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.

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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 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). 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. High risk was defined referring to D’Amico Risk Classification (stage ≥ T2c or PSA >20 ng ml⁻¹ or GS ≥8). 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.

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) | 0.536*|
| <70, n (%)                                           | 275 (65.8)    | 253 (66.2)            | 22 (61.1)         |       |
| ≥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) | 0.003*|
| Baseline PSA (ng ml⁻¹), mean (s.d.)                  | 50.32 (447.47) | 50.79 (468.02)        | 45.38 (33.77)     |       |
| <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)      | <0.001*|
| <7, n (%)                                            | 251 (60.0)    | 246 (66.4)            | 5 (13.9)          |       |
| ≥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*|

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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  |
| PSADP (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.

PBx IDC-P predicts prognosis in high-risk PCa

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: 2.101–6.727, 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).

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. 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
In addition, 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

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   |

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 | Model with | Increase (%) | P    |
|---------------|------------|--------------|------|
| IDC-P (%)     | IDC-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 |

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

| Characteristics | 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           | –                    | –                  |          |
| >20             | 1.861               | 1.194–2.902 | 0.006 | 1.378 | 0.851–2.234 | 0.193 |
| Positive core number |               |                      |                    |          |
| <7              | Reference           | –                    | –                  |          |
| ≥7              | 1.929               | 1.217–3.058 | 0.005 | 1.457 | 0.876–2.425 | 0.147 |
| ISUP grade      |                     |                      |                    |          |
| 1, 2, 3         | Reference           | –                    | –                  |          |
| 4, 5            | 2.289               | 1.462–3.585 | 0.000 | 1.258 | 0.731–2.167 | 0.407 |
| cT stage        |                     |                      |                    |          |
| <3a             | Reference           | –                    | –                  |          |
| ≥3a             | 1.715               | 1.031–2.851 | 0.038 | 1.763 | 1.040–2.990 | 0.035 |
| Adjuvant therapy|                     |                      |                    |          |
| Yes             | Reference           | –                    | –                  |          |
| No              | 2.058               | 1.314–3.223 | 0.002 | 1.255 | 0.754–2.090 | 0.383 |

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.
In 1998, Cohen et al.\textsuperscript{28} 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.\textsuperscript{27} This indication was proven from another angle by Kweldam et al.\textsuperscript{46} 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,\textsuperscript{44} 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.\textsuperscript{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.\textsuperscript{3,42} 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.\textsuperscript{3,43,45} 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 resistant 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.

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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 | No IDC-P | P | IDC-P | 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) |
| ≥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) |
| 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) |
| 2 (7 [3 + 4])                          | 129 (33.8)   | 1 (2.8)  |       | 9 (3.3) | 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) |
| ≥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) |
| 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) |
| ≥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) |
| 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

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