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ORIGINAL ARTICLE

Clinical significance of IDC-P as predictive factor after intensity-modulated radiation therapy

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Abstract

The clinical significance of intraductal carcinoma of the prostate (IDC-P) in men with nonmetastatic prostate cancer (PCa) treated with high-dose external-beam radiation therapy remains unclear. The aim of this study was to evaluate the impact of IDC-P in men who received intensity-modulated radiation therapy (IMRT) for nonmetastatic PCa. All patients with high-risk (H-R) and very high–risk (VH-R) PCa who received IMRT between September 2000 and December 2013 at our institution were analyzed retrospectively. We re-reviewed biopsy cores for the presence of IDC-P. Treatment consisted of IMRT (median: 78 Gy at 2 Gy per fraction) plus 6-month neoadjuvant hormonal therapy (HT). In total, 154 consecutive patients with H-R and VH-R PCa were analyzed. Intraductal carcinoma of the prostate was present in 27.9% (n = 43). The median follow-up period was 8.4 years. The 10-year PCa-specific survival, biochemical failure (BF), clinical failure, and castration-resistant PCa rates were 90.0%, 47.8%, 27.5%, and 24.5% in patients with IDC-P, and 96.6%, 32.6%, 10.8%, and 7.0% in those without IDC-P, respectively (p = 0.12, 0.04, 0.0031, and 0.012, respectively). In multivariable analysis, IDC-P was not identified as an independent predictive factor for BF (p = 0.26). The presence of IDC-P was correlated with a significantly higher incidence of disease progression in men with H-R and VH-R PCa who received IMRT, although it was not identified as an independent predictive factor for BF. Further investigations are needed to determine the significance of IDC-P as an independent predictive factor for survival outcomes.

KEYWORDS
high-risk, intensity-modulated radiation therapy, intraductal carcinoma of the prostate, prostate cancer, very high–risk

Abbreviations: A-HT, adjuvant hormonal therapy; BF, biochemical failure; CF, clinical failure; CRPC, castration-resistant prostate cancer; EBRT, external-beam radiation therapy; GG, grade group; HE, hematoxylin and eosin; HR, hazard ratio; H-R, high-risk; HT, hormonal therapy; IDC-P, intraductal carcinoma of the prostate; IMRT, intensity-modulated radiation therapy; iPSA, initial prostate-specific antigen; IQR, interquartile range; IR, intermediate-risk; ISUP, International Society of Urological Pathology; MVA, multivariable analysis; NA-HT, neoadjuvant hormonal therapy; OS, overall survival; PCa, prostate cancer; PCSS, prostate cancer–specific survival; PSA, prostate-specific antigen; RP, radical prostatectomy; S-HT, salvage hormonal therapy; UVA, univariate analysis; VH-R, very high–risk.

1 | INTRODUCTION

Prostate cancer (PCa) shows heterogenous pathological features. Intraductal carcinoma of the prostate (IDC-P) has been reported as an adverse pathological form of PCa, characterized as retrograde extension of PCa cells to pre-existing prostatic ducts.[1] Currently, the presence of IDC-P is listed as an adverse prognostic factor independent of the Gleason grading system in the current guideline of the European Association of Urology.[2]

Reports on the prognostic impact of IDC-P among men with nonmetastatic PCa who received definitive external-beam radiation therapy (EBRT) are limited, because most previous studies on nonmetastatic PCa were conducted in the setting of radical prostatectomy (RP).[3–5] To our knowledge, no prospective study has been conducted, and only two retrospective studies on definitive EBRT have been reported,[6,7] mainly involving patients with intermediate-risk (IR) PCa or those with high-risk (H-R) PCa treated with a suboptimal dose (≤70 Gy with conventional fractionation). The clinical significance of IDC-P in men with H-R and very high–risk (VH-R) PCa who received the current standard high-dose EBRT remains unclear. Therefore, we aimed to assess the impact of IDC-P in men who received intensity-modulated radiation therapy (IMRT) for H-R and VH-R PCa.

2 | MATERIALS AND METHODS

This study followed the tenets of the Helsinki Declaration, with approval from the institutional ethical review board (approval number: R1898). Written informed consent was obtained from all patients.

2.1 | Patients

We retrospectively reviewed our institutional radiotherapy database, and searched for eligible patients. The eligibility criteria were as follows: (1) nonmetastatic PCa categorized into H-R or VH-R groups at the initial diagnosis according to National Comprehensive Cancer Network risk classification ver. 2. 2019,[8] specifically, PCa with at least one of the following risk features: ≥T3a, initial prostate-specific antigen (iPSA) > 20 ng/ml, or Gleason score sum ≥8 at the initial pathological evaluation; (2) treated with conventional fractionated IMRT between September 2000 and December 2013 at our institution; (3) underwent systematic prostate needle biopsy with ≥6 cores at our institution. Patients whose biopsy had been performed at other institutions were excluded from this analysis because their histological specimens could not be re-reviewed. Patients with castration-resistant PCa (CRPC) at the initiation of IMRT were also excluded.

2.2 | Re-review of pathological specimens and pathological evaluation

Hematoxylin and eosin (HE)-stained slides of all available cores from prostate needle biopsy were systematically re-reviewed by a dedicated genitourinary pathologist (T.T.) who was blinded to the patients' information and clinical outcomes. The following pathological parameters were revised: the presence of IDC-P, cribriform pattern, perineural invasion, and grade group (GG) according to the 2014 ISUP consensus.[1] Intraductal carcinoma of the prostate was defined according to the McNeal criteria[9] and diagnosed based on HE staining.

2.3 | Treatment

We previously reported the details of our institutional treatment protocol.[10,11] In brief, treatments consisted of short-term neoadjuvant hormonal therapy (NA-HT) and IMRT.

For IMRT, only the prostate and seminal vesicles were treated with a total of 78 Gy in 39 fractions, which was reduced by 4–8 Gy in patients with risk factors for rectal bleeding. Between February 2006 and September 2009, prophylactic whole-pelvic nodal irradiation using simultaneous integrated boost IMRT was applied for a part of patients with multiple unfavorable risks, with a dose of 78 Gy for the prostate and seminal vesicles, and 58.5 Gy for the pelvic nodal area, in 39 fractions.[11]

For HT, all patients received short-term NA-HT, which basically comprised 6 months of combined androgen blockade. No adjuvant HT (A-HT) was applied.

2.4 | Patient follow-up and salvage treatment for recurrence

After the completion of IMRT, patients were followed every 1–4 months during the first 2 years and every 4–6 months thereafter. Instead of the application of long-term A-HT, patients who developed recurrence after IMRT were treated with salvage HT (S-HT) in the early phase after recurrence (basically PSA > 4.0 ng/ml). No additional radiographic study after IMRT was required, unless an increase in the PSA level or symptoms suggesting clinical failure (CF) were observed. Before initiating salvage therapy, computed tomography and bone scintigraphy were conducted. No androgen receptor axis–targeted agents or chemotherapies were used in a castration-sensitive state.

2.5 | Statistical analyses

Chi-square analysis or the Mann-Whitney U test was used to compare the characteristics of patients and treatment with versus without IDC-P. Chi-square analysis was used to compare the initial pattern of CF between patients with versus without IDC-P.

Time zero was defined as the date of IMRT initiation. The Kaplan-Meier method was used to estimate overall survival (OS) and PCa-specific survival (PCSS), and the cumulative incidence method accounting for death without each event being a competing risk was used to calculate biochemical failure (BF), CF, and CRPC. Patients

who were lost to follow-up with best supportive care due to disease progression were categorized as "died from PCa" at the time of the final visit. Biochemical failure was defined as the earliest timing of a PSA increase of >2.0 ng/ml above the nadir according to the Phoenix definition,[12] CF, or the initiation of HT due to disease progression. Clinical failure was defined as recurrent disease confirmed via radiographic studies. The definition of CRPC was as follows: PSA increase >2.0 ng/ml above the nadir with testosterone <50 ng/dl or during HT (except off-period of intermittent HT), change in the contents of S-HT due to disease progression, or CF during salvage therapy.

The Cox proportional hazard model or Fine and Gray's regression model was used to estimate the hazard ratio (HR) in univariate analysis (UVA). Multivariable analysis (MVA) using Fine and Gray's regression model was performed to evaluate the impact of the presence of IDC-P on BF. Along with the presence of IDC-P, the following reported predictive factors were included as covariates: GG (continuous), iPSA (>20 vs. ≤20 ng/ml), clinical T stage (T3–4 vs. T1–2), rate of positive core (continuous), and age at the initiation of IMRT (continuous).[13] Due to the small number of events of PCa-specific mortality, CF, or CRPC, MVA was conducted only for BF. Prior to MVA for BF, we performed

TABLE 1 Patients and treatment characteristics of the entire cohort and the cohorts stratified by the presence of IDC-P

Clinical characteristic	Total ($n = 154$)	IDC-P (+) ($n = 43$)	IDC-P (−) ($n = 111$)	p value
Age				
Median (IQR), year-old	72 (69–76)	73 (69–76)	72 (69–76)	0.75**
T stage, *n* (%)				
T1–2	48 (31.2)	6 (14.0)	42 (37.8)	0.0074*
T3a–4	106 (68.8)	37 (86.0)	69 (62.2)	
T1:T2:T3a:T3b:T4, *n*	13:35:73:30:3	0:6:22:13:2	13:29:51:17:1	
iPSA				
Median (IQR), ng/ml	23.0 (13.1–38.3)	21.7 (11.9–46.2)	23.0 (13.4–37.2)	0.97**
≤20, *n* (%)	58 (37.7)	18 (41.9)	40 (36.0)	0.63*
>20, *n* (%)	96 (62.3)	25 (58.1)	71 (64.0)	
Grade group (2014 ISUP), *n* (%)				
1	8 (5.2)	0 (0.0)	8 (7.2)	<0.001**
2	28 (18.2)	0 (0.0)	28 (25.2)	
3	14 (9.1)	0 (0.0)	14 (12.6)	
4	36 (23.4)	10 (23.3)	26 (23.4)	
5	68 (44.2)	33 (76.7)	35 (31.5)	
Positive core rate				
Median (IQR), %	50.0 (33.7–75.0)	50.0 (38.8–87.5)	50.0 (25.0–62.5)	0.0023**
Cribriform pattern, *n* (%)				
Present	72 (46.8)	34 (79.1)	38 (34.2)	<0.001*
Absent	82 (53.2)	9 (20.9)	73 (65.8)	
Perineural invasion, *n* (%)				
Present	20 (13.0)	14 (32.6)	6 (5.4)	<0.001*
Absent	134 (87.0)	29 (67.4)	105 (94.6)	
Duration of NA-HT				
Median (IQR), month	6.8 (5.4–7.9)	6.7 (5.3–8.0)	6.8 (5.5–7.9)	0.83**
IMRT dose to the prostate, *n* (%)				
78 Gy	100 (64.9)	24 (55.8)	76 (68.5)	0.231*
74 Gy	39 (25.3)	15 (34.9)	24 (21.6)	
70 Gy	15 (9.7)	4 (9.3)	11 (9.9)	
Prophylactic WPRT, *n* (%)				
Not applied	143 (92.9)	37 (86.0)	106 (95.5)	0.090*
Applied	11 (7.1)	6 (14.0)	5 (4.5)	

Note: *Chi-square test; **Mann-Whitney U test.

Abbreviations: IDC-P, intraductal carcinoma of the prostate; IMRT, intensity-modulated radiation therapy; iPSA, initial prostate-specific antigen; IQR, interquartile range; ISUP, International Society of Urological Pathology; NA-HT, neoadjuvant hormonal therapy; WPRT, whole-pelvic radiation therapy.

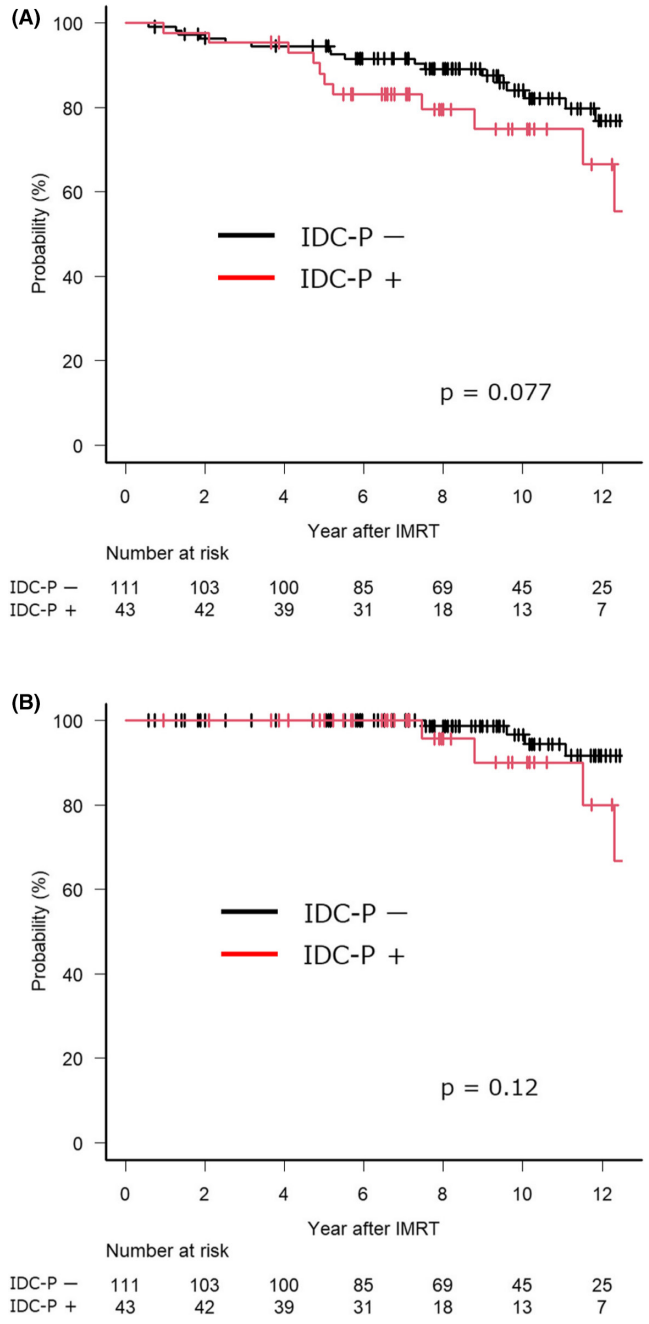

FIGURE 1 Kaplan-Meier curves for overall survival (A) and prostate cancer–specific survival (B) rates after intensity-modulated radiation therapy (IMRT) stratified by the presence of intraductal carcinoma of the prostate (IDC-P). IMRT, intensity-modulated radiation therapy

Spearman's rank-order correlation between the presence of IDC-P and GG (continuous) to eliminate the risk of multicollinearity in MVA. The calculated correlation coefficient was 0.46, leading to it being considered appropriate to include the two factors in MVA.

A P value < 0.05 denoted significance. All statistical analyses were performed using EZR version 1.41,[14] which is a graphical user interface for R version 3.6.1 (The R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Patient and treatment characteristics

We identified 172 consecutive patients who met the eligibility criteria. Among them, five patients were downgraded to unfavorable IR or lower after the re-review of histological specimens, IMRT was discontinued in two (at 38 and 66 Gy due to the patient's request or a poor general condition), and bone metastasis at the initial diagnosis was retrospectively detected in one patient. In addition, 10 patients received A-HT after the completion of IMRT. These 18 patients were excluded, and the remaining 154 patients were included in the analysis.

The median patient age was 72 (interquartile range [IQR]: 69–76) years at the initiation of IMRT. The median iPSA level was 23.0 (IQR: 13.1–38.3) ng/ml. Approximately two-thirds of patients had GG 4–5 ($n = 104$) (at the re-review) or ≥T3a disease ($n = 106$). The median number of core biopsies was 8 (IQR: 8–8). The median positive core rate was 50.0 (IQR: 33.7–75.0) %. Intraductal carcinoma of the prostate was present in 27.9% ($n = 43$). The median IDC-P positive core rate among the patients with IDC-P was 12.5 (IQR: 12.5–29.2) %. When stratified by the IDC-P status, patients with IDC-P had a significantly advanced stage or pathological features (Table 1). Of note, all patients with IDC-P had disease with ≥GG 4 PCa ($p < 0.001$). Patients' characteristics and comparisons are summarized in Table 1.

For IMRT, the median prescribed dose to the prostate was 78 (IQR: 74–78) Gy delivered at 2 Gy per fraction. Prophylactic pelvic nodal irradiation was performed in 7.1% ($n = 11$). Neoadjuvant hormonal therapy was administered to all patients with a median duration of 6.8 (IQR: 5.4–7.9) months. Treatment characteristics and comparisons are summarized in Table 1.

3.2 | Oncological outcomes and association with the presence of IDC-P

The median follow-up period was 8.4 (IQR: 6.3–11.5) years. There were nine deaths due to PCa with a median period of 10.0 (IQR: 8.8–11.5) years after IMRT, and 44.4% of these patients ($n = 4$) had IDC-P. In UVA, although not significant, the presence of IDC-P was associated with poorer OS (HR: 1.92, 95% confidence interval [CI]: 0.93–3.97, $p = 0.077$). The differences in the OS and PCSS are illustrated in Figure 1A,B. Overall survival and PCSS rates are summarized in Table 2.

During follow-up, 33.8% ($n = 52$), 13.6% ($n = 21$), and 11.0% ($n = 17$) developed BF, CF, and CRPC, with median periods of 3.2 (IQR: 1.6–5.9), 4.8 (IQR: 2.9–8.1), and 5.2 (IQR: 3.9–7.4) years after IMRT, respectively. Intraductal carcinoma of the prostate was presented in 36.5% ($n = 19$) of patients with BF, 52.4% ($n = 11$) of those with CF, and 52.9% ($n = 9$) of those with CRPC, respectively. The initial patterns of CF among the patients with IDC-P ($n = 11$) were distant metastasis in 45.4% ($n = 6$), pelvic lymph node metastasis in 36.4% ($n = 4$), both distant and pelvic lymph node

metastasis in 9.1% ($n = 1$), and local recurrence in 9.1% ($n = 1$) respectively, while those among the patients without IDC-P ($n = 10$) were distant metastasis in 40% ($n = 4$), pelvic lymph node metastasis in 40% ($n = 4$), and local recurrence in 20% ($n = 2$), respectively ($p = 0.706$). In UVA, the presence of IDC-P was significantly correlated with a higher incidence of BF (HR: 1.79, 95% CI: 1.03–3.13, $p = 0.04$), CF (HR: 3.52, 95% CI: 1.53–8.10, $p = 0.0031$), and CRPC (HR: 3.38, 95% CI: 1.31–8.74, $p = 0.012$) (Table 2). The differences in the cumulative incidences of disease progression (BF, CF, and CRPC) are illustrated in Figure 2A–C. The cumulative incidence rates of BF, CF, and CRPC are summarized in Table 2. In MVA for BF, the presence of IDC-P was not found to be an independent predictive factor with adjustment for other covariates (HR: 1.49, 95% CI: 0.74–3.00, $p = 0.26$). Meanwhile, GG (HR: 1.37, 95% CI: 1.07–1.76, $p = 0.014$), iPSA (HR: 5.78, 95% CI: 2.50–13.33, $p < 0.001$), and younger age (HR: 0.92, 95% CI:0.88–0.97, $p = 0.0016$) were detected as independent predictive factors of BF. The details of UVA and MVA for BF are summarized in Table 3.

3.3 | Oncological outcomes among ISUP GG 4–5 prostate cancer

As all patients with IDC-P had GG 4–5 disease, we additionally investigated the clinical significance of the presence of IDC-P among those with GG 4–5 disease. There were 104 patients who had GG 4–5 PCa. Among them, IDC-P was present in 41.3% ($n = 43$). On UVA, although not significant, the presence of IDC-P was associated with a higher incidence of CF (HR: 2.08, 95% CI: 0.88–4.89, $p = 0.095$). There were no significant differences in OS (HR: 1.83, 95% CI: 0.81–4.09, $p = 0.14$), PCSS (HR: 2.17, 95% CI: 0.54–8.74, $p = 0.28$), BF (HR: 1.38, 95% CI: 0.76–2.52, $p = 0.29$), or CRPC (HR: 2.37, 95% CI: 0.83–6.71, $p = 0.11$) between patients with or without IDC-P. The difference in survival outcomes and cumulative incidence of disease progression are presented in Figures 3 and 4.

4 | DISCUSSION

In the current study, we retrospectively evaluated the impact of IDC-P in men who received IMRT for H-R and VH-R PCa. The presence of IDC-P was correlated with a significantly higher rate of disease progression (BF, CF, and CRPC), although it was not detected as an independent predictive factor for BF in MVA. To the best of our knowledge, this is the first study to evaluate the clinical significance of IDC-P among patients with H-R and VH-R PCa treated with IMRT.

It has been reported that IDC-P represents an advanced stage and pathological features of a tumor, and is correlated with a higher risk of disease progression and poor survival outcome.[3,15–21] According to a population-based study of men undergoing RP, PCa patients with IDC-P showed a higher Gleason score, advanced T stage, lymph node metastases, and positive surgical margins.[15] Subsequently, IDC-P was correlated with a threefold increase in PCa-specific mortality (HR: 3.0, 95% CI: 1.5–5.7, $p < 0.01$). In the

TABLE 2 Oncological and survival outcomes of the entire cohort and the cohorts stratified by the presence of IDC-P

	Total	IDC-P (+)	IDC-P (–)	Univariate comparison IDC-P: + vs. –		
	($n = 154$)	($n = 43$)	($n = 111$)	HR	95% CI	p value
Overall survival, % (95% CI)						
5-year	92.0 (86.3–95.4)	85.6 (70.6–93.2)	94.5 (88.1–97.5)	1.92	0.93–3.97	0.077
10-year	81.5 (73.1–87.6)	74.8 (56.0–86.5)	84.0 (73.9–90.5)			
PCa-specific survival, % (95% CI)						
5-year	100.0 (N/A–N/A)	100.0 (N/A–N/A)	100.0 (N/A–N/A)	2.86	0.76–10.66	0.12
10-year	95.1 (87.3–98.2)	90.0 (65.2–97.4)	96.6 (86.7–99.2)			
Biochemical failure, % (95% CI)						
5-year	25.5 (18.8–32.7)	38.0 (23.3–52.5)	20.6 (13.5–28.8)	1.79	1.03–3.13	0.04
10-year	36.8 (28.2–45.5)	47.8 (28.2–65.0)	32.6 (23.0–42.5)			
Clinical failure, % (95% CI)						
5-year	8.0 (4.4–13.1)	18.9 (8.7–32.0)	3.8 (1.2–8.7)	3.52	1.53–8.10	0.0031
10-year	15.4 (9.4–22.8)	27.5 (12.8–44.3)	10.8 (5.1–18.8)			
CRPC progression, % (95% CI)						
5-year	5.4 (2.5–9.8)	9.4 (2.9–20.6)	3.8 (1.2–8.7)	3.38	1.31–8.74	0.012
10-year	11.5 (6.6–18.0)	24.5 (10.2–42.1)	7.0 (3.0–13.1)			

Abbreviations: 95% CI, 95% confidence interval; CRPC, castration-resistant prostate cancer; HR, hazard ratio; IDC-P, intraductal carcinoma of the prostate; N/A, not available; PCa, prostate cancer.

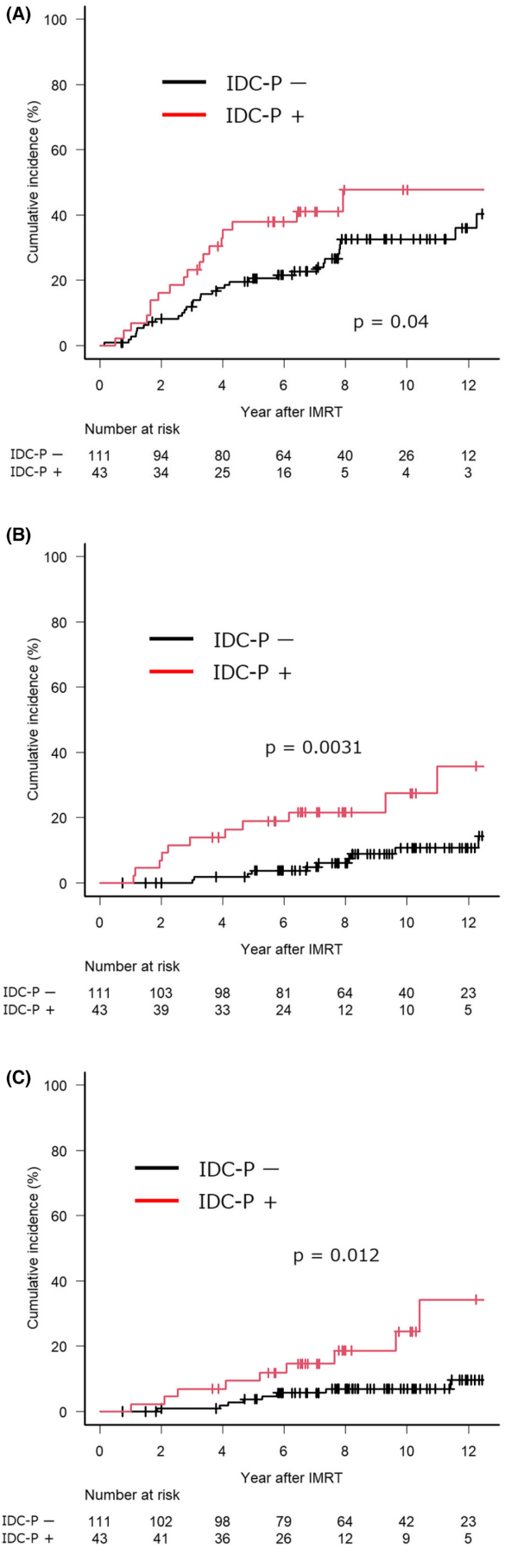

FIGURE 2 Cumulative incidence curves of biochemical failure (A), clinical failure (B), and castration-resistant prostate cancer (C) after intensity-modulated radiation therapy (IMRT) stratified by the presence of intraductal carcinoma of the prostate (IDC-P)

current study, the presence of IDC-P was correlated with aggressive and advanced PCa (Table 1), and patients with IDC-P had a significantly higher rate of BF than those without it (47.8 vs. 32.6% at 10 years, respectively, $p = 0.04$). However, the presence of IDC-P was not detected as an independent predictive factor for BF after adjustment with other unfavorable risk factors (HR: 1.49, 95% CI: 0.74–3.00, $p = 0.26$) in MVA. We propose two hypotheses to explain our negative results.

In the first hypothesis, confounding between IDC-P and other risk factors, such as high PSA levels, GG, or advanced T stage, counteracted the impact of IDC-P on BF in MVA. Our cohort consisted of H-R and VH-R PCa populations. Of note, all patients with IDC-P had GG 4–5 disease based on our pathological review. On the contrary, previous studies on definitive EBRT investigated the impact of IDC-P mainly among IR PCa patient populations.[6,7] According to a retrospective pathological review of 237 men with GG 2–3 nonmetastatic PCa treated with EBRT by Martin et al., IDC-P with a cribriform pattern was independently correlated with inferior BF-free survival (HR: 4.22, 95% CI: 2.08–8.53, $p < 0.0001$).[6] Approximately three-quarters of the patients included in that study had favorable or unfavorable IR PCa. Similarly, according to the retrospective analysis by Kwast et al., IDC-P was an independent predictive factor for early BF (< 36 months) after EBRT in their IR PCa cohort (HR: 7.26, 95% CI: 1.73–30.42, $p = 0.0067$).[7] However, among patients in their H-R PCa cohort who received EBRT (median: 70 Gy in conventional fractions) plus long-term HT, the presence of IDC-P was not detected as a predictive factor for CF-free survival after adjustment for the Gleason score in MVA (HR: 2.6; 95% CI: 0.97–7.14, $p = 0.06$), although it was significant in UVA.[7] This observation was consistent with our findings in that the difference became nonsignificant after adjustment for other risk factors. In IR PCa, the impact of IDC-P could be relatively emphasized due to a lack of other unfavorable risk factors, such as high PSA levels, high GG, or advanced T stage. On the other hand, in H-R and VH-R PCa, the effects of these unfavorable risk factors may have masked the impact of IDC-P, which subsequently led to the negative results regarding a predictive factor for disease progression in H-R and VH-R PCa. In addition, as all of our patients received short-term NA-HT alone, the incidence of BF in the current study may have been strongly affected by other unfavorable risk factors. Therefore, IDC-P may not act as an independent predictive factor for BF in H-R and VH-R PCa, despite acting as one in IR PCa.

In the second hypothesis, the negative impact of IDC-P on BF in MVA was secondary to low sensitivity for IDC-P due to sampling error via core needle biopsy. Most previous investigations regarding the impact of IDC-P after curative treatment were performed in the setting of RP.[3] Low sensitivity of needle biopsy has been reported. According to pathological investigation of 455 men who underwent prostate

TABLE 3 Univariate and multivariable analyses of risk factors for biochemical failure

	Univariate analysis			Multivariable analysis		
Factor	HR	95% CI	*p* value	HR	95% CI	*p* value
IDC-P: + vs. −	1.79	1.03–3.13	0.04	1.49	0.74–3.00	0.26
Grade group (2014 ISUP): (continuous)	1.42	1.07–1.86	0.014	1.37	1.07–1.76	0.014
Grade group 5 (2014 ISUP): + vs. −	2.78	1.59–4.86	<0.001	–	–	–
Positive core rate (continuous)	1.02	1.00–1.03	0.0068	1.00	0.99–1.01	0.69
iPSA: >20 ng/ml vs. ≤20 ng/ml	6.27	2.68–14.67	<0.001	5.78	2.50–13.33	<0.001
Clinical T stage: T3–4 vs. T1–2	1.11	0.61–2.03	0.73	0.65	0.33–1.25	0.2
Age: (continuous)	0.93	0.88–0.97	0.0017	0.92	0.88–0.97	0.0016

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; IDC-P, intraductal carcinoma of the prostate; iPSA, initial prostate-specific antigen; ISUP, International Society of Urological Pathology.

biopsy and RP, Ericson et al. reported that the sensitivity of biopsy to detect IDC-P and/or cribriform morphology was limited to 56.5%.[22] Intraductal carcinoma of the prostate and/or cribriform morphology in RP specimens was correlated with adverse pathological findings, whereas those detected in biopsy specimens were not correlated with an adverse pathology. They concluded that this conflicting result was likely due to the low sensitivity of biopsy. In the current study, IDC-P was detected in 27.9% of all patients and 41.3% of GG4–5 patients, respectively. As our pathological evaluation was based solely on needle biopsy specimens, this may have influenced our results.

Despite the limitations discussed above, our findings are novel in that IDC-P was significantly correlated with worse CRPC progression, which is considered a more appropriate surrogate for survival outcomes than BF.[23] In the current study, a more than threefold increase of HR in CRPC progression (HR: 3.38, 95% CI: 1.31–8.74, $p = 0.012$) was observed in the patients with IDC-P in UVA. Our observation was consistent with results in previous reports for metastatic PCa.[21,24,25] According to a retrospective analysis of metastatic PCa with GS 8–10 by Zhao et al., the presence of IDC-P was detected as an independent predictive factor for shorter time of CRPC (HR: 4.031, 95% CI: 1.104–14.710, $p = 0.0035$) and, subsequently, was independently correlated with poorer OS (HR: 2.499, 95% CI: 1.302–4.796, $p = 0.006$).[24] Furthermore, Yamamoto et al. reported that, even among CRPC cases (with distant metastasis at initial diagnosis), the presence of IDC-P was independently correlated with poorer cancer-specific survival (HR: 2.62, 95% CI: 1.12–6.09, $p = 0.026$).[25] These results from the current and previous investigations indicate that the presence of IDC-P is a predictive factor not only for failure after initial treatments but also for acquiring resistance to systemic therapies. Therefore, the presence of IDC-P can be a promising candidate as a predictive factor of survival outcomes among nonmetastatic PCa patients treated with definitive EBRT. The upfront use of androgen receptor axis–targeted agents or

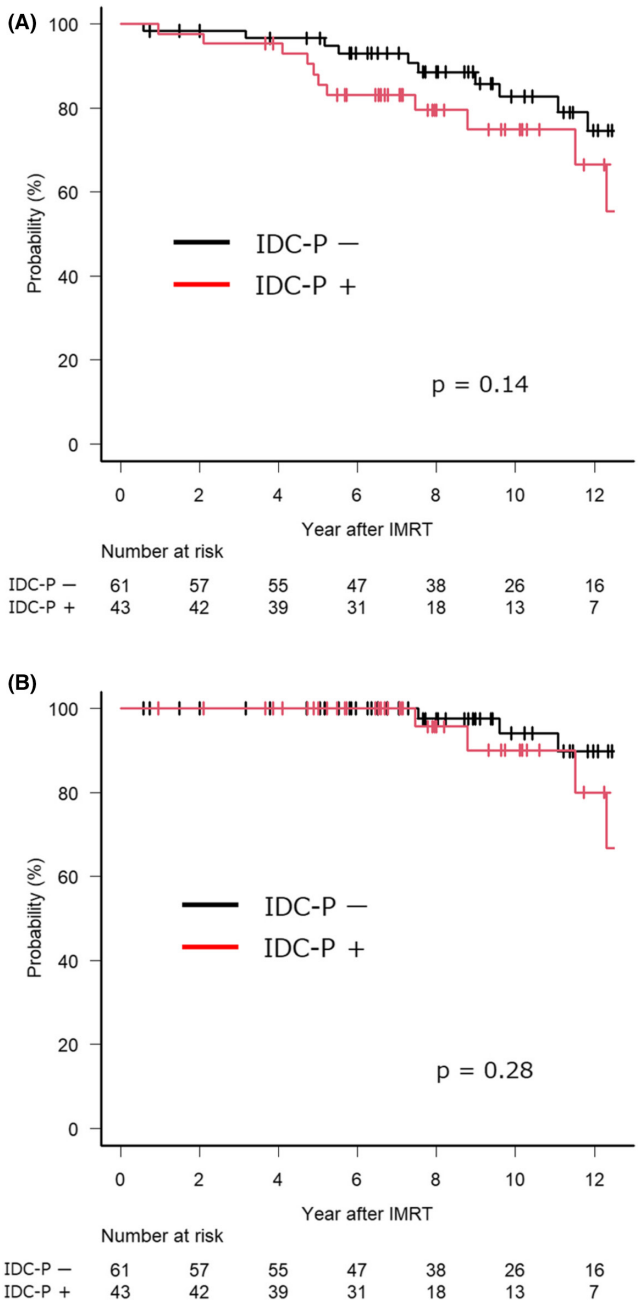

FIGURE 3 Kaplan-Meier curves for overall survival (A) and prostate cancer–specific survival (B) rates among grade group 4–5 prostate cancer after intensity-modulated radiation therapy (IMRT) stratified by the presence of intraductal carcinoma of the prostate (IDC-P)

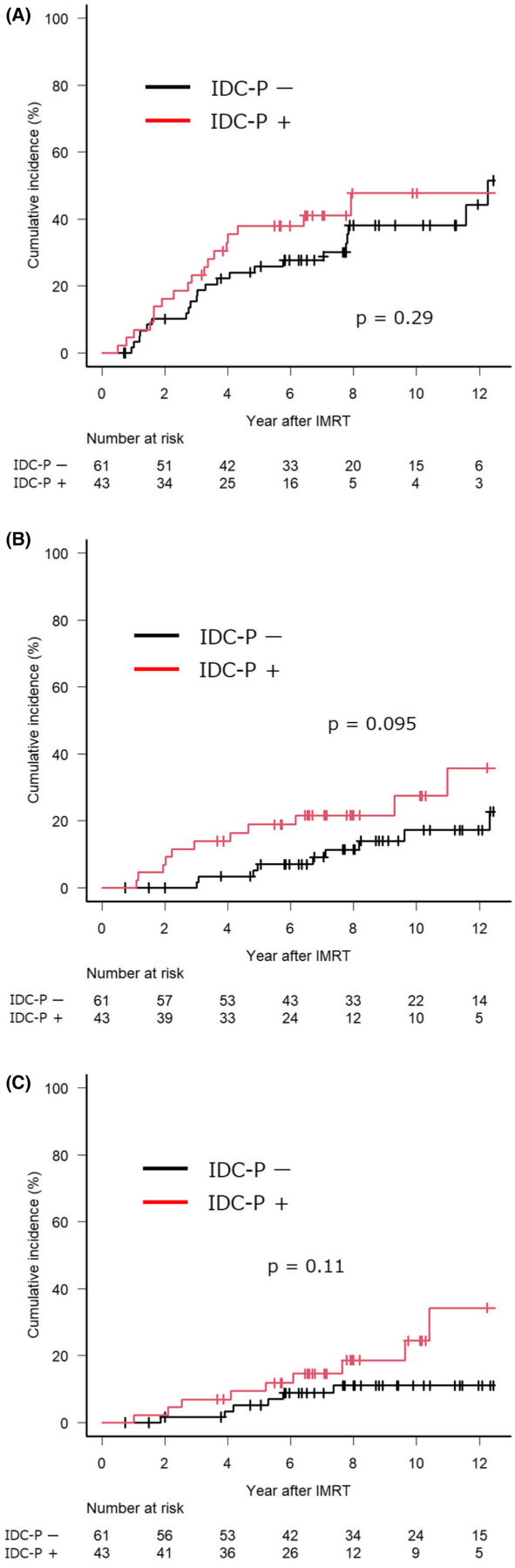

FIGURE 4 Cumulative incidence curves of biochemical failure (A), clinical failure (B), and castration-resistant prostate cancer (C) in grade group 4–5 prostate cancer after intensity-modulated radiation therapy (IMRT) stratified by the presence of intraductal carcinoma of the prostate (IDC-P)

docetaxel for hormone-sensitive metastatic PCa patients yielded better oncologic outcomes in several recent randomized controlled trials.[26] Although speculative, the use of those agents in combination with EBRT may be a promising therapeutic strategy against PCa with IDC-P. Our findings should be further investigated from the aspects of both diagnostic significance and treatment strategy for patients with IDC-P, especially in the setting of prospective trials with larger cohorts.

Our study had several limitations, including its retrospective nature and analysis of only a small cohort. Firstly, the pathological review was performed solely using HE-stained slides of needle biopsy specimens, and immunohistochemical staining to detect IDC-P was not applied. However, according to the current consensus, immunohistochemical staining is not essential for diagnosis of IDC-P.[27] Therefore, our results can be applied to current daily clinical practice. Secondly, we performed MVA only for BF due to a small number of events. Lastly, as discussed above, our patients only received short-term NA-HT (median: 6.8 months) because we designed the treatment protocol before the combination of long-term A-HT for unfavorable PCa was established as the standard of care. Our results may not be applicable to patients treated with the current standard long-term HT. However, instead of the application of long-term A-HT, patients were salvaged early after BF (PSA>4.0 ng/mL). This early salvage method was shown to be a viable alternative to long-term A-HT among locally advanced PCa patients who received definitive EBRT in a phase III randomized controlled trial: nonmetastatic CRPC-free survival rate at 5 years, 84.8% in the long-term A-HT group versus 82.8% in the early S-HT group ($p = 0.5619$).[28] Therefore, our results are consequently considered appropriate for assessing CRPC rates and survival outcomes, although those regarding BF may be partly limited by the lack of long-term A-HT, as discussed above. For these reasons, our findings regarding the clinical significance of IDC-P are not conclusive but merely hypothesis generating. Nevertheless, we believe that our results provide baseline data on the clinical significance of IDC-P among H-R and VH-R PCa patients treated with IMRT, as well as a focal point for further research in this area. Given the paucity of evidence based on prospective trials assessing the significance of IDC-P, these findings are of particular importance.

In conclusion, this study showed that the presence of IDC-P was correlated with a significantly higher incidence of disease progression in men with H-R and VH-R PCa who received IMRT, although it was not detected as an independent predictive factor. Further investigations are warranted to confirm our findings.

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DISCLOSURE

The authors have no conflict of interest. This document has been checked by a professional medical editor, who is a native speaker of English.

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