Asian Journal of Andrology (2020) 22, 519–525
www.asiaandro.com; www.ajandrology.com

Open Access

ORIGINAL ARTICLE

Prostate Cancer

Intraductal carcinoma of the prostate in prostate biopsy samples: correlation with aggressive pathological features after radical prostatectomy and prognostic value in high-risk prostate cancer

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Intraductal carcinoma of the prostate (IDC-P) is an aggressive pathological pattern of prostate cancer (PCa). We investigated the association of IDC-P in prostate biopsy (PBx) with several pathological features after radical prostatectomy (RP) and its prognostic value in high-risk PCa. A total of 418 patients with high-risk PCa after RP were included in this study. IDC-P and its architectural patterns were identified according to the 2016 World Health Organization Classification. Chi-squared test and logistic regression were used to investigate the correlation between IDC-P and post-RP pathological features. Kaplan–Meier curves and Cox regression were applied to explore the prognostic value of IDC-P. IDC-P was identified in PBx in 36/418 (8.6%) patients. Logistic regression indicated that IDC-P in PBx was independently associated with several pathological features of RP, including Gleason score 8–10 ($P < 0.001$), seminal vesicular invasion ($P < 0.001$), and pathological T (pT) 3a ($P = 0.043$). Patients with IDC-P in PBx manifested poorer biochemical-free survival (BFS) than those without IDC-P (37.47 months *vs* not reached, $P < 0.001$). The addition of IDC-P in several prognostic nomograms could improve the predictive accuracy of these tools. We conclude that IDC-P in PBx is positively associated with several aggressive pathological features after RP in high-risk PCa. In addition, IDC-P in PBx could effectively predict the BFS of high-risk PCa patients after RP.

Asian Journal of Andrology (2020) **22**, 519–525; doi: 10.4103/aja.aja_117_19; published online: 08 November 2019

Keywords: biopsy; high risk; intraductal carcinoma of the prostate; prognosis; prostate cancer

INTRODUCTION

Intraductal carcinoma of the prostate (IDC-P), a histologically and morphologically discrete prostate cancer (PCa) entity first proposed in 1985, is considered a biologically aggressive form accompanied by conspicuous architectural and cytological atypia. Although rare in the overall unselected PCa population, the prevalence of IDC-P in the high-risk group is higher, indicating its close association with the aggressiveness of PCa.[1–3] IDC-P has been associated with relatively poorer response to not only surgery or radiotherapy, but also chemotherapy and androgen deprivation therapy (ADT).[3–11]

Previous reports have demonstrated the association of IDC-P with several prognostic factors, such as tumor volume, Gleason score (GS), extraprostatic extension (EPE), positive surgical margin (PSM), and biochemical failure rate.[12–16] However, most of these findings with IDC-P were derived from radical prostatectomy (RP) specimens, and the prognostic role of IDC-P in prostate biopsies (PBx) is not well known. Whether IDC-P in PBx can effectively predict adverse pathological parameters and even clinical outcomes after RP is of importance, as this may provide insights into patient prognosis prior to RP. For instance, whether a comprehensive multimodal treatment plan should be conducted in a certain patient and subsequent local or systemic therapies after RP can also be determined.

We recently found that different architectural patterns of IDC-P were associated with different survival outcomes in patients with metastatic PCa.[17] Therefore, we considered whether different IDC-P subtypes in PBx could also pose differential prognostic impacts on patients with high-risk localized PCa. These differential impacts may be significant and necessary for clinical pathologists to decide whether to report IDC-P subtypes and for surgeons to make reasonable and individualized multimodal therapeutic schedules.

The objective of this study was to assess the feasibility of using the presence of IDC-P in PBx and its subtypes in PBx to predict adverse pathological parameters and patient prognosis among high-risk PCa (stage ≥ T2c or prostate-specific antigen [PSA] >20 ng ml^{-1} or GS ≥8) in a Chinese population. In addition, the potential significance of IDC-P in PBx was validated in several current prognostic nomograms to evaluate its prognostic power in patients with high-risk PCa receiving RP.

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Received: 09 February 2019; Accepted: 01 September 2019

PATIENTS AND METHODS

Patients

A total of 418 patients diagnosed with high-risk PCa from 2010 to 2017 in West China Hospital (Chengdu, China) were included in this study. All patients underwent transperineal ultrasound-guided (TPUS) 12-core prostate biopsy at the initial diagnosis. Preoperative examinations included the following: PSA, computed tomography (CT)/magnetic resonance imaging (MRI), digital rectal examination, prostate biopsy, bone scan, blood count, liver and kidney functions, coagulation function, blood-borne infectious disease, electrocardiogram and pulmonary function, and heart Doppler ultrasound if the patient was old and had underlying diseases such as hypertension. RP was then carried out for each case; because China is a developing country, the choice of surgical modalities between laparoscopic surgery and robotic-assisted laparoscopic radical prostatectomy (RALP) mostly relied on the patient's financial condition. IDC-P in both biopsy and RP specimens was defined by the Epstein criteria[18] and was further subclassified as pattern-1 (loose cribriform or micropapillary pattern with either marked nuclear atypia or comedonecrosis) or pattern-2 (solid or dense cribriform pattern) according to the 2016 WHO Classification (**Figure 1**).[19] The pathological evaluation of IDC-P was carried out by two experienced urinary pathologists independently.

The following baseline characteristics were collected for all patients: age; presurgery index: baseline PSA, perineural invasion (PNI), the International Society of Urological Pathology (ISUP) grading (Gleason score), positive core numbers, the National Comprehensive Cancer Network (NCCN) risk group, clinical T (cT) stage, and surgical type; and postsurgery index: PNI, EPE, seminal vesicular invasion (SVI), pathological T (pT) stage, surgical margins, adjuvant therapeutic, and PSA level at 3 months after RP. The definition of ISUP grading was according to the International Society of Urological Pathology 2014 grade groups.[20] High risk was defined referring to D'Amico Risk Classification (stage ≥ T2c or PSA >20 ng ml^{-1} or GS ≥8).[21] The median follow-up time of the whole cohort was 42.0 months.

Endpoint definition

We defined post-RP biochemical recurrence (BCR) as two consecutive PSA >0.2 ng ml^{-1} after the PSA had fallen to undetectable levels. Biochemical-free survival (BFS) was defined as the time duration between initial diagnosis and the time of BCR.

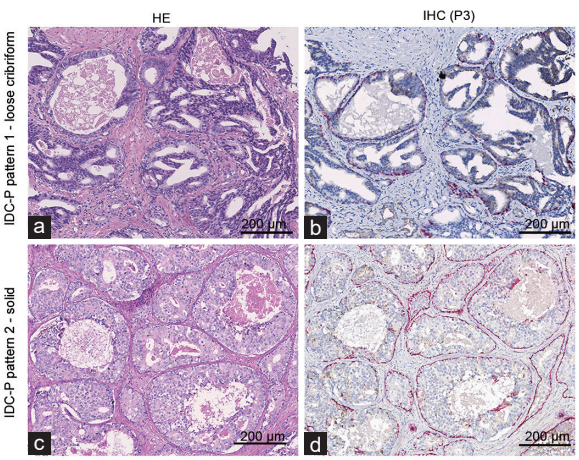

Figure 1: Histopathological features of IDC-P architectural patterns: (**a**) IDC-P pattern 1 - loose cribriform with H and E. (**b**) IDC-P pattern 1 - loose cribriform with IHC (P3). (**c**) IDC-P pattern 2 - solid with H and E. (**d**) IDC-P pattern 2 - solid with IHC (P3). Magnification, ×200. IDC-P: intraductal carcinoma of the prostate; HE: hematoxylin and eosin; IHC: immunohistochemistry.

Ethics approval and consent to participate and publication

Medical Ethics Committee of West China Hospital of Sichuan University has approved this study protocol. Every relevant detail has been explained to the patient himself, and written consent forms were obtained from each patient. Consent for publication was obtained from the patients involved in this study. The study was performed in accordance with the Declaration of Helsinki. Original data and materials in this study can be provided.

Statistical methods

Numerical factors were described as mean and standard deviation (s.d.) or median and interquartile range (IQR), whereas categorical factors were presented as frequency and percentage. Chi-squared test was used to compare the baseline characteristics between patients with and without IDC-P in PBx. Univariate and multivariate logistic regressions were applied in predicting the association between preoperative IDC-P in PBx and the pathological characteristics of RP specimens. Kaplan–Meier curve and log-rank test were used to compare the BFS of patients in different groups. Cox regression was applied in the univariate and multivariate analyses of BFS. In the logistic and Cox regression, variables with $P < 0.05$ in univariate analyses were included in the multivariate analyses. In addition, concordance index (C-index) was used to evaluate and compare the prognostic predictive accuracy of several nomograms before and after adding IDC-P (in PBx specimen) into these models.

Data analyses in this study were performed using R software (version 3.5.1, http://www.R-project.org) and SPSS (version 25.0, IBM Corp., Armonk, NY, USA). All tests were two-sided. $P < 0.05$ was considered statistically significant.

RESULTS

Patient baseline characteristics

Among the total of 418 patients, IDC-P was diagnosed in 36/418 (8.6%) PBx specimens and was confirmed in all RP specimens without exception. An additional nine patients were confirmed for IDC-P presence in RP specimens (45/418, 10.8%). The concordance rate of IDC-P between PBx and RP was 97.8%. The 36 IDC-P-positive patients consisted of 21 (58.3%) IDC-P pattern-1 and 15 (41.7%) IDC-P pattern-2 patients. Most patients in our cohort underwent RALP (200/418, 47.8%), followed by laparoscopic (132/418, 31.6%) and open approaches (86/418, 20.6%). After surgery, due to severity of disease, physician discretion, and patient choice, 158/418 (37.8%) patients received adjuvant therapies. Compared with patients without IDC-P, those with IDC-P in PBx had higher opportunity to obtain adjuvant therapy (132/382, 34.6% *vs* 26/36, 72.2%, respectively; $P < 0.001$). Detailed preoperative clinicopathological characteristics are shown in **Table 1**.

The association of IDC-P in PBx with presurgery clinicopathological parameters

In terms of presurgical indexes, compared with patients without IDC-P, patients with IDC-P harbored higher baseline PSA level ($P = 0.002$), higher biopsy ISUP grading/GS ($P < 0.001$), higher proportion of positive biopsy cores ($P < 0.001$), and higher NCCN risk group ($P < 0.001$; **Table 1**).

The value of IDC-P in PBx in predicting post-RP pathological characteristics

Compared with patients without IDC-P, patients with IDC-P in PBx were accompanied with higher detection of PNI ($P = 0.046$), EPE

Table 1: Baseline characteristics of patients according to the presence or absence of intraductal carcinoma of the prostate in prostate biopsy specimens

Characteristics	*Total (n=418)*	*Without IDC-P (n=382)*	*With IDC-P (n=36)*	*P*
Age (year), median (IQR)	69.00 (64.00–73.00)	69.00 (64.00–73.00)	69.50 (64.25–73.75)	
<70, *n* (%)	275 (65.8)	253 (66.2)	22 (61.1)	0.536*
≥70, *n* (%)	143 (34.2)	129 (33.8)	14 (38.9)	
Baseline PSA (ng ml^{-1}), median (IQR)	17.36 (10.05–35.50)	16.74 (9.82–29.78)	33.57 (14.50–78.08)	
Baseline PSA (ng ml^{-1}), mean (s.d.)	50.32 (447.47)	50.79 (468.02)	45.38 (33.77)	0.003#
Baseline PSA (ng ml^{-1})				
<20, *n* (%)	241 (57.7)	229 (59.9)	12 (33.3)	0.002*
≥20, *n* (%)	177 (42.3)	153 (40.1)	24 (66.7)	
PNI in PBx, *n* (%)				
Yes	32 (8.1)	28 (7.8)	4 (11.8)	0.505*
No	361 (91.9)	331 (92.2)	30 (88.2)	
ISUP grading (Gleason score) in PBx, *n* (%)				
1 (6)	60 (14.4)	60 (15.7)	0	<0.001*
2 (7 [3+4])	130 (31.1)	129 (33.8)	1 (2.8)	
3 (7 [4+3])	101 (24.2)	96 (25.1)	5 (13.9)	
4 (8)	48 (11.5)	45 (11.8)	3 (8.3)	
5 (9–10)	79 (18.9)	52 (13.6)	27 (75.0)	
Positive core numbers, median (IQR)	5.5 (3–9)	5 (3–8)	10 (7.25–12)	
<7, *n* (%)	251 (60.0)	246 (66.4)	5 (13.9)	<0.001*
≥7, *n* (%)	167 (40.0)	136 (35.6)	31 (86.1)	
NCCN risk group, *n* (%)				
Intermediate	140 (33.5)	140 (36.6)	0	<0.001*
High	120 (28.7)	117 (30.6)	3 (8.3)	
Very high	158 (37.8)	125 (32.7)	33 (91.7)	
cT stage, *n* (%)				
<T3a	166 (39.7)	151 (39.5)	15 (41.7)	0.802*
≥T3a	252 (60.3)	231 (60.5)	21 (58.3)	
Surgical type, *n* (%)				
Open	86 (20.6)	85 (22.3)	1 (2.8)	0.006*
Laparoscopic	132 (31.6)	122 (31.9)	10 (27.8)	
Robotic-assisted laparoscopic	200 (47.8)	175 (45.8)	25 (69.4)	
IDC-P-RP (+), *n* (%)	45 (10.8)	9 (2.4)	36 (100.0)	–
PNI in RP specimen, *n* (%)				
Yes	236 (56.5)	210 (55.0)	26 (72.2)	0.046*
No	182 (43.5)	172 (45.0)	10 (27.8)	
EPE in RP specimen, *n* (%)				
Yes	180 (43.1)	212 (55.5)	26 (72.2)	0.053*
No	238 (56.9)	170 (44.5)	10 (27.8)	
SVI in RP specimen, *n* (%)				
Yes	82 (19.6)	61 (16.0)	21 (58.3)	<0.001*
No	336 (80.4)	321 (84.0)	15 (41.7)	
pT stage, *n* (%)				
T2	141 (33.7)	136 (35.6)	5 (13.9)	<0.001*
T3a	183 (43.8)	173 (45.3)	10 (27.8)	
T3b	81 (19.4)	62 (16.2)	19 (52.8)	
T4	13 (3.1)	11 (2.9)	2 (5.6)	
Surgical margins, *n* (%)				
Positive	133 (31.9)	112 (29.3)	21 (58.3)	<0.001*
Negative	285 (68.2)	270 (70.7)	15 (41.7)	
Adjuvant therapy, *n* (%)				
No	260 (62.2)	250 (65.4)	10 (27.8)	<0.001*
Yes	158 (37.8)	132 (34.6)	26 (72.2)	
PSA in 3 months after RP (ng ml^{-1}), median (IQR)	0.01 (0.003–0.09)	0.009 (0.003–0.05)	0.23 (0.02–1.74)	
PSA in 3 months after RP (ng ml^{-1}), mean (s.d.)	0.94 (6.47)	0.33 (1.41)	7.59 (21.04)	<0.001#
PSA in 3 months after RP (ng ml^{-1})				

Contd...

Table 1: Contd...

Characteristics	*Total (n=418)*	*Without IDC-P (n=382)*	*With IDC-P (n=36)*	*P*
<0.2, *n* (%)	297 (71.1)	282 (86.0)	15 (50.0)	<0.001*
≥0.2, *n* (%)	61 (14.6)	46 (14.0)	15 (50.0)	
PSA nadir (ng ml^{-1}), median (IQR)	0.01 (0.003–2.60)	0.003 (0.003–2.50)	0.65 (0.003–5.00)	
PSA nadir (ng ml^{-1}), mean (s.d.)	1.64 (3.11)	1.51 (2.50)	3.13 (6.88)	<0.001
PSA nadir (ng ml^{-1})				
<0.2, *n* (%)	256 (61.2)	242 (63.3)	13 (36.7)	<0.001*
≥0.2, *n* (%)	162 (38.8)	140 (36.7)	23 (63.9)	

*P values were calculated through Chi-squared test for categorical variables, #P values were calculated through Student's t-test for quantitative variables. IDC-P: intraductal carcinoma of the prostate; PBx: prostate biopsies; PSA: prostate-specific antigen; s.d.: standard deviation; IQR: interquartile range; ISUP: International Society of Urological Pathology; NCCN: National Comprehensive Cancer Network; cT: clinical T; RP: radical prostatectomy; PNI: perineural invasion; EPE: extraprostatic extension; SVI: seminal vesicular invasion; pT: pathological T

(P = 0.053), SVI (P < 0.001), higher pT stage (P < 0.001), higher incidence of PSM (P < 0.001), and higher PSA level at 3 months of RP (P < 0.001; **Table 1**).

Multivariate logistic regression indicated that IDC-P was an independent predictor for more aggressive GS (8–10) (odds ratio [OR]: 13.056; 95% confidence interval [CI]: 5.188–32.857, P < 0.001), advanced pT stage (pT ≥3a) (OR: 2.822; 95% CI: 1.031–7.723, P = 0.043), higher probability of SVI (OR: 4.822; 95% CI: 2.216–10.935, P < 0.001), and PSM (OR: 2.033; 95% CI: 0.944–4.376, P = 0.070; **Table 2**). Moreover, we also performed analysis using IDC-P data from RP specimens to compare with that from PBx. The concordance of IDC-P incidence between PBx and RP specimens was about 97.8%, and the results showed that IDC-P in both PBx and RP shared similar predictive value (**Supplementary Table 1**).

The prognostic value of IDC-P in PBx in predicting BFS

At the end of the follow-up, BCR occurred in 79/418 (18.9%), 15/36 (41.7%), and 64/382 (16.8%) of total patients, patients with IDC-P, and patients without IDC-P, respectively. Kaplan–Meier curve showed that the 5-year BCR rate for the total cohort was 41.0%. Survival analysis showed that patients with IDC-P in PBx manifested poorer BFS than those without IDC-P (median BFS: 37.5 months *vs* not reached; **Figure 2a**). Further subgroup analyses indicated that either IDC-P pattern-1 or pattern-2, separately, was still significantly related to shorter BFS than those without IDC-P. Although without statistical significance, patients with IDC-P pattern-2 were numerically associated with shorter time to biochemical failure than patients with IDC-P pattern-1 (median BFS: 21.90 *vs* 37.47 months, P = 0.617; **Figure 2b**).

As shown in **Table 3**, except for the presence of IDC-P, factors including baseline PSA, positive core numbers, cT stage, and ISUP grading were also prognosticators of BFS in univariate analyses. Notably, IDC-P demonstrated the highest hazard ratio (HR) among all predictors (IDC-P total: HR: 3.731, 95% CI: 2.101–6.627, P < 0.001; IDC-P pattern-1: HR: 3.276, 95% CI: 1.554–6.903, P = 0.002; IDC-P pattern-2: HR: 4.430, 95% CI: 2.014–9.744, P < 0.001). In multivariate analyses, both IDC-P and cT stage were predictors of BFS (IDC-P pattern-1: HR: 2.299, 95% CI: 1.019–5.183, P = 0.045; IDC-P pattern-2: HR: 2.821, 95% CI: 1.178–6.758, P = 0.020; cT stage ≥3a: HR: 1.763, 95% CI: 1.040–2.990, P = 0.035). Similar analyses were performed using IDC-P data from RP specimens, and surprisingly, the presence of IDC-P from RP specimens was not an independent prognosticator among patients with high-risk PCa (**Supplementary Table 2**).

Validation of the prognostic value of IDC-P in PBx in several nomograms

To better ascertain the prognostic value of IDC-P in PBx, it was then used as a parameter in several predictive nomograms. Addition of IDC-P in these classical nomograms could statistically improve their predictive power (**Table 4**). The increase in C-index after adding IDC-P for prognosis nomograms, including the D'Amico nomogram, gleason, prostate-specific antigen, seminal vesicle and margin status (GPSM) score, Cancer of the Prostate Risk Assessment (CAPRA) score, Partin table, and Stephenson score, were 0.025, 0.003, 0.017, 0.014, and 0.022, respectively. We applied IDC-P data from RP specimens in GPSM score for a second validation as it was a postoperative nomogram. Although the absolute growth of the model's C-index was higher when using IDC-P in RP than PBx (0.009 *vs* 0.003), the results from IDC-P in PBx and RP were not significantly different (P = 0.054 and P = 0.057) (**Table 4** and **Supplementary Table 3**).

To note, we have performed a propensity score matching analysis and validated all our results (data shown in **Supplementary Table 3–6**).

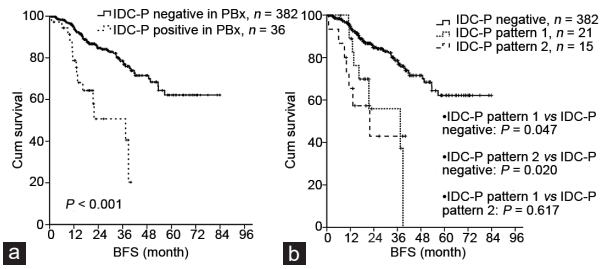

Figure 2: (**a**) The presence of IDC-P as a prognosticator for biochemical recurrence in the high-risk group of prostate cancer patients. (**b**) Two patterns of IDC-P showed differentiating tendency in predicting biochemical recurrence. IDC-P: intraductal carcinoma of the prostate; BFS: biochemical-free survival.

DISCUSSION

During clinical work, determining a precise and accurate treatment for cancer patients is challenging and relies heavily on our in-depth understanding of the tumor nature. Several pathological entities with predictive prognostic value provide a unique opportunity to achieve the goal of determining an effective and personalized treatment plan. In this retrospective study, we explored the clinical value of IDC-P in PBx from several aspects. First, we found that the presence of IDC-P in PBx, as well as its subtypes, could predict some adverse pathological features and was in close correlation with patient prognosis (BFS). Second, the addition of IDC-P in several commonly used nomograms improved their predictive value for prognosis.

The incidence of IDC-P varies from 2.1% to 56% in different stages of disease.[2] Compared with metastatic and castration-resistant PCa, IDC-P prevalence in patients with localized PCa is relatively lower. Due to variable diagnostic criteria and a disunified definition

Table 2: Associations between intraductal carcinoma of the prostate in prostate biopsies and radical prostatectomy pathological characteristics

Characteristics	*Univariate* analysis		*Multivariate* analysis*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
GS, (6–7)/(8–10)	14.896 (6.017–36.877)	<0.001	13.056 (5.188–32.857)	<0.001
SVI	7.367 (3.597–15.089)	<0.001	4.822 (2.216–10.935)	<0.001
EPE	2.085 (0.978–4.443)	0.057	–	–
pT (3a)	3.428 (1.303–9.019)	0.013	2.822 (1.031–7.723)	0.043
PSM	3.375 (1.679–6.785)	0.001	2.033 (0.944–4.376)	0.070

*Multivariate analyses included IDC-P, age, PSA, Gleason score (PBx), and cT stage. IDC-P: intraductal carcinoma of the prostate; PBx: prostate biopsies; RP: radical prostatectomy; OR: odds ratio; CI: confidence interval; GS: Gleason score; SVI: seminal vesicular invasion; EPE: extraprostatic extension; pT: pathological T; PSA: prostate-specific antigen; cT: clinical T; PSM: positive surgical margin; –: not available

Table 3: Univariate and multivariate survival analyses of the association between intraductal carcinoma of the prostate in prostate biopsies and biochemical-free survival

	Univariate analysis			*Multivariate analysis*		
	HR	*95% CI*	*P*	*HR*	*95% CI*	*P*
IDC-P versus no IDC-P	3.731	2.101–6.627	0.000	2.415	1.238–4.711	0.010
IDC-P pattern						
Pattern 1 versus no IDC-P	3.276	1.554–6.903	0.002	2.299	1.019–5.183	0.045
Pattern 2 versus no IDC-P	4.430	2.014–9.744	0.000	2.821	1.178–6.758	0.020
Age (year)						
≤70	Reference	–	–			
>70	1.340	0.850–2.112	0.208			
Baseline PSA (ng ml^{-1})						
≤20	Reference	–	–	Reference	–	–
>20	1.861	1.194–2.902	0.006	1.378	0.851–2.234	0.193
Positive core number						
<7	Reference	–	–	Reference	–	–
≥7	1.929	1.217–3.058	0.005	1.457	0.876–2.425	0.147
ISUP grade						
1, 2, 3	Reference	–	–	Reference	–	–
4, 5	2.289	1.462–3.585	0.000	1.258	0.731–2.167	0.407
cT stage						
<3a	Reference	–	–	Reference	–	–
≥3a	1.715	1.031–2.851	0.038	1.763	1.040–2.990	0.035
Adjuvant therapy						
Yes	Reference	–	–	Reference	–	–
No	2.058	1.314–3.223	0.002	1.255	0.754–2.090	0.383

IDC-P: intraductal carcinoma of the prostate; PBx: prostate biopsies; BFS: biochemical-free survival; HR: hazard ratio; CI: confidence interval; PSA: prostate-specific antigen; ISUP: international society of urological pathology; cT: clinical T; –: not available

Table 4: Concordance index of four commonly used nomograms for prostate cancer prognosis prediction – before and after the addition of intraductal carcinoma of the prostate

	Model without IDC-P (%)	*Model with IDC-P (%)*	*Increase (%)*	*P*
D'Amico nomogram	67.0	69.5	2.5	0.004
GPSM score-PBx IDC-P	68.9	69.2	0.3	0.054
GPSM score-RP IDC-P	68.9	69.8	0.9	0.057
CAPRA score	70.0	71.7	1.7	0.061
Partin table	75.1	76.5	1.4	0.029
Stephenson score	69.4	71.6	2.2	0.032

IDC-P: intraductal carcinoma of the prostate; GPSM: gleason, prostate-specific antigen, seminal vesicle, and margin status; RP: radical prostatectomy; PBx: prostate biopsy; CAPRA: Cancer of the Prostate Risk Assessment

for IDC-P in clinical practice in different medical centers,[22–24] the incidence of IDC-P showed robust disparity.[11,25–27] In addition, localized PCa with different recurrence risk was another factor involved in the differential detection of IDC-P. For instance, Watts and his colleagues reported that the incidence of IDC-P in localized PCa (prospectively collected PBx) was as low as 2.8%,[27] whereas, in the present study, the IDC-P detection rate among patients with high recurrence risk increased to 8.6%.

Previous studies showed that IDC-P was marked by a rather poor prognosis,[13,28,29] but this observation was mostly limited to RP specimens.[11,30–34] For patients who are not surgical candidates or not inclined to undergo RP, their initial or subsequent treatment relies mainly on biopsy results. In addition, being able to detect IDC-P in PBx can provide additional prognostic value in advance and help guide the initial treatment prior to RP. Our results showed that the detection of IDC-P in preoperative needle biopsy specimens could independently predict some of the pathological characteristics of the RP specimen, namely GS, SVI, pT stage, and PSM, and the predictive value of IDC-P in PBx was not less than that of the RP samples. This trend was also seen in the studies of Watts, Guo, and Khani.[35–37] Therefore, the value of studying the IDC-P in PBx lies in its predictive value, as well as the ability to determine if a definitive treatment is called for.[26,38,39]

In 1998, Cohen *et al*.[25] stated that in the preoperative model, IDC-P should be singled out as the first parameter to consider, as it indicated the poorest outcome. Epstein found that even if the PBx was classified as GS 6, patients with IDC-P on PBx or TURP still presented aggressive tumor progression.[37] This indication was proven from another angle by Kweldam *et al*.[40] who regarded IDC-P-negative patients with GS 3 + 4 = 7 on PBx similar to those with GS 6 in terms of survival and suggested these patients therefore should be provided active surveillance. Nevertheless, despite being morphologically distinct and proposed as an exclusion criterion for active surveillance,[41] IDC-P is not included in the currently used classification and staging systems such as TNM classification, GS, and European Association Urology risk groups. This study presented the association between IDC-P status in PBx and patient prognosis, which was consistent with the previous studies, *i.e*., the presence of IDC-P was related to higher BCR rate and worse disease-specific survival.[25,26,33,35,37,40] However, a study of 283 patients diagnosed as PCa with PBx showed the negative predictive value of IDC-P in cancer-specific survival. We assume this difference may be due to the choice of primary endpoint (cancer-specific survival *vs* BFS). This adverse prognostic association with BFS is not true to IDC-P in RP specimens during our multivariate analysis, because the nine patients in our cohort whose biopsy samples did not show IDC-P presence while RP specimens all showed a low proportion of IDC-P in RP specimens (1%–10%).

Even though the trend of poorer prognosis in IDC-P (+) patients has been found in the present studies, the specific survival time still differs, indicating an inherit heterogeneity in IDC-P. Therefore, the difference between two IDC-P patterns was analyzed in terms of BFS, and we found that pattern-2 presented a higher hazard ratio. This finding indicates that not only the presence but also the pathological pattern of IDC-P should be mentioned to provide more treatment-related information for clinicians.

In terms of treatment influence, IDC-P seems more pervasive in cohorts previously treated with any kind of systemic therapy compared with those who do not receive ADT or chemotherapy at all.[7,42] More specifically, our previous work and a few other studies have observed the persistency or even increase of the characteristic morphological features of IDC-P after initial ADT and/or chemotherapy.[3,7,43–45] Notably, in our study results, even with a higher proportion of patients receiving ADT in the IDC-P (+) group, the patients still demonstrated a poorer prognosis, indicating that IDC-P might have an intrinsic insensitivity for ADT. This indicated that IDC-P could likely be inherently insensitive or even resistive to systemic treatment.

In spite of focusing on IDC-P in isolation, we also managed to validate its application value by adding it to several well-acknowledged prognostic nomograms. To the best of our knowledge, the current study is the first to take the adverse prognostic influence of IDC-P into consideration in five nomograms for posttreatment prognosis prediction of patients after RP, namely the D'Amico nomogram, GPSM score, CAPRA score, Partin table, and Stephenson score. The results seemed promising, because the C-index values of these four nomograms were all increased. However, the C-index increased values of the GPSM score and CAPRA score were not as obvious as the others, and we assumed it was due to the fact that these two nomograms had more original indexes than the others.

The present study is not devoid of limitations. First, our study nature of a single-institute retrospective type is an inherent deficiency; however, our patient cohort serves as a valuable supplement for understanding and research into IDC-P among Chinese patients. Second, our clinicians tend to provide adjuvant endocrinal therapies for patients with IDC-P presence more radically compared with regular patients. However, we are convinced that if an obvious BFS benefit can still be observed in this case, this provides more reasons to believe that the disparity arising from the presence of IDC-P does exist.

Finally, we would like to emphasize the clinical application value of this study. The detection of IDC-P in PBx could imply higher risk of BCR and shorter BFS. Notably, this finding in a Chinese population provides a deeper understanding of IDC-P. In addition to the presence of IDC-P, we also found in the survival analysis that the two IDC-P subtypes displayed different prognosis. As a consequence, these findings are evidence for the recommendation to include the finding of IDC-P, as well as its subtypes, on a PBx report. In addition, adding IDC-P into current nomograms for predicting prognosis could be useful for patient management. Furthermore, initiating the appropriate treatment plan for patients with IDC-P in PBx is a new challenge for clinicians and requires more basic lab-based studies in the future.

CONCLUSION

In this study, we explored the clinical value of IDC-P in preoperative PBx. The results showed that IDC-P in biopsy specimens could predict some pathological results and that different IDC-P patterns were associated with clinical outcomes (BCR and BFS). In addition, adding IDC-P as a new index in several prognostic nomograms increased the C-indexes. IDC-P should thus be considered a promising prognostic indicator for PCa patients in the future. This retrospective study in Chinese patients provided ethnographic heterogeneity to our current understanding of IDC-P.

AUTHOR CONTRIBUTIONS

SZ and JGZ are the main characters in coming up with the idea and writing this manuscript. JRC, ZHL, and GXS mainly did statistical work. JRC also participated in the revision process. ZPW, YCN, and JDD mainly took part in the follow-up section (making all the phone calls and collecting the survival data of patients). PFS and HZ reviewed the manuscript and offered revision suggestions. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

REFERENCES

1 Montironi R, Cheng L, Lopez-Beltran A, Scarpelli M, Montorsi F. A better understating of the morphological features and molecular characteristics of intraductal carcinoma helps clinicians further explain prostate cancer aggressiveness. *Eur Urol* 2015; 67: 504–7.
2 Porter LH, Lawrence MG, Ilic D, Clouston D, Bolton DM, *et al*. Systematic review links the prevalence of intraductal carcinoma of the prostate to prostate cancer risk categories. *Eur Urol* 2017; 72: 492–5.
3 Zhao T, Liao B, Yao J, Liu J, Huang R, *et al*. Is there any prognostic impact of intraductal carcinoma of prostate in initial diagnosed aggressively metastatic prostate cancer? *Prostate* 2015; 75: 225–32.
4 Van der Kwast T, Al Daoud N, Collette L, Sykes J, Thoms J, *et al*. Biopsy diagnosis of intraductal carcinoma is prognostic in intermediate and high risk prostate cancer patients treated by radiotherapy. *Eur J Cancer* 2012; 48: 1318–25.
5 McNeal JE, Yemoto CE. Spread of adenocarcinoma within prostatic ducts and acini: morphologic and clinical correlations. *Am J Surg Pathol* 1996; 20: 802–14.
6 O'Brien C, True LD, Higano CS, Rademacher BL, Garzotto M, *et al*. Histologic changes associated with neoadjuvant chemotherapy are predictive of nodal metastases in patients with high-risk prostate cancer. *Am J Clin Pathol* 2010; 133: 654–61.
7 O'Brien BA, Cohen RJ, Wheeler TM, Moorin RE. A post-radical-prostatectomy nomogram incorporating new pathological variables and interaction terms for improved prognosis. *BJU Int* 2011; 107: 389–95.
8 Efstathiou E, Abrahams NA, Tibbs RF, Wang X, Pettaway CA, *et al*. Morphologic characterization of preoperatively treated prostate cancer: toward a post-therapy histologic classification. *Eur Urol* 2010; 57: 1030–8.
9 Zhao J, Shen P, Sun G, Chen N, Liu J, *et al*. The prognostic implication of intraductal

carcinoma of the prostate in metastatic castration-resistant prostate cancer and its potential predictive value in those treated with docetaxel or abiraterone as first-line therapy. *Oncotarget* 2017; 8: 55374–83.
10 Chen Z, Chen N, Shen P, Gong J, Li X, *et al*. The presence and clinical implication of intraductal carcinoma of prostate in metastatic castration resistant prostate cancer. *Prostate* 2015; 75: 1247–54.
11 Kimura K, Tsuzuki T, Kato M, Saito AM, Sassa N, *et al*. Prognostic value of intraductal carcinoma of the prostate in radical prostatectomy specimens. *Prostate* 2014; 74: 680–7.
12 Robinson BD, Epstein JI. Intraductal carcinoma of the prostate without invasive carcinoma on needle biopsy: emphasis on radical prostatectomy findings. *J Urol* 2010; 184: 1328–33.
13 Kovi J, Jackson MA, Heshmat MY. Ductal spread in prostatic carcinoma. *Cancer* 1985; 56: 1566–73.
14 Mcneal JE, Yemoto CM. Spread of adenocarcinoma within prostatic ducts and acini: morphologic and clinical correlations. *Am J Clin Pathol* 1996; 20: 802–14.
15 Wilcox G, Soh S, Chakraborty S, Scardino PT, Wheeler TM. Patterns of high-grade prostatic intraepithelial neoplasia associated with clinically aggressive prostate cancer. *Hum Pathol* 1998; 29: 1119–23.
16 Rubin MA, de La Taille A, Bagiella E, Olsson CA, O'Toole KM. Cribriform carcinoma of the prostate and cribriform prostatic intraepithelial neoplasia: incidence and clinical implications. *Am J Clin Pathol* 1998; 22: 840–8.
17 Zhao J, Liu J, Sun G, Zhang M, Chen J, *et al*. The prognostic value of the proportion and architectural patterns of intraductal carcinoma of the prostate in patients with *de novo* metastatic prostate cancer. *J Urol* 2019; 201: 759–68.
18 Guo CC, Epstein JI. Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance. *Mod Pathol* 2006; 19: 1528–35.
19 Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of tumours of the urinary system and male genital organs-part b: prostate and bladder tumours. *Eur Urol* 2016; 70: 106–19.
20 Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, *et al*. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: definition of grading patterns and proposal for a new grading system. *Am J Clin Pathol* 2016; 40: 244–52.
21 D'Amico AV, Whittington R, Malkowicz SB, Fondurulia J, Chen MH, *et al*. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. *J Clin Oncol* 1999; 17: 168–72.
22 Trudel D, Downes MR, Sykes J, Kron KJ, Trachtenberg J, *et al*. Prognostic impact of intraductal carcinoma and large cribriform carcinoma architecture after prostatectomy in a contemporary cohort. *Eur J Cancer* 2014; 50: 1610–6.
23 Dong F, Yang P, Wang C, Wu S, Xiao Y, *et al*. Architectural heterogeneity and cribriform pattern predict adverse clinical outcome for Gleason grade 4 prostatic adenocarcinoma. *Am J Surg Pathol* 2013; 37: 1855–61.
24 Kweldam CF, Wildhagen MF, Steyerberg EW, Bangma CH, van der Kwast TH, *et al*. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. *Mod Pathol* 2015; 28: 457–64.
25 Cohen RJ, Chan WC, Edgar SG, Robinson E, Dodd N, *et al*. Prediction of pathological stage and clinical outcome in prostate cancer: an improved pre-operative model incorporating biopsy-determined intraductal carcinoma. *Br J Urol* 1998; 81: 413–8.
26 Der Kwast TH, Daoud NA, Collette L, Sykes J, Thoms J, *et al*. Biopsy diagnosis of intraductal carcinoma is prognostic in intermediate and high risk prostate cancer patients treated by radiotherapy. *Eur J Cancer* 2012; 48: 1318–25.
27 Watts K, Li J, Magi-Galluzzi C, Zhou M. Incidence and clinicopathological characteristics of intraductal carcinoma detected in prostate biopsies: a prospective cohort study. *Histopathology* 2013; 63: 574–9.
28 Efstathiou E, Abrahams NA, Tibbs RF, Wang X, Pettaway CA, *et al*. Morphologic characterization of preoperatively treated prostate cancer: toward a post-therapy histologic classification. *Eur Urol* 2010; 57: 1030–8.
29 Porter L, Lawrence MG, Ilic D, Clouston D, Bolton DM, *et al*. Systematic review links the prevalence of intraductal carcinoma of the prostate to prostate cancer risk categories. *Eur Urol* 2017; 72: 492–5.
30 Kryvenko O, Gupta N, Virani N, Schultz D, Gomez J, *et al*. Gleason score 7 adenocarcinoma of the prostate with lymph node metastases: analysis of 184 radical prostatectomy specimens. *Arch Pathol Lab Med* 2013; 137: 610–7.
31 Dong F, Yang P, Wang C, Wu S, Xiao Y, *et al*. Architectural heterogeneity and cribriform pattern predict adverse clinical outcome for Gleason grade 4 prostatic adenocarcinoma. *Am. J Surg Pathol* 2013; 37: 1855–61.
32 Kweldam CF, Wildhagen MF, Steyerberg EW, Bangma CH, Der Kwast TH, *et al*. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. *Mod Pathol* 2015; 28: 457–64.
33 Trudel D, Downes MR, Sykes J, Kron K, Trachtenberg J, *et al*. Prognostic impact of intraductal carcinoma and large cribriform carcinoma architecture after prostatectomy in a contemporary cohort. *Eur J Cancer* 2014; 50: 1610–6.
34 Mcneal JE, Reese JH, Redwine EA, Freiha FS, Stamey TA. Cribriform adenocarcinoma of the prostate. *Cancer* 1986; 58: 1714–9.
35 Watts KE, Li J, Magigalluzzi C, Zhou M. Incidence and clinicopathological characteristics of intraductal carcinoma detected in prostate biopsies: a prospective cohort study. *Histopathology* 2013; 63: 574–9.
36 Guo CC, Epstein JI. Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance. *Mod Pathol* 2006; 19: 1528–35.
37 Khani F, Epstein JI. Prostate biopsy specimens with Gleason 3+3 = 6 and intraductal carcinoma: radical prostatectomy findings and clinical outcomes. *Am J Surg Pathol* 2015; 39: 1383–9.
38 Morais CL, Han JS, Gordetsky J, Nagar M, Anderson AE, *et al*. Utility of PTEN and ERG immunostaining for distinguishing high-grade PIN from intraductal carcinoma of the prostate on needle biopsy. *Am J Surg Pathol* 2015; 39: 169–78.
39 Morais CL, Herawi M, Toubaji A, Albadine R, Hicks J, *et al*. PTEN loss and ERG protein expression are infrequent in prostatic ductal adenocarcinomas and concurrent acinar carcinomas. *Prostate* 2015; 75: 1610–9.
40 Kweldam CF, Kummerlin IP, Nieboer D, Verhoef EI, Steyerberg EW, *et al*. Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. *Mod Pathol* 2016; 29: 630–6.
41 Montironi R, Hammond EH, Lin DW, Gore JL, Srigley JR, *et al*. Consensus statement with recommendations on active surveillance inclusion criteria and definition of progression in men with localized prostate cancer: the critical role of the pathologist. *Virchows Arch B Cell Pathol Incl Mol Pathol* 2014; 465: 623–8.
42 Porter LH, Lawrence MG, Ilic D, Clouston D, Bolton DM, *et al*. Systematic review links the prevalence of intraductal carcinoma of the prostate to prostate cancer risk categories. *Eur Urol* 2017; 72: 492–5.
43 Chen Z, Chen N, Shen P, Gong J, Li X, *et al*. The presence and clinical implication of intraductal carcinoma of prostate in metastatic castration resistant prostate cancer. *Prostate* 2015; 75: 1247–54.
44 Brien CO, True LD, Higano CS, Rademacher BL, Garzotto M, *et al*. Histologic changes associated with neoadjuvant chemotherapy are predictive of nodal metastases in patients with high-risk prostate cancer. *Am J Surg Pathol* 2010; 133: 654–61.
45 Porter LH, Hashimoto K, Lawrence MG, Pezaro C, Clouston D, *et al*. Intraductal carcinoma of the prostate can evade androgen deprivation, with emergence of castrate-tolerant cells. *BJU Int* 2018; 121: 971–8.

Supplementary Table 1: Associations between intraductal carcinoma of the prostate in radical prostatectomy and radical prostatectomy pathological characteristics

	OR (95% CI)	*P-univariate*	*OR (95% CI)*	*P-multivariate*[*]
GS (6–7/8–10)	4.152 (2.191–7.867)	0.000	3.770 (1.949–7.249)	0.000
EPE	1.996 (1.015–3.924)	0.045	1.996 (1.015–3.924)	0.045
pT (3a)	1.895 (0.909–3.948)	0.088	–	–
PSM	2.500 (1.337–4.672)	0.004	1.802 (0.920–3.528)	0.086

[*]Multivariate analyses included IDC-P, age, PSA, Gleason grade (PBx) and cT stage. IDC-P: intraductal carcinoma of the prostate; RP: radical prostatectomy; GS: gleason score; EPE: extraprostatic extension; pT: pathological T; PSM: positive surgical margin; OR: odds ratio; CI: confidence interval; cT: clinical T

Supplementary Table 2: Univariate and multivariate survival analyses of the association between intraductal carcinoma of the prostate in radical prostatectomy and biochemical-free survival

	Univariate analysis			*Multivariate analysis*		
	HR	*95% CI*	*P*	*HR*	*95% CI*	*P*
IDC-P-RP						
No	Reference	–	–	Reference	–	–
Yes	2.161	1.157–4.037	0.016			0.236
Age						
≤70	Reference	–	–	Reference	–	–
>70	1.340	0.850–2.112	0.208			
Baseline PSA (ng/mL)						
≤20	Reference	–	–	Reference	–	–
>20	1.861	1.194–2.902	0.006			0.100
Positive core numbers						
<7	Reference	–	–	Reference	–	–
≥7	1.929	1.217–3.058	0.005	1.676	1.033–2.720	0.037
ISUP grade						
1, 2, 3	Reference	–	–	Reference	–	–
4, 5	2.289	1.462–3.585	0.000			0.094
cT stage						
<3a	Reference	–	–	Reference	–	–
≥3a	1.715	1.031–2.851	0.038	1.699	1.013–2.850	0.045

IDC-P: intraductal carcinoma of the prostate; RP: radical prostatectomy; PBx: prostate biopsies; PSA: prostate-specific antigen; CI: confidence interval; HR: hazard ratio; ISUP: international society of urological pathology; cT: clinical T

Supplementary Table 3: Concordance index of four commonly used nomograms for prostate cancer prognosis prediction-before and after the addition of intraductal carcinoma of the prostate after propensity score matching

	Model without IDC-P (%)	*Model with IDC-P (%)*	*Increase (%)*	*P*
D'Amico nomogram	61.6	69.5	7.9	0.008
GPSM score	62.4	63.3	0.9	0.040
CAPRA score	63.0	66.3	3.3	0.009
Partin table	61.6	67.5	5.9	0.008
Stephenson score	63.0	68.0	5	0.007

GPSM: gleason, prostate-specific antigen, seminal vesicle, and margin status; CAPRA: cancer of the prostate risk assessment; IDC-P: intraductal carcinoma of the prostate

Supplementary Table 4: Baseline characteristics of patients according to the presence or absence of intraductal carcinoma of the prostate in prostate biopsies specimens

Characteristics	*Total cohort*		*P*	*After propensity score matching*		*P*
	No IDC-P	*IDC-P*		*No IDC-P*	*IDC-P*	
Number of patients	382	36		108	36	
Age (year)						
Median (IQR)	69.00 (64.00–73.00)	69.50 (64.25–73.75)		69.00 (65.00–72.00)	69.50 (64.3–73.8)	
<70, *n* (%)	253 (66.2)	22 (61.1)	0.536		22 (61.1)	0.921
≥70, *n* (%)	129 (33.8)	14 (38.9)		39 (36.1)	14 (38.9)	
Presurgery						
Baseline PSA (ng/mL)						
Median (IQR)	16.74 (9.82–29.78)	33.57 (14.50–78.08)		24.76 (15.77)	33.57 (14.50–78.08)	
Mean (s.d.)	50.79 (468.02)	45.38 (33.77)		126.27 (878.00)	45.38 (33.77)	
<20, *n* (%)	229 (59.9)	12 (33.3)	0.002	45 (41.7)	12 (33.3)	0.491
≥20, *n* (%)	153 (40.1)	24 (66.7)		63 (58.3)	24 (66.7)	
PNI						
Yes	28 (7.8)	4 (11.8)	0.505	16 (16.0)	4 (11.8)	0.777
No	331 (92.2)	30 (88.2)		84 (84.0)	30 (88.2)	
ISUP grading (Gleason score)						
1 (6)	60 (15.7)	0	<0.001	1 (0.9)	0 (0.0)	0.072
2 (7 [3 + 4])	129 (33.8)	1 (2.8)		9 (8.3)	1 (2.8)	
3 (7 [4 + 3])	96 (25.1)	5 (13.9)		21 (19.4)	5 (13.9)	
4 (8)	45 (11.8)	3 (8.3)		25 (23.1)	3 (8.3)	
5 (9–10)	52 (13.6)	27 (75.0)		52 (48.1)	27 (75.0)	
Positive core numbers						
Median (IQR)	5.0 (3.0–8.0)	10.0 (7.3–12.0)		10.0 (6.0–11.8)	10.0 (7.0–12.0)	
<7, *n* (%)	246 (66.4)	5 (13.9)	<0.001	30 (27.8)	6 (16.7)	0.267
≥7, *n* (%)	136 (35.6)	31 (86.1)		78 (72.2)	30 (83.3)	
NCCN risk group						
Intermediate	140 (36.6)	0	<0.001	3 (2.8)	0 (0.0)	0.586
High	117 (30.6)	3 (8.3)		10 (9.3)	3 (8.3)	
Very high	125 (32.7)	33 (91.7)		95 (88.0)	33 (91.7)	
cT stage						
<T3a	151 (39.5)	15 (41.7)	0.802	43 (39.8)	17 (47.2)	0.558
≥T3a	231 (60.5)	21 (58.3)		65 (60.2)	19 (52.8)	
Surgical type						
Open	85 (22.3)	1 (2.8)	0.006	9 (8.3)	1 (2.8)	0.429
Laparoscopic	122 (31.9)	10 (27.8)		34 (31.5)	10 (27.8)	
Robotic-assisted laparoscopic	175 (45.8)	25 (69.4)		65 (60.2)	25 (69.4)	

IDC-P: intraductal carcinoma of the prostate; PSA: prostate-specific antigen; EPE: extraprostatic extension; SVI: seminal vesicular invasion; RP: radical prostatectomy; PNI: perineural invasion; s.d.: standard deviation; NCCN: national comprehensive cancer network; cT: clinical T

Supplementary Table 5: Associations between intraductal carcinoma of the prostate in prostate biopsies and RP pathological characteristics after propensity score matching

	OR (95% CI)	*P-univariate*	*OR (95% CI)*	*P-multivariate*[*]
GS (6–7/8–10)	2.105 (0.799–5.548)	0.132	–	–
SVI	2.288 (1.061–4.932)	0.035	3.479 (0.912–13.279)	0.068
EPE	1.720 (0.754–3.924)	0.198	–	–
pT (3a)	1.771 (0.621–5.051)	0.285	–	–
PSM	2.116 (0.983–4.555)	0.055	5.682 (1.340–24.098)	0.018

[*]Multivariate analyses included IDC-P, age, PSA, gleason grade (PBx) and cT stage (complete table was in supplementary data). IDC-P: intraductal carcinoma of the prostate; RP: radical prostatectomy; PBx: prostate biopsies; GS: gleason score; SVI: seminal vesicular invasion; EPE: extraprostatic extension; PSM: positive surgical margin; OR: odds ratio; CI: confidence interval; cT: clinical T

Supplementary Table 6: Univariate and multivariate survival analyses of the association between intraductal carcinoma of the prostate in prostate biopsies and biochemical-free survival after propensity score matching

	Univariate analysis		*P*	*Multivariate analysis*		*P*
	HR	*95% CI*		*HR*	*95% CI*	
IDC-P						
0	Reference	–	–	Reference	–	–
1	2.174	1.131–4.181	0.020	2.174	1.131–4.181	0.020
Pattern 1	1.916	0.854–4.299	0.115	1.916	0.854–4.299	0.115
Pattern 2	2.568	1.099–5.998	0.029	2.568	1.099–5.998	0.029
Age						
≤70	Reference	–	–	Reference	–	–
>70	1.705	0.917–3.168	0.092	–	–	–
Baseline PSA (ng/mL)						
≤20	Reference	–	–	Reference	–	–
>20	1.018	0.537–1.929	0.956	–	–	–
Positive core numbers						
<7	Reference	–	–	Reference	–	–
≥7	0.666	0.320–1.386	0.277	–	–	–
ISUP grade						
1,2,3	Reference	–	–	Reference	–	–
4,5	0.677	0.355–1.293	0.238	–	–	–
cT stage						
<3a	Reference	–	–	Reference	–	–
≥3a	2.607	0.801–2.607	0.112	–	–	–
Adjuvant therapy						
Yes	Reference	–	–	Reference	–	–
No	0.924	0.488–1.751	0.809	–	–	–

IDC-P: intraductal carcinoma of the prostate; RP: radical prostatectomy; PBx: prostate biopsies; PSA: prostate-specific antigen; CI: confidence interval; HR: hazard ratio; cT: clinical T; ISUP: international society of urological pathology