3. Distribution of index density of percentage of biopsy positive cores (Id-BPC, %/mL), defined as the ratio of percentage of biopsy positive cores (BPC) on prostate volume (PV). Id-BPC was higher in patients with unfavorable pathology (median 0.83, interquartile range: 0.47 – 1.82) than in cases

with favorable pathology (median 0.43, interquartile range: 0.28 – 1.05) in the surgical specimen and the difference was significant (odds ratio = 2.187; 95% CI: 1.541 – 3.103; $p < 0.0001$).

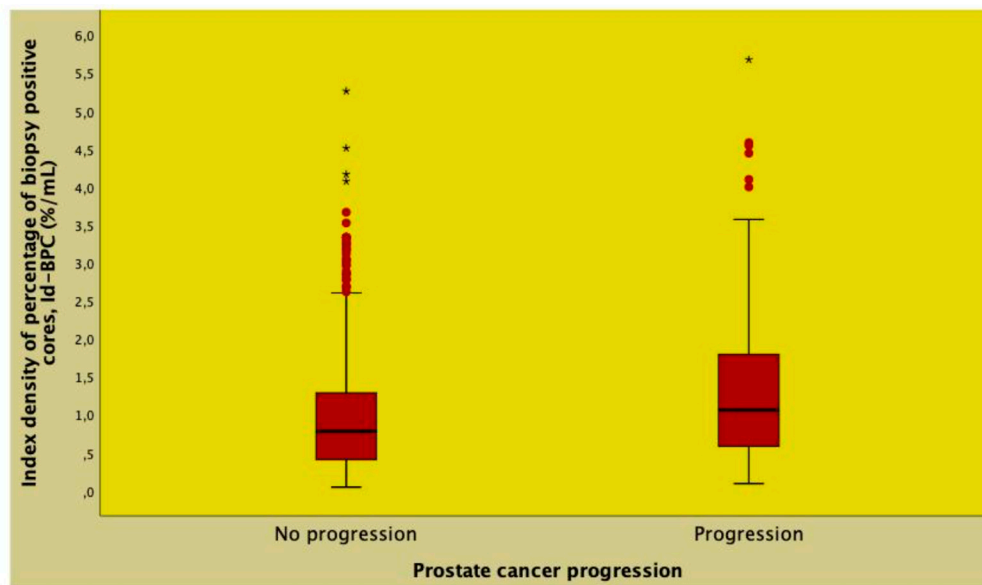


Figure 4. Distribution of index density of percentage of biopsy positive cores (Id-BPC, %/mL), defined as the ratio of percentage of biopsy positive cores (BPC) on prostate volume (PV). Id-BPC was higher in patients experiencing prostate cancer progression (median 1.06, interquartile range: 0.57 – 1.80) than in non-progressing cases (median 0.77, interquartile range: 0.40 – 1.29) and the difference was significant (hazard ratio = 1.454; 95% CI: 1.274 – 1.697; $p < 0.0001$).

4. Discussion

The 10-year mortality rate for clinically treated PCa varies between 1.2% and 13.7%, depending on prognostic risk classes. The Cambridge Prognostic Groups (CPG) risk classification, which includes 5 clinical risk classes defined by basal PSA levels, tumor grades, and stages, seems to provide the most accurate definition of these risk classes. However, this system overlooks BPC as a crucial prognostic factor in stratifying low to intermediate-risk classes [1,2,13,14]. The 15-year PCa-specific mortality rate after radical prostatectomy (RP) ranged from 2.2% to 12% as reported by the randomized Protec trial from England and an uncontrolled study conducted in North America, respectively. Additionally, the former study highlighted that there was no difference in disease-specific mortality between the monitored (AS) and actively treated groups (RP, RT), while the latter emphasized the need for new clinical markers specifically associated with PCa's lethal biology [4,15]. Biochemical recurrence is a crucial endpoint for evaluating PCa patients treated with curative intent. The EAU has developed and validated prognostic risk classes of biochemical recurrence by considering PSA dynamics, such as PSA doubling time (PSA-DT) after RP or interval to biochemical failure (IBF) after RT, as well as tumor grade groups at biopsy or pathology, based on the chosen curative intent modality [16,17]. Based on a meta-analysis of the EAU biochemical risk classes, it has been found that atypical PSA dynamics (short PSA-DT or IBF) and high-tumor grades are unfavorable prognostic factors, increasing the risk of PCa-specific mortality after RP. Only short IBF is linked to PCa-specific mortality after curative RT [16]. Currently, the occurrence of PCa biochemical recurrence in approximately 25% of RP-treated patients does not necessarily lead to disease-specific death, ranging from 1.2% to 13%. However, the high velocity of PSA post-operative dynamics and unfavorable tumor grades and stages are considered unfavorable prognostic factors for disease progressing to metastases, leading to lower cancer-specific survival rates. Nevertheless, the tumor load density of positive biopsy cores has not been investigated as a prognostic factor of disease progression. Our study revealed that the Id-BPC is a more powerful prognostic factor than BPC alone in the PCa progression. As the Id-BPC increased, patients were more likely to experience disease progression, while those with low id-BPC were less susceptible to such progression. Notably, even after accounting for other significant factors related to unfavorable pathology, the Id-BPC remained

an independent predictor of unfavorable prognosis following surgical treatment with curative intent, as per EAU risk classes. These findings are groundbreaking and have significant implications for both basic science and clinical practice. In PCa patients treated with RARP eventually associated with ePLND, analyzing surgical specimens is crucial for predicting disease prognosis. The pathological ISUP tumor grade system remains the most reliable prognostic factor of BCR after RP with curative intent. As ISUP grade groups increase, patients are more likely to experience BCR [18]. Tumor extension within the prostate and/or to loco-regional lymph nodes is also pivotal, since extra-prostatic extension (pT3a), seminal vesical invasion (pT3b), and PLNI (pN1) disease are unfavorable prognostic factors that impair the natural history of the treated disease with curative intent [19,20]. As such, unfavorable pathology, including ISUP grade groups greater than 1 and/or non-organ confined disease (pT3a, pT3b, pN1), represents the best way to identify potential disease progression [1,2,18–20]. Each validated nomogram incorporates the BPC, which is crucial in calculating the final risk score [1,2,8,9]. While the BPC is already an important parameter in assessing unfavorable tumor pathology to predict PLNI, the influence of the Id-BPC has yet to be assessed. In our study, patients with higher Id-BPC were more prone to unfavorable pathology in the surgical specimen, including non-indolent tumors for non-organ confined disease and/or tumor grade groups greater than one. As Id-BPC increased, patients were more likely to have unfavorable pathology, while a decrease in Id-BPC was often associated with indolent disease in the surgical specimen. It's noteworthy that Id-BPC was a stronger predictor of unfavorable pathology in the surgical specimen than BPC. Clinical studies have shown that there's a clear correlation between prostate volume and PCa biology. A pioneering study revealed that PSAD was positively linked to the risk of PCa in men undergoing prostate biopsy. Patients with higher PSAD were more likely to have cancer detection in smaller prostate sizes than those with benign prostatic hyperplasia (BPH) [21]. A large study including 939 subjects undergoing prostate biopsies found that cancer detection rates were significantly higher for small prostates (61% for PV < 30 mL) and lower for large prostates (37% for PV > 50 mL) [22]. An early study that analyzed a new prostate volume model, defined as the ratio of the volume of the transition zone to the volume of the peripheral zone of the prostate (PV index), showed that patients with low PV index were more likely to have positive cores associated with high tumor loads and grades. Interestingly, the risk of PCa was increased by small prostates, predominantly represented by peripheral zone volume, and decreased by large prostates, sustained by large transitional zone volumes and associated with the presence of chronic prostatic inflammation [23,24]. A dated trial, which analyzed 325 patients treated with surgery, discovered that PSAD served as a powerful predictor of unfavorable pathology in the surgical specimen and biochemical recurrence. Specifically, patients with higher PSAD levels were more likely to have unfavorable pathology and experience BCR. This was particularly true for patients with smaller prostates, as they tended to have higher PSAD, a greater likelihood of unfavorable disease, and BCR. Interestingly, the researchers suggested that PSAD could potentially serve as a correcting factor for PSA produced by benign epithelium [25]. Another large study conducted in North America investigated 1602 PCa patients treated with RP and found that smaller prostates were more likely to have unfavorable disease and BCR. The researchers, while hypothesizing that low PV may be related to low androgen levels, concluded that PV was an impacting variable that should be included in nomograms useful for clinical practice [26]. These findings emphasize the importance of understanding prostate growth biology in aging males and provide insights into the results of our study. Our research has shown that the Id-BCR is a significant and independent clinical prognostic factor for disease progression, particularly in cases of unfavorable tumor pathology, in a large series of patients from all EAU risk classes surgically treated with curative intent. So far, Id-BPC has been able to trace the main steps of PCa's natural history. Our findings suggest that high tumor load densities are underpinned by local factors, promoting exponential growth rates and expanding locally by invading the prostatic capsule and seminal vesicles, which increases the likelihood of progression to nearby regional lymph nodes. These patterns are sustained by tumors that are either highly undifferentiated or invasive, exhibiting high frequencies of dynamic genetic mutations. Unfavorable tumor grade and/or stage merely scratches the surface of these complex phenomena. In theory, higher tumor load densities in small prostates may indicate an unfavorable microenvironment, where lower testosterone densities are to be expected than in larger prostates, which are predominantly sustained by benign hyperplasia, as demonstrated by clinical investigations on this topic [27].

The results of our study could have clinical implications. Id-BCR could represent a valuable clinical parameter for clustering PCa patients into prognostic risk classes, where tumor under grading and/or under staging can challenge managing treatment options. As Id-BPC increased, patients were more likely to have unfavorable pathology in the surgical specimen and experience disease progression. Conversely, as Id-BCR decreased, subjects were more likely to have indolent disease in the surgical specimen and less likely to experience disease progression. To select appropriate treatments for patients, effective clinical markers are necessary to assess the aggressive PCa biology. Although BPC remained an effective predictor of PCa natural history in our study, Id-BCR showed greater potential in predicting unfavorable pathology. Therefore, it could be included in new nomograms for predicting the risk of unfavorable pathology and as an effective clinical prognostic factor for disease progression. Tumor load density should be considered when planning clinical investigative studies on the subject. The next step could be categorizing the variable to find an appropriate cut-off value for selecting a subset of patients at increased risk for both unfavorable pathology and disease progression.

While our study has some limitations, it also has notable strengths. One limitation is that it was a retrospective study with procedures performed by multiple surgeons. PSA-DT and extension of cancer involvement within each core were not evaluated because they were not available in all cases. Additionally, PV was not always evaluated at our institution, and Id-BPC was not evaluated for PCa-specific mortality. However, the data collection was prospective and the procedures were performed by experienced surgeons. Furthermore, the investigated factor was evaluated in a large case series that was operated on in a single tertiary referral center. Finally, Id-BPC was assessed for unfavorable pathology and disease progression, which is a stronger endpoint than BCR.

5. Conclusions

Id-BCR proved to be a valuable and independent prognostic factor in predicting disease progression in PCa patients surgically treated with curative intent. The study found that higher levels of Id-BPC were associated with a higher likelihood of unfavorable pathology in the surgical specimen and disease progression. Therefore, Id-BCR serves as an important clinical marker of PCa biology.

Ethics Approval and Consent to Participate: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Azienda Ospedaliera Universitaria Integrata of Verona. Written informed consent was obtained from all subjects involved in the study.

Consent for Publication: Written informed consent was obtained from all subjects involved in the study.

Author Contributions: ABP provided the study design and conception, the manuscript's drafting, and the statistical analyses. A Bianchi and SG provided the manuscript's drafting, analyses, and interpretation of data. ES, SC, F Montanaro, A Baielli, FA, DB, GMP, and AF carried out data collection. RR, AV, MB, VDM, F Migliorini, MAC, and AA provided supervision and critical revision of the manuscript for important intellectual contents. All authors read and approved the final version of the manuscript.

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Abbreviations

AS: active surveillance

ASA: Association of Anesthesiologists

BMI: body mass index

BPC: percentage of biopsy-positive cores

EAU: European Association of Urology

ECE: extracapsular extension

ePLND: extended pelvic lymph node dissection

IBF: interval to biochemical failure
 Id-BPC: index density of percentage of biopsy-positive cores
 IQR: interquartile ranges
 ISUP: International Society of Urological Pathology
 mpMRI: multiparametric resonance imaging
 NCCN: National Comprehensive Cancer Network
 PCa: prostate cancer
 PLNI: pelvic lymph node invasion
 PSAD: PSA density
 PSA-DT: PSA doubling time
 PV: prostate volume
 RARP: robot-assisted radical prostatectomy
 RP: radical prostatectomy
 RT: radiation therapy
 SVI: seminal vesicle invasion
 TRUS: transrectal ultrasound
 WW: watchful waiting

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