

Index Density of Percentage of Biopsy Positive Cores, the Ratio of Percentage of Biopsy Positive Cores on Prostate Volume, has a Strong Prognostic Impact on Clinical Prostate Cancer Progression After Robotic Surgery: Results in 1047 Consecutive Patients Treated in a Single Tertiary Referral Centre

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Article

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Simple Summary

Prostate cancer is one of the most common cancers in men, and identifying which patients are at a higher risk of disease progression following surgery remains a significant clinical challenge. Current risk assessment often relies on the percentage of biopsy samples containing cancer, but this measure does not account for prostate size. In this study, we evaluated whether combining the percentage of positive biopsy samples with prostate volume to create a measure of tumour density could better predict cancer progression after robotic surgery. We analysed data from 1047 patients treated over an eight-year period and found that this tumour density measure was a stronger predictor of disease recurrence than the percentage of positive biopsy samples alone. These findings suggest that incorporating tumour density into clinical evaluations could improve risk stratification, helping physicians to better understand tumour aggressiveness and guide patient management decisions.

Abstract

Background/Objectives: To evaluate index density (Id) of percentage of biopsy positive cores (BPC), the ratio of BPC on prostate volume (Id-BPC), as a prognostic factor of clinical prostate cancer (PCa) progression after robotic surgery. **Methods:** The study included 1047 consecutive patients who were treated in a period ranging from January 2013 to December 2021. The risk of disease progression, which was defined as at least the occurrence of biochemical and/or loco-regional and metastases recurrence, was evaluated by Cox's proportional hazards. **Results:** Disease progression, which occurred in 237 (22.6%) patients after a mean (95% CI) follow-up of 82.5 (80.1 – 84.9) months, was predicted by Id-BPC which was stronger than BPC itself; accordingly, as biopsy tumor load densities increased, so patients were more likely to experience disease progression not only after adjusting for clinical variables (hazard ratio = 1.55; 95% CI: 1.32 – 1.83; $p < 0.0001$), but also for unfavorable pathology (hazard ratio = 1.37; 95% CI: 1.21 – 1.56; $p < 0.0001$), as well. **Conclusions:** The risk of clinical PCa progression after robotic surgery was independently predicted by Id-BPC which was stronger than BPC; accordingly, as Id-BPC increased so patients were more likely to experience disease progression; likewise, Id-BPC could be a useful clinical marker of cancer biology.

Keywords: prostate cancer; robot assisted radical prostatectomy; biochemical recurrence; prostate cancer progression; prostate biopsy; percentage of biopsy positive cores; prostate volume; tumor index density

1. Introduction

The epidemic issue of prostate cancer (PCa) is actually managed by either the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) societies that continuously update guidelines for clinically localized disease which is stratified by prognostic risk classes in order to plan appropriate management options varying from monitoring strategies, such as active surveillance or watchful waiting, to active treatments, which include surgery, most frequently performed by robot assisted radical prostatectomy (RARP) approach eventually associated with extended pelvic lymph node dissection (ePLND) or by radiation therapy (RT); nevertheless, combined treatments are also considered for high risk classes, as well [1,2]. Likewise, prognostic risk classes are not homogenous and more efforts are required in order to further stratify subsets within each group having more or less aggressive disease with the aim of avoiding over as under treatments that may impair quality of life of patients who are more likely to have longer survival rates after PCa screening, as it has been recently demonstrated [1–4]. So far, the actual critical issue is defining new factors that may stratify PCa prognostic risk classes; accordingly, although molecular biology is the future, it is still far to be available in routine clinical practice; nevertheless, multiparametric resonance imaging (mpMRI), although useful in disease diagnosis, is not reproducible and its staging potential is also questionable [5,6]. Likewise, BPC represents one of the most powerful clinical parameters for stratifying prognostic risk classes and for computing nomograms evaluating the risk of pelvic lymph node invasion, as well; accordingly, it is one of the strongest parameters defining PCa biology together with basal prostate specific antigen (PSA), tumor grade and stage [1,2,5,6]. Nevertheless, it has not yet been evaluated in combination with prostate volume (PV) as cancer index density factor, which is the ratio of BPC on PV (Id-BPC); accordingly, we have recently demonstrated that it was a predictor stronger than just BPC of adverse pathology in the surgical specimens of PCa intermediate and high-risk EAU prognostic categories, as well [7,8]. Likewise, that Id-BPC could be a prognostic factor stronger than BPC for disease progression after robotic surgery has not yet been tested as hypothesis, which was what we investigated in this study, accordingly.

2. Materials and Methods

2.1. Selection of the Investigated Patient Population

The study was retrospective observational and did not require any formal ethical approval, as shown by the included document which was produced by the Territorial Ethics Committee for trials performed in a period up to September 25th of the year 2024. From January 2013 to December 2021, 1047 operated PCa patients with available follow-up were selected after excluding subjects with androgen deprivation or prior active treatments. Main including criteria were at least 12 standard random biopsy cores and measurement of prostate volume by trans rectal ultrasound (TRUS) methods. According to recommendations, RARP eventually associated with ePLND, which was developed according to a standard anatomical template including external iliac, obturator, Cloquet’s and Marcille’s regions; likewise, surgical procedures were performed by 5 skilled urologists [7].

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

Clinically, patients were assessed for age (years), body mass index (BMI; kg/m²), PSA (ng/mL), PV (mL), BPC (percentage), grade and stage of prostate tumors. In each case, prostate cancer index density (Id-BPC; %/mL) was calculated as the ratio of BPC on PV. Surgical specimens were assessed

for cancer features including grade, stage, surgical margins and pelvic lymph nodes which were counted and assessed for invasion by the dedicated pathologist. Tumor grades referred to the ISUP system while cancer stage to the TNM system. Patients were followed-up, according to recommendations; likewise, at PSA persistence/recurrence, imaging modalities were considered in order to restage the disease and plan further treatments, which were taken in a multidisciplinary setting including urologists, radiation-oncologists and oncologists in order to optimize recommendations with patient’s personal issues [1,2]. Disease progression was defined as the event of biochemical persistence/recurrence and/or loco-regional or systemic progression.

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

The anatomical/clinical model of Id-BPC is illustrated in Figure 1. We assumed that constant BPC percentages related to PV variations produce different cancer densities; accordingly, as volumes increase, so densities decrease and vice versa; as an example, tumors with BPC of 10% and ISUP 3 may develop in an PV of 30 mL (Id-BCPD = 0.33), of 60 mL (Id-BPCD = 0.16) as in 90 mL (Id-BPCD = 0.11); however, tumor load density is higher in the first case that should show more aggressive tumor biology when compared with the other two, as well. The former assumption implies that a positive association is to be expected of Id-BPC with adverse pathology and disease progression, as well; accordingly, the former has been demonstrated while the latter has to be proven in the present study [8,9].

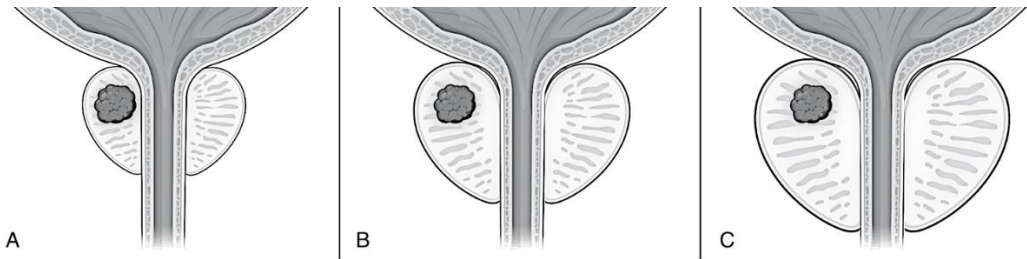


Figure 1. Clinical model of prostate cancer index density of percentage of biopsy positive cores, the ratio of percentage of biopsy positive cores on prostate volume (ID-BPC; %/mL). Description and assumptions of the model are reported in the section materials and methods of the manuscript.

2.4. Statistical Methods

Continuous variables were measured for medians with interquartile ranges (IQR). Categorical factors were assessed for frequencies (percentages). Overall surgical pathology associations of ISUP grade groups with adverse pathology including extra-prostatic extension (ECE and/or SVI) and PLNI were tested with the Chi squared test while the risk of unfavourable ISUP pathology with increasing BPC and Id-BPC were assessed by the logistic regression model. The length of time between surgery and the clinical outcome of interest (disease progression) or the last follow-up was measured as time to event occurrence. Factors associated with the risk of disease progression were evaluated by Cox’ model including univariate and multivariate analysis. Id-BPC adjusted Kaplan-Meier estimator curves of factors associated with the risk of disease progression were eventually displayed. The software used to run the analysis was IBM-SPSS version 26. All tests were two-sided with $p < 0.05$ considered to indicate statistical significance.

3. Results

3.1. Positive Association of Biopsy Features (Id-BPC and BPC) with Pathology ISUP Grades Impacting on Extra-Prostatic Extension (pT3) and PLNI (pN1)

The investigated population included 1047 cases who were distributed by EAU categories as low risk 297 (28.4%), intermediate risk 527 (50.3%) and high-risk 223 (21.3%). Extended PLND was

performed in 666 subjects with a median (interquartile range) of counted lymph nodes of 25 (19 – 31). Overall, associations of pathology ISUP grade groups with adverse specimen findings (ECE, SVI, PLNI) and prostate biopsy features (BPC; Id-BPC) are shown in Table 1; accordingly, as ISUP grade groups increased from 1 to 5, so patients were more likely to have non-organ confined disease (pT3 stage) and PLNI, as well; likewise, as BPC and Id-BPC rates increased, so patients were more likely have adverse tumour grades in the surgical specimen; however, Id-BPC showed a stronger association than BPC, as well.

Table 1. Associations of increasing pathology ISUP with other specimen (tumour stage, surgical margins, nodal stage) and prostate cancer biopsy features.

	Population	ISUP ¹ 1	ISUP 2	ISUP 3	ISUP 4	ISUP 5	<i>p-value</i>
Number (%)	1047	116 (11.1)	411 (39.3)	293 (28)	157 (15.0)	70 (6.6)	
pT2	823 (78.6)	115 (99.1)	371 (90.3)	222 (75.8)	87 (55.4)	28 (40)	<0.001
pT3	224 (21.4)	1 (0.9)	40 (9.7)	71 (24.2)	70 (44.6)	42 (60)	
R0	224 (21.4)	103 (88.8)	321 (78.1)	229 (78.2)	101 (64.3)	29 (41.7)	<0.001
R1	264 (25.2)	13 (11.2)	90 (21.9)	64 (21.8)	56 (35.7)	41 (58.7)	
pNx/0	963 (92.0)	116 (100.0)	407 (99.0)	275 (93.9)	124 (79.0)	41 (58.6)	<0.001
pN1	84 (8.0)	0 (0.0)	4 (1.0)	18 (6.1)	33 (21.0)	29 (41.4)	
BPC	31.2 (20.0 - 50.0)	21.4 (14.4 - 35.5)	28.5 (16.6 - 43.7)	33.3 (20.0 - 50.0)	40.0 (21.4 - 57.9)	46.6 (33.3 - 67.1)	<0.001
OR (95% CI)		1.0	1.02 (1.01 - 1.03)	1.03 (1.02 - 1.04)	1.040 (1.03 - 1.05)	1.05 (1.04 - 1.07)	
<i>p-value</i>			<0.001	<0.001	<0.001	<0.001	
Id-BPC	0.81 (0.43 - 1.87)	0.48 (0.28 - 1.10)	0.79 (0.40 - 1.25)	0.82 (0.46 - 1.42)	0.97 (0.58 - 1.61)	1.23 (0.70 - 1.90)	<0.001
OR (95% CI)		1.0	1.93 (1.33 - 2.80)	2.33 (1.59 - 3.40)	2.76 (1.86 - 4.10)	3.50 (2.29 - 5.35)	
<i>p-value</i>			<0.001	<0.001	<0.001	<0.001	

Legend: ISUP, International Society of Urologic Pathology system of prostate cancer grading; BPC, pT, TNM tumor stage; R, surgical margin status (positive for R1); pN, TNM staging of pelvic lymph nodes (positive for pN1; unkown/negative for pNx/0); BPC, percentage of biopsy positive cores; Id-BPC, prostate cancer index density (ratio of BPC on prostate volume; OR, odds ratio; CI, confidence interval.

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

Demography of the investigated population stratified by disease progression, which occurred in 237 patients (22.5%) after a mean (95% CI) follow-up of 82.5 (80.1-84.9) months is reported in Table 2, which shows that, on univariate analysis, standard clinical factors (age, PSA, ISUP, cT, cN) were positive predictors of PCa progression; likewise, while BPC and Id-BPC also associated with the risk of disease progression, the former showed a weaker association (HR = 1.02; 95% CI: 1.01 – 1.02; *p* < 0.001) than the latter (HR = 1.47; 95% CI: 1.29 – 1.67; *p* < 0.001), as well. Overall, deaths occurred in 30 (2.9%) patients of whom 7 (0.7%) due to PCa. Radiation therapy was delivered in 194 (18.5%) patients with salvage intent in 79 (7.5%), as well. Of the followed-up patients, 202 (19.3%) were under androgen blockade.

Table 2. Associations of increasing pathology ISUP with other specimen (tumor stage, surgical margins, nodal stage) and prostate cancer biopsy features.

	Population	No PCa progression	Pca progression	Univariate analysis	
Number (%)	1047	810 (77.4)	237 (22.6)	HR (95% CI)	<i>p-value</i>
Age (years)	65 (60 - 70)	65 (59.7 - 70.0)	65 (61 - 70)	1.03	0.002

				(1.01 - 1.05)	
BMI (kg/m^2)	25.7 (23.9 - 28.1)	25.8 (23.9 - 28.1)	25.6 (23.8 - 28.1)	0.99 (0.95 - 1.03)	0.50
PV (mL)	40 (30 - 50)	40 (30 - 50)	39 (30 - 50)	1.005 (0.10 - 1.01)	0.18
PSA (ng/mL)	6.6 (5.0 - 9.1)	6.3 (4.9 - 8.5)	8 (5.4 - 12.5)	1.04 (1.03 - 1.04)	<0.001
ISUP 1	361 (34.5)	308 (38)	53 (22.3)	Ref	
ISUP 2/3	554 (52.9)	432 (53.3)	122 (51.5)	2.78 (2.01 - 3.86)	<0.001
ISUP 4/5	132 (12.6)	70 (8.7)	62 (26.2)	6.66 (4.59 - 9.66)	<0.001
cT1	600 (57.3)	477 (58.9)	123 (51.9)	Ref	
cT2/3	447 (42.7)	333 (41.1)	114 (48.1)	2.13 (1.65 - 2.77)	<0.001
cN0	990 (94.6)	775 (95.7)	215 (90.7)	Ref	
cN1	57 (5.4)	35 (4.3)	22 (9.3)	2.84 (1.82 - 4.42)	<0.001
BPC (%)	31.2 (20 - 50)	28.5 (16.6 - 43.7)	42.8 (25.0 - 64.2)	1.02 (1.01 - 1.02)	<0.001
Id-BPC (%/mL)	0.81 (0.43 - 1.37)	0.74 (0.39 - 1.25)	1.07 (0.57 - 1.81)	1.47 (1.29 - 1.67)	<0.001

Legend: HR, hazard ratio; CI, confidence interval; BPC, percentage of biopsy positive cores; Id-BPC, prostate cancer index density (ratio of BPC on prostate volume).

3.3. Prognostic Impact of Id-BPC on Clinical PCa Treated with Robotic Surgery

As shown in Table 3, Id-BPC demonstrated a meaningful prognostic impact that was always stronger than BPC after adjusting for clinical factors (HR = 1.587; 95% CI: 1.306 – 1.929; *p* < 0.001), EAU risk classes (HR = 1.386; 95% CI: 1.218 – 1.578; *p* < 0.001) and adverse pathology features (HR = 1.246; 95% CI: 1.904 – 1.418; *p* < 0.001), as well.

Table 3. Multivariate analysis of prostate cancer progression after robotic surgery by Id-BPC and BPC after adjusting for clinical parameters, EAU prognostic risk classes and pathology factors in 1047 cases.

Statistics	Id-BPC (%/mL)		BPC (%)	
	HR (95% CI)	<i>p</i> - value	HR (95% CI)	<i>p</i> - value
After adjusting for clinical factors (*)	1.587 (1.306 - 1.929)	<0.001	1.015 (1.008 - 1.021)	<0.001
After adjusting for EAU risk classes	1.386 (1.218 - 1.578)	<0.001	1,017 (1.012 - 1.022)	<0.001
EAU intermediate vs low risk	3.193 (1.218 - 4.675)	<0.001	3.248 (2.216 - 4.760)	<0.001
EAU high vs low risk	7.566 (5.094 - 11.239)	<0.001	7.022 (4.713 - 10.462)	<0.001
After adjusting for adverse pathology	1.246 (1.094 - 1.418)	<0.001	1.012 (1.006 - 1.017)	<0.001
ISUP 4/5 vs ISUP 1/3	2.698 (1.998 - 3.644)	<0.001	2.652 (1.961 - 3.587)	<0.001
pT3 vs pT2	1.595 (1.182 - 2.152)	0.002	1.558 (1.152 - 2.107)	0.004
pN1 vs pN0/x	2.981 (2.147 - 4.140)	<0.001	2.625 (1.872 - 3.672)	<0.001

Legend: OR, odds ratio; HR, hazard ratio; CI: confidence interval; (*), including age, BMI, PSA, ISUP, cT, cN (see also Table 2); BPC (%), percentage of biopsy positive cores; Id-BPC, index density of BPC, the ratio of BPC on prostate volume (%/mL); EAU, European Association of Urology clinical prognostic risk classes.

Figure 2 including Figures 2a and 2b illustrates disease progression risk curves by EAU risk classes adjusted for Id-BPC densities up to and above the median (0.81%/mL); accordingly, for the different levels of EAU prognostic risk classes, survival distributions were significantly worse for the

latter when compared with the former (Mantel Cox test: $p < 0.001$); as a result, Id-BPC demonstrated stratifying prediction along EAU classes, as well.

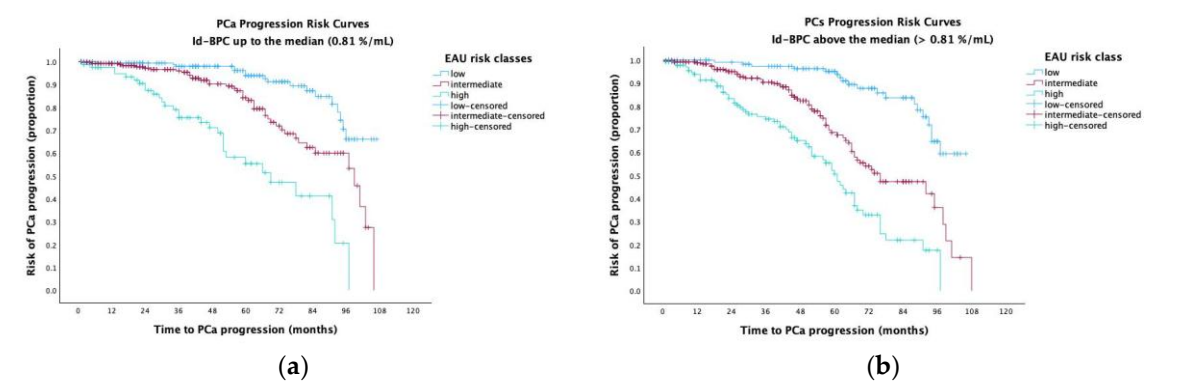


Figure 2. Kaplan Meier risk curves of prostate cancer progression through different levels of EAU risk classes adjusted for index density of percentage of biopsy positive cores (Id-BPC) up to the median 0.81%/mL (a) and above the median (b); accordingly, survival distributions were significantly worse for the latter when compared with the former (Mantel Cox test: $p < 0.001$). See Table 3 and results for further details.

4. Discussion

The 10-year mortality of clinically treated PCa ranges from 1.2% to 13.7%; accordingly, these rates depend on prognostic risk classes that seem to be better defined by the Cambridge Prognostic Groups (CPG) risk classification, which includes 5 clinical risk classes defined by basal PSA, grades and stages of diagnosed tumors; however, this system does not consider Id-BPC as a prognostic factor that is an important parameter for stratifying low through intermediate risk classes, as well [10,11]. The 15-year PCa specific mortality after radical prostatectomy has been reported to vary from 2.2% to 12% according to the randomized Protect trial from England and a non- controlled study from the North America, respectively; moreover, the former stressed out the point that there was no difference of disease specific mortality among monitored (AS) or actively treated groups (RP, RT), while the latter outlined the point that novel clinical markers specifically associated with PCa lethal biology are needed [12,13]. Biochemical recurrence is an important endpoint for evaluating PCa treated with curative intent; accordingly, EAU has developed and validated prognostic risk classes of biochemical recurrence considering as criteria 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 through to the curative intent modality; accordingly, short PSA-DT less than 1 year or IBF < 18 months as well as biopsy or pathology tumor grades with Gleason score between 8-10 (ISUP 4/5 defining lethal disease) for surgically or radiation treated patients, respectively [14,15]. Interestingly, metanalysis of the EAU biochemical risk classes showed that atypical PSA dynamics (short PSA-DT or IBF) as high-tumor grades were unfavorable prognostic factors associated with PCa specific mortality after radical prostatectomy while only short IBF predicted disease specific mortality after curative RT, as well [14]. Likewise, the European study of PCa screening has recently shown that after a median follow-up of 23 years disease specific mortality was 13% lower in the screening group, as a result, more prognostic factors are required in order to plan risk adopted approaches with the aim of reducing harmful effects of both overdiagnosis and overtreatment, as well [3,4]. So far, PCa biochemical recurrence, which occur in about 25% of patients treated with radical prostatectomy, is not necessary followed by disease specific death, which ranges from 1.2% to 13%; moreover, high velocity of PSA post-operative dynamics as lethal tumor grades (ISUP 4/5) are adverse prognostic factors for disease progressing to metastases with reduced cancer specific survival, accordingly. Nevertheless, Id-BPC has not yet been evaluated as prognostic factor of disease progression, as well. In our study, we showed that disease progression was predicted by Id-BPC, which was stronger than BPC; accordingly, as index density of BPC increased, so patients were more likely to undergo disease progression; conversely, patients presenting with low index density of BPC were less likely to

experience disease progression, as well. Interestingly, after adjusting for standard clinical factors, EAU prognostic risk classes and adverse pathology features in the surgical specimen, Id-BPC still remained a strong factor predicting unfavorable prognosis after surgical treatment with curative; accordingly, these results represent a novelty with impacts on basic science and implications in clinical practice, as well.

In PCa patients treated with RARP eventually associated with ePLND, analysis of surgical specimens is pivotal for disease prognosis. Accordingly, the pathological ISUP tumor grade system remains the strongest prognostic factor of biochemical progression after radical prostatectomy with curative intent; so far, as ISUP grade groups increase, so patients are more likely to experience biochemical progression with ISUP grade group 1 having the best prognosis for being less likely associated with significant PCA, as well [16]. 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) are adverse prognostic factors impairing the natural history of the treated disease with curative intent, as well [17,18]. So far, unfavorable pathology including ISUP grade groups greater than 1 and/or non-organ confined disease (pT3a, pT3b, pN1) represent the best way to identify features of progressing disease; likewise, in this prospective, the potential role of Id-BPC, which implies the novel concept of cancer density at biopsy stage of PCa, has not yet been investigated, as well [1,2,16–18]. In our study, patients presenting with cancer densities at the biopsy stage were more likely to have unfavorable pathology in the surgical specimen including cancers that were not indolent for being associated with non-organ confined disease and/or tumor grade groups greater than one, as well. Accordingly, as Id-BPC increased, so patients were more likely to have unfavorable pathology. Conversely, as densities of positive biopsy cores decreased, so subjects were more likely to have indolent disease in the surgical specimen, as well. Interestingly, id-BPC was a stronger than BPC in predicting the risk of adverse pathology in the surgical specimen; likewise, these findings confirm our prior results showing that this factor was closely related to adverse cancer biology in the surgical specimen of EAU intermediate and high-risk classes thus allowing stratification within these categories; accordingly, such findings suggested that Id-BPC could have also a leading role for predicting disease progression, which has been demonstrated in the present study of 1047 consecutive patients including all EAU prognostic risk classes treated by robotic surgery, as well [8,9].

According to clinical studies, there is an evident relation between prostate volume and PCa biology. A pioneering study showed that PSAD was a positive factor associated with the risk of PCa in men undergoing biopsies; accordingly, as PSAD increased so patients were more likely to have cancer detection that was related to prostate sizes, which were smaller than those with benign prostatic hyperplasia (BPH) [19]. A large study including 939 subjects undergoing prostate biopsies found out that cancer detection rates were significantly higher for small sized prostates (61% for PV < 30 cc) and lower for large prostates (37% for PV > 50 cc) [20]. An early study while investigating on a new prostate volume model, defined as the ratio of the volume of the transition to the peripheral zone of the prostate (prostate volume index), showed that patients with low PV index, which was sustained by low total prostate volumes, were more likely to have positive cores associated with high tumor loads and grades; interestingly, the risk of PCa was increased by the small sized prostates, which were prevalently represented by volumes of the peripheral zone, and decreased by large sized prostates, which were sustained by large transitional zone volumes and associated with the presence of prostatic chronic inflammation, as well [21,22]. A dated trial while investigating 325 patients treated with surgery discovered that PSAD was a strong positive predictor of biochemical recurrence after predicting unfavorable pathology in the surgical specimen; accordingly, as PSAD increased so patients were more likely to have unfavorable pathology and to experience biochemical progression; so far, smaller prostates while determining higher PSA densities associated with both unfavorable disease as well with PCa biochemical progression; interestingly, researchers hypothesized that PSAD could be a correcting factor for PSA produced by benign epithelium [23]. Another large study from North America investigated on 1602 PCa patients treated with RP and found out that smaller

prostates were more likely not only to have unfavorable disease in terms of tumor grade and stage in the surgical specimen, but also at greater risk of disease progression; accordingly, researchers while hypothesizing that low PV may be related to low levels of androgens concluded that prostate size was an impacting variable, which should be included in nomograms that would be useful for clinical practice, as well [24]. These findings, while outlining the importance of prostate growth biology in the aging male, can also explain the results of our study, which demonstrated that Id-BPC was stronger than BPC for predicting adverse pathology and disease progression in a large series of patients including all EAU risk classes surgically treated with curative intent. So far, Id-BPC was able to trace out the main steps of PCa natural history. These results suggest that high tumor load densities are sustained by local factors promoting exponential growth rates, which expand locally thus invading the prostatic capsule as the seminal vesicles, where progression to local regional lymph nodes is more likely. Accordingly, these patterns are sustained by highly undifferentiated and/or invasive cancers, which bear high rates of dynamic genetic mutations in which adverse tumor grade and/or stage is only the tip of the iceberg. Likewise, overall higher Id-BPC densities indicate tumors expanding and compressed by a limiting environment, which is prostate volume; accordingly, as compressed tumors expand, they suffer increasing chronic hypoxia inducing increased mutational loads promoting metastasis and transformation of PCa cells; moreover, chronic hypoxia induce production of factors which increase expression of androgen receptors that explain disease progression and castration resistance, as well [25,26].

Our study has shown that prostate cancer density at biopsy (Id-BPC) is a new parameter relating BPC to PV; accordingly, this factor allows stratification of patients within each EAU prognostic risk class, which have the issue of both upgrading/downgrading and/or upstaging/down staging of clinically detected prostate tumors, as well. Accordingly, as Id-BPC increased, so patients were more likely to have unfavorable pathology features in the surgical specimen as well as to undergo disease progression; conversely, as index density of BPC decreased, so subjects were more likely to have indolent disease in the surgical specimen and less likely to progress. Nevertheless, the most important finding of the study is that Id-BPC allows prognostic stratification within all EAU risk classes, which turns useful for both urologist and radiation oncologist for managing clinically localized disease. Finally, the novel concept of tumor density of clinical PCa should be considered as part of the assumptions to considerate when planning clinical investigative studies on the subject. Our study suffers several limits, which may be listed as follows. First it was retrospective with procedures performed by several surgeons. Second, PSA-DT, extension of cancer involvement within each core were not evaluated for not being available in all cases. Third, PV was not always evaluated at our institution. Fourth, Id-BPC has not been evaluated for PCa specific mortality.

Nevertheless, our study has strengths, as well. First procedures were performed by skilled surgeons. Second, the investigated factor was evaluated in a large series of cases who were operated in a single tertiary referral center. Third, all surgical specimens were evaluated by our dedicated pathologist. Fourth, Id-BPC was assessed first for unfavorable pathology and then for disease progression, which is a stronger endpoint than biochemical recurrence.

5. Conclusions

Progression of clinical PCa along EAU risk classes was predicted by Id-BPC, which was stronger than BPC; accordingly, as Id-BPC increased so patients were more likely to experience disease progression; likewise, it also allowed prognostic stratification within EAU risk classes; as a result, it might represent a novel clinical marker of PCa biology.

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Abbreviations

The following abbreviations are used in this manuscript:

BPC	Biopsy-Positive Cores
ECE	Extracapsular Extension
Id-BPC	Index Density of Biopsy-Positive Cores
ISUP	International Society of Urological Pathologists Classification
mpMRI	Multiparametric Magnetic Resonance Imaging
PCa	Prostate Cancer
PLNI	Pelvic Lymph Node Invasion
PV	Prostate Volume
RARP	Robot-Assisted Radical Prostatectomy
R1	Positive Surgical Margin
SVI	Seminal Vesicle Invasion

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