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Original Article

Heterogeneous clinicopathological features of intraductal carcinoma of the prostate: a comparison between "precursor-like" and "regular type" lesions

Kosuke Miyai[1], Mukul K Divatia[1], Steven S Shen[1,3], Brian J Miles[2], Alberto G Ayala[1,3], Jae Y Ro[1,3]

[1]Department of Pathology and Genomic Medicine, [2]Department of Urology, Houston Methodist Hospital, [3]Weill Cornell Medical College of Cornell University, Houston, TX, USA

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Abstract: Intraductal carcinoma of the prostate (IDC-P) has been described as a lesion associated with intraductal spread of invasive carcinoma and consequently aggressive disease. However, there are a few reported cases of pure IDC-P without an associated invasive component, strongly suggesting that this subset of IDC-P may represent a precursor lesion. We compared the clinicopathological features between the morphologically "regular type" IDC-P and "precursor-like" IDC-P. IDC-P was defined as follows; 1) solid/dense cribriform lesions or 2) loose cribriform/micropapillary lesions with prominent nuclear pleomorphism and/or non-focal comedonecrosis. We defined precursor-like IDC-P as follows; 1) IDC-P without adjoining invasive adenocarcinoma but carcinoma present distant from the IDC-P or 2) IDC-P having adjoining invasive microcarcinoma (less than 0.05 ml) and showing a morphologic transition from high-grade prostatic intraepithelial neoplasia (HGPIN) to the IDC-P. IDC-P lacking the features of precursor-like IDC-P was categorized as regular type IDC-P. Of 901 radical prostatectomies performed at our hospital, 141 and 14 showed regular type IDC-P and precursor-like IDC-P in whole-mounted specimens, respectively. Regular type IDC-P cases had significantly higher Gleason score, more frequent extraprostatic extension and seminal vesicle invasion, more advanced pathological T stage, and lower 5-year biochemical recurrence-free rate than precursor-like IDC-P cases. Multivariate analysis revealed nodal metastasis and the presence of regular type IDC-P as independent predictors for biochemical recurrence. Our data suggest that IDC-P may be heterogeneous with variable clinicopathological features. We also suggest that not all IDC-P cases represent intraductal spread of pre-existing invasive cancer, and a subset of IDC-P may be a precursor lesion.

Keywords: Prostate, intraductal carcinoma of prostate, high-grade prostatic intraepithelial neoplasia

Introduction

Intraductal carcinoma of the prostate (IDC-P) is characterized by a proliferation of malignant secretory cells within prostatic duct/acini that demonstrates marked architectural and cytologic atypia [1-5]. Four histological subtypes of IDC-P have been described including solid, dense cribriform (less than 50% lumen in a duct), loose cribriform (more than 50% lumen in a duct), and micropapillary. The first diagnostic criterion is a solid or dense cribriform pattern. If the first criterion is not present, a diagnosis of IDC-P can still be made if loose cribriform or micropapillary pattern exhibits one of the following changes: a) prominent nuclear pleomorphism (nuclear size greater than 6x normal) or b) non-focal comedonecrosis (>1 duct showing comedonecrosis) [6]. It has been observed that the concurrent invasive adenocarcinoma in IDC-P is associated with high Gleason score, large tumor volume, extraprostatic extension of carcinoma, positive surgical margins, and accelerated disease progression [1, 5-9]. Therefore, a number of studies have advocated that if IDC-P is diagnosed in a biopsy specimen, an immediate re-biopsy or even definitive therapy is recommended in the absence of documented invasive carcinoma [6, 7].

As diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN) also encompass architectural complexity and cytologically

atypical cells within prostatic ducts/acini, the relationship between HGPIN and IDC-P has been debated. HGPIN, a well-recognized neoplastic precursor lesion of invasive cancer, is often present in glands as an isolated lesion that has not yet developed invasive cancer [10]. In contrast, IDC-P has been reported to be almost always associated with invasive high-grade cancer [10-12].

Several molecular studies by using allelotyping analysis, comparative genomic hybridization (CGH), and analysis of *ETS* gene aberrations have shown that IDC-P harbors genetic changes that are more commonly seen in Gleason pattern 4/5 cancers than in HGPIN or Gleason pattern 3 cancers [13-15]. Based on these morphologic and molecular evidences, IDC-P has been reported to be closely associated with high-grade invasive adenocarcinoma. In this context, IDC-P most likely represents intraductal spread of corresponding high-grade invasive carcinoma as a late event of prostate carcinogenesis but conversely may represent the initial pre-invasive carcinogenic event as HGPIN.

Thus, there is a broad morphologic spectrum between HGPIN and IDC-P, especially lesions with a cribriform architecture. McNeal et al observed that, in some cases, there were "transitive glands" resembling IDC-P associated with HGPIN [16-18]. Similar results have been reported in the Lo-MYC and Hi-MYC transgenic mouse model [19]. The authors state that intraductal cribriform lesions resembling IDC-P represent an intermediate step in progression from HGPIN to microinvasive carcinoma in mice, and this progression is triggered by MYC overexpression [19]. In addition, a few cases of solitary IDC-P without an associated invasive carcinoma have been reported [7, 20]. These findings suggest that at least a subset of IDC-P may act as a precursor lesion in the HGPIN pathway of invasive cancer or possibly as a separate *de novo* pathway. Although rare cases of "precursor-like" IDC-P have been described in previous studies [7, 20], the difference of clinicopathological significance between regular and precursor-like types of IDC-P has never been investigated.

In the present study, we reviewed the histologic features of 901 consecutive radical prostatectomy specimens prepared by the whole mount specimen technique and recorded the presence of regular type and precursor-like IDC-P. The presence of regular type and precursor-like IDC-P was correlated with patient's age, important tumor pathologic parameters, and status of biochemical recurrence with the aim of determining clinicopathological significance of precursor-like IDC-P. These data would allow us to determine whether these two types of IDC-P have a similar clinical significance or not, and would be helpful to in further elucidating the complex pathogenesis of IDC-P.

Materials and methods

Cases and clinical information

This study was approved by Houston Methodist Hospital Institutional Review Board. The series consisted of 901 prostate cancer cases which were retrieved from the files of the Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, USA. All patients underwent radical prostatectomy operated by a single surgeon between 2006 and 2012, and none had received preoperative hormonal or radiation therapies. In keeping with previously established protocols [21, 22], biochemical recurrence was defined as serum prostate specific antigen (PSA) ≥0.2 ng/ml after a previously undetectable serum PSA value.

Histological evaluation

All radical prostatectomy specimens were processed using a standard protocol in our institution. A transverse cut was made through the mid portion of the prostate and small samples of tissue were taken for tissue banking. The prostate was then approximated and glued together using super glue. Subsequently, the prostate was placed in neutral buffered formalin, and allowed to fix for at least 24 hours. Following formalin fixation, the prostate was inked to identify laterality. The apical and bladder neck margins were removed and radially sectioned in a cervical cone-like fashion. The seminal vesicles were amputated, sliced, and entirely submitted, except for a small fragment that is immediately frozen and saved as normal control. The sections of the apex, bladder neck, and seminal vesicles (average: 13 sections) were submitted entirely as conventional small tissue blocks. The remainder of the specimen was transversely cut at 3-5 mm intervals from

apex to base and submitted as whole-mount sections (mean, 5 sections; range, 4-8 sections). Hematoxylin-eosin (H&E) stained slides were prepared from each paraffin block.

All slides were then marked with ink during microscopic evaluation to outline the boundaries of all foci of invasive carcinoma and IDC-P. A map of areas with invasive cancer was used to determine cancer volume (a percentage of invasive tumor volume in a total of prostate volume). The volume of the prostate was calculated using the formula for a prolate ellipsoid, defined as length×height×width×0.523 (correction factor for a prolate ellipsoid) [23]. Invasive cancer volume was calculated by the grid method [23]. Briefly, a transparent grid of premeasured squares (0.3 cm) was placed over the slides, and the number of squares overlying carcinoma was counted; the total number of squares per case is multiplied by the area of each square (0.09 cm^2), and the sum was multiplied by the thickness of each slide of the prostatectomy. Slice thickness was calculated by dividing the measurement of the long axis of the prostate minus 6 mm for conization by the total number of slices of the prostate. Based on previously published criteria [17, 18], microcarcinoma was designated as any cancer with a greatest dimension of 4 mm or less confined to a single level of section or a sum of 5 mm between two adjacent sections. All microcarcinomas were less than 0.05 ml in volume. According to the updated criteria of Gleason scoring [24, 25], all cases were subdivided to two groups: total Gleason score of prostatectomy specimen was <8 or ≥8. Pathological T (pT) staging of disease was performed according to the 7th American Joint Committee on Cancer (AJCC) Staging Manual [26]. Patients were categorized into two subgroups; pT2 or pT3-4. Positive surgical margin, lymphovascular invasion, extraprostatic extension, seminal vesicle invasion, and lymph node metastasis were tabulated as "present" or "absent."

Regular type and "precursor-like" IDC-P

Presence of IDC-P was recorded on H&E stained sections by two genitourinary pathologists (KM and JYR) using previously published criteria [6, 27-30]. IDC-P was defined as one or both of following patterns; 1) solid/dense cribriform lesions or 2) loose cribriform or micropapillary lesions with prominent nuclear pleomorphism (i.e. nuclear size greater than 6x normal) and/or non-focal comedonecrosis (>1 duct showing comedonecrosis). When IDC-P was detected, the percentage of IDC-P component in a total volume of tumor (i.e. a total volume of IDC-P and adjoining invasive carcinoma) was also recorded. According to the previously published criteria [27], adjoining invasive carcinoma was defined as carcinoma intermixed with IDC-P or within 3mm distant from the border of IDC-P. We defined precursor-like IDC-P as one of following patterns: 1) IDC-P without identifiable adjoining invasive carcinoma or 2) IDC-P having adjoining invasive microcarcinoma and showing a clear morphologic transition from HGPIN to typical IDC-P (**Figure 1**). The morphologic transition from HGPIN to IDC-P was designated that typical morphologic findings of HGPIN and IDC-P were intermixed within a single intraductal lesion. IDC-P which did not fulfill the above criteria of precursor-like IDC-P was categorized as regular type IDC-P. HGPIN was morphologically represented by the presence of both of the following patterns: 1) an intraductal proliferation with flat, tufting, micropapillary, or loose cribriform architecture and with nucleoli easily visible at ×20 magnification, and 2) a lesion involving ≤6 glands involvement, less than 1 mm in size, and glands without a branching/irregular contour [10]. HGPIN which did not show the morphologic transition to IDC-P was also recorded. When basal cells were not clearly identified on H&E stained sections (i.e. only for conventional small slides of apical, bladder neck, and seminal vesicles), immunohistochemical staining for high molecular weight cytokeratin (HMWCK) and p63 was performed to confirm the presence of basal cells. The staining was performed using automatic strainers from Ventana (Ventana Medical Systems, Tucson, AZ) with an enzyme-conjugated polymer complex. The primary antibodies and their dilutions were as follows: HMWCK 1:200 (Dako, Carpinteria, CA) and p63 1:100 (Neomarker, Fremont, CA).

Statistical analysis

The association between parameters linked with regular type or precursor-like IDC-P and other clinicopathologic parameters of known prognostic significance (i.e. Gleason score, tumor volume, surgical margin status, lymphovascular invasion, extraprostatic extension, seminal vesicle invasion, pT stage, lymph node

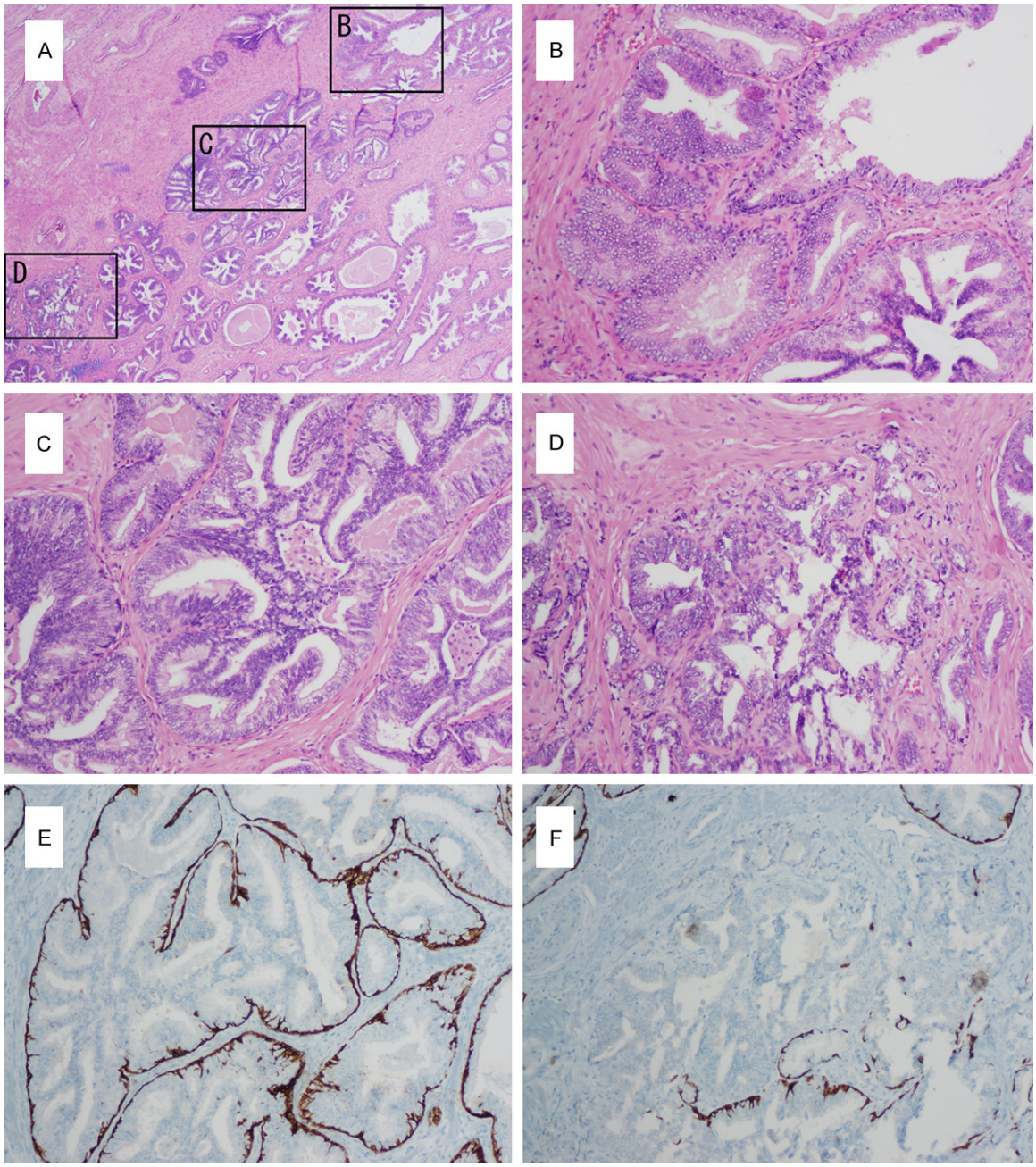

Figure 1. Precursor-like intraductal carcinoma of the prostate (IDC-P). (A) A case with a intraductal lesion having adjoining invasive microcarcinoma and showing recognizable morphologic transition from high-grade prostatic intraepithelial neoplasia (HGPIN) to IDC-P. (B) HGPIN component. (C) IDC-P component with dense cribriform pattern and necrosis. (D) Invasive microcarcinoma component with Gleason patterns 3 and 4. Immunohistochemical staining for high molecular weight cytokeratin highlighting the presence of basal cells in IDC-P component (E) and the absence of basal cell in invasive microcarcinoma component (F). Hematoxylin and eosin stain, original magnification ×20 for (A) and ×100 for (B-D). Immunoperoxidase stain, original magnification ×100 for (E and F).

metastasis) were analyzed by the chi square test, Fisher's exact test, or the Mann-Whitney *U* test. Biochemical recurrence rate was calculated using the Kaplan-Meier method, and comparisons were made using the log-rank test. Cox proportional hazards regression analysis was used to determine the impact of the types of IDC-P (i.e. regular type or precursor-like IDC-P) and other clinicopathological parameters on biochemical recurrence. Statistical calculations

Table 1. Comparison of clinicopathological variables of regular type and precursor-like IDC-P

Variables	Types of IDC-P		*P* value
	Regular (n = 141)	Precursor-like (n = 14)	
Mean age (year)	63	63	0.98
The presence of HGPIN[a] (%)	70 (50)	10 (71)	0.10
Gleason score ≥8 (%)	73 (52)	3 (21)	**0.027**
Mean % tumor volume	30	23	0.052
Positive surgical margin (%)	26 (18)	3 (21)	0.74
Lymphovascular invasion (%)	15 (11)	0 (0)	0.22
Extraprostatic extension (%)	64 (45)	1 (9)	**0.0040**
Seminal vesicle invasion (%)	41 (29)	0 (0)	**0.010**
Pathological T stage ≥3 (%)	75 (53)	1 (9)	**0.00073**
Lymph node metastasis (%)	16 (11)	0 (0)	0.20
5-year BCR-free rate	61%	93%	**0.0032**

BCR, biochemical recurrence; HGPIN, high-grade prostatic intraepithelial neoplasia; IDC-P, intraductal carcinoma of the prostate. [a]HGPIN without the morphologic transition to IDC-P. Bold values indicate statistical significances.

were performed using R software (version 2.8.1). Differences at $P<0.05$ were considered statistically significant.

Results

Among 901 cases, 155 (17.2%) cases showed IDC-P which fulfilled the diagnostic criteria. The mean percentage of IDC-P in a total volume of tumor (i.e. a total volume of IDC-P and adjoining invasive carcinoma) ranged from 5 to 95% with a mean of 30% (median, 20%). In 155 cases with IDC-P, 90 cases showed HGPIN which fulfilled the diagnostic criteria. Of these, 73 cases showed HGPIN without the morphologic transition to IDC-P, 10 cases showed HGPIN with the morphologic transition to IDC-P, and 7 cases had both types of HGPIN. In 17 cases which had HGPIN showing the morphologic transition to IDC-P, all these intraductal lesions had adjoining invasive carcinoma: 11 microcarcinomas and 6 invasive carcinomas which did not fulfilled criteria of microcarcinoma. In 155 cases with IDC-P, 141 were categorized as regular type and 14 as precursor-like IDC-P. The mean (median; range) age of the patients with regular IDC-P was 63 years (63.0; 49 to 78) and for precursor-like IDC-P was 63 years (63.5; 54 to 70). Among 14 cases with precursor-like IDC-P, 3 cases did not show adjoining invasive cancer; however, at least one focus of invasive carcinoma was present but distant from IDC-P (i.e. no examined case with IDC-P completely lacked invasive carcinoma). The 11 remaining cases had IDC-P with adjoining invasive microcarcinoma and the morphologic transition from HGPIN to IDC-P. In all 11 cases, the percentages of IDC-P in a total volume of tumor were more than 80%. These cases showed at least one focus of invasive carcinoma which did not fulfilled criteria of microcarcinoma, but these carcinomas were distant from IDC-P.

Relationship between clinicopathological parameters and types of IDC-P

Clinicopathological parameters in regular type and precursor-like IDC-P are summarized in **Table 1**. HGPIN without the morphologic transition to IDC-P was observed in 70 (50%) cases with regular type IDC-P and in 10 (71%) cases with precursor-like IDC-P; no statistically significant difference between the two groups was observed ($P = 0.10$). Prostate cancer with Gleason score 8 or more on the prostatectomy specimen was observed in 73 (52%) cases with regular type IDC-P and in 3 (21%) cases with precursor-like IDC-P; a statistically significant difference between the two groups ($P = 0.027$) was observed. The mean (median; range) percentages of invasive tumor volume in the total of prostate volume were 30% (20; 5 to 95) in patient with regular type IDC-P and 23% (10; 5 to 85) in patients with precursor-like IDC-P. There was no significant difference in the frequency of invasive tumor volume between cases with regular type and precursor-like IDC-P ($P = 0.052$). Positive surgical margin status was observed in 26 (18%) cases with regular type IDC-P and in 3 (21%) with precursor-like IDC-P. Lymphovascular invasion was detected in 15 (11%) with regular type IDC-P and in none of cases with precursor-like IDC-P. There was no significant difference in the frequency of positive surgical margin and lymphovascular invasion between cases with regular type and precursor-like IDC-P ($P = 0.74$ and $P = 0.22$, respectively). Extraprostatic extension and seminal vesicle invasion were detected in 64 (45%) and 41 (29%) cases with regular type IDC-P and 1 (9%) and no (0%) cases with precursor-like IDC-P, respectively. The frequencies of extraprostatic extension and seminal

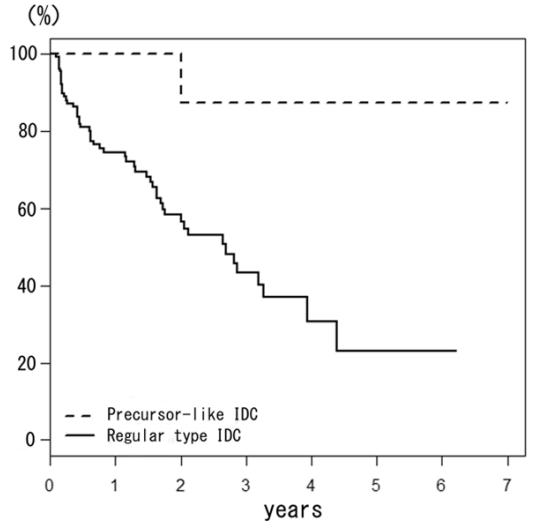

Figure 2. Kaplan-Meier estimates of biochemical recurrence-free survival for 151 patients with intraductal carcinoma of the prostate (IDC-P), stratified by regular type or precursor-like IDC-P. Solid line curve for cases with regular type IDC-P (n = 137), and dashed line curve for cases with precursor-like IDC-P (n = 14).

vesicle invasion were significantly higher in cases with regular type IDC-P than those in cases with precursor-like IDC-P (P = 0.0040 and P = 0.010, respectively). With respect to pT stage of the prostatectomy specimen, 75 (53%) regular type IDC-P cases and 1 (9%) precursor-like IDC-P case were staged as pT3 or pT4 (P = 0.00073). Lymph node metastasis was detected in 16 (11%) cases with regular type IDC-P and in none of the cases with precursor-like IDC-P (P = 0.20).

Biochemical recurrence

Follow-up was available on 151 of 155 patients with IDC-P (mean 28 months (mos), median 24 mos, range: 1 to 86 mos). 55 of 151 (36%) patients experienced biochemical recurrence during follow-up: 54 of 137 patients with regular type IDC-P and 1 of 14 patients with precursor-like IDC-P. The 5-year biochemical recurrence-free rates were 61% and 93% in patients with regular type IDC-P and precursor-like IDC-P, respectively. Biochemical recurrence curves for 151 patients with IDC-P, stratified by types of IDC-P are presented in **Figure 2**. The type of IDC-P was significantly associated with the risk of biochemical recurrence based on log-rank test (P = 0.0032).

Cox univariate analysis including 8 parameters showed that lymphovascular invasion (P = 0.011), extraprostatic extension (P = 0.011), seminal vesicle invasion (P = 0.0018), advanced pT stage (P = 0.0016), lymph node metastasis (P<0.0001), and presence of regular type IDC-P (P = 0.018) were correlated with biochemical recurrence (**Table 2A**). Cox multivariate analysis including these 6 variables identified that presence of regular type IDC-P (P = 0.044) and nodal metastasis (P<0.0001) are the only two independent predictors for biochemical recurrence (**Table 2B**).

Discussion

In clinical and pathologic parlance, IDC-P is a distinct entity and should be distinguished from HGPIN, a well-known precursor lesion of invasive prostate carcinoma [1, 4-10]. In contrast to HGPIN, the pathogenesis of IDC-P is still a matter of debate. McNeal et al [1] investigated 51 prostate cancers with IDC-P and reported that IDC-P was almost never seen in the absence of invasive carcinoma, and the corresponding invasive component was usually high grade (Gleason score 8 or more than 8). In addition, invasive carcinomas with IDC-P had a significantly worse prognosis than those without IDC-P component. Using polymorphic markers, Dawkins et al [13] reported that loss of heterozygosity (LOH) was not present in Gleason pattern 3 cancer, infrequent in HGPIN (9%) and Gleason pattern 4 cancer (29%), but common in IDC-P (60%). Bettendorf et al [14] analyzed HGPIN, IDC-P, and invasive carcinoma by employing an allelotyping study for LOH on *TP53* and *RB1* genes and by CGH. LOH on both genes was detected frequently in IDC-P (52%), and tumor tissue in extraprostatic extension (44%), and rarely in HGPIN (19%) and benign prostatic tissue (17%). On CGH analysis, 8 (73%) of 11 IDC-P cases showed chromosomal imbalances in contrast to HGPIN where lacked chromosomal imbalances. Han et al [15] used break-apart fluorescence *in situ* hybridization to assess *ETS* gene aberrations, the most common of which is the *EMPRSS2-ERG* fusion in prostate cancer, in a cohort of 16 cribriform HGPIN and 48 IDC-P. *ERG* gene rearrangement was found in 75% (36 of 48) of IDC-P components and in none (0 of 16) of HGPIN components, and the *ERG* gene status was highly concordant between IDC-P and adjacent invasive

Table 2. Cox regression model estimates of the significance of predictive factors for biochemical recurrence

Variables	*P*-value	RR (95% CI)
A. Univariate Cox regression model		
Gleason score (≥8 vs. <8)	0.051	1.71 (1.00-2.95)
Positive surgical margin	0.13	1.63 (0.87-3.06)
Lymphovascular invasion	**0.011**	2.84 (1.27-6.36)
Extraprostatic extension	**0.011**	2.02 (1.18-3.45)
Seminal vesicle invasion	**0.0018**	2.44 (1.40-4.27)
Pathological T stage (2 vs. 3 or more)	**0.0016**	2.48 (1.41-4.35)
Lymph node metastasis	**<0.0001**	7.75 (3.75-16.00)
Regular type IDC-P (vs. precursor-like IDC-P)	**0.018**	11.01 (1.51-80.33)
B. Multivariate Cox regression model		
Lymphovascular invasion	0.66	1.22 (0.49-3.02)
Extraprostatic extension	0.67	0.82 (0.33-2.04)
Seminal vesicle invasion	0.80	1.10 (0.52-2.34)
Pathological T stage (2 vs. 3 or more)	0.36	1.66 (0.57-4.87)
Lymph node metastasis	**<0.0001**	5.33 (2.36-12.05)
Regular type IDC-P (vs. precursor-like IDC-P)	**0.044**	7.96 (1.05-60.01)

CI, confidence interval; IDC-P, intraductal carcinoma of the prostate; RR, relative risk. Bold values indicate statistical significances.

prostate cancer. These morphologic and molecular genetic evidences have suggested that IDC-P represents a late-stage intraductal spread of adjusting high-grade invasive carcinoma.

However, a few cases of IDC-P without an associated invasive carcinoma element have been reported [7, 20]. In a series of 107 incidental microcarcinomas (less than 0.05 cm^3), McNeal et al [17] detected that 51 cases had strong evidence of transition between microcarcinoma and HGPIN through a characteristic intermediate morphologic stage of transitive glands, some of which resembled IDC-P. Recently, Iwata et al [19] reported a novel morphologic "intermediate step" between HGPIN and invasive carcinoma in the Lo-MYC and Hi-MYC transgenic mouse model, which develop HGPIN and invasive carcinoma as a result of MYC overexpression in the mouse prostates. The intermediate step lesion called cribriform prostatic intraepithelial neoplasia/carcinoma *in situ* (PIN/CIS) in their study showed dense cribriform pattern with marked nuclear atypia and morphologically resembled IDC-P [19]. Under MYC overexpression, the cribriform PIN/CIS demonstrated a spectrum of progression from HGPIN to microinvasive carcinoma in mice. In our study, we found 3 cases with isolated IDC-P that were not related to an accompanying invasive carcinoma component and 11 cases with IDC-P which had adjoining invasive microcarcinoma and showed clear morphologic transition from HGPIN to typical IDC-P. These rare cases with precursor-like IDC-P components suggest that a subset of IDC-P might represent a precursor lesion in the spectrum of consecutive pathway from HGPIN to invasive cancer or possibly as a separate *de novo* pathway.

In the present study, cases with regular type IDC-P components showed higher Gleason score (≥8; $P = 0.027$), more frequent extraprostatic extension ($P = 0.040$) and seminal vesicle invasion ($P = 0.010$), and more advanced pT stage ($P = 0.00073$) than cases with precursor-like IDC-P components. Cases with regular type IDC-P were significantly associated with the high risk of biochemical recurrence over cases with precursor-like IDC-P based on log-rank test ($P = 0.0032$). In addition, Cox multivariate analysis showed that apart from nodal metastasis, the presence of regular IDC-P was the only other independent predictor for biochemical recurrence. These data indicate that IDC-P might be composed of heterogeneous groups of lesions with variable clinicopathological features and outcomes. Further molecular genetic studies are needed to confirm the hypothesis that at least some IDC-P lesions represent a true precursor lesion of invasive carcinoma, similar to that of atypical complex hyperplasia of endometrium and ductal carcinoma in situ of breast [31, 32].

Studies have documented that the presence of IDC-P is associated with multiple adverse prognostic factors, thus it is important to recognize and to report the presence of IDC-P in radical prostatectomy samples [1, 5-9]. In general, the various growth patterns of IDC-P fall into Gleason pattern 4/5 categories of the 2005 modified Gleason grading scheme [9]. McNeal

et al [1] found that invasive cancers with minimal IDC-P components did not appear to belong in a morphologically or prognostically different group from invasive cancers without IDC-P and suggested an arbitrary minimum value of 10% IDC-P component of a total cancer volume, or at least 0.5 cm^3 to qualify a tumor as having this type of intraductal lesion. Therefore, some authors indicated that given its prognostic significance, the amount or percent of IDC-P should be reported in radical prostatectomy specimen as well [9]. However, our data suggest that even if a significant amount or percentage of IDC-P fulfilling the previously published criteria is observed, cases with precursor-like IDC-P do not always have an aggressive behavior or poor prognosis. We propose that IDC-P cases with no identifiable adjoining invasive cancer or cases with morphologic transition between HGPIN and IDC-P should be included in the present diagnostic criteria of IDC-P.

In summary, the present data demonstrate that precursor-like IDC-P is rarely identified in radical prostatectomy specimen, and patients with precursor-like IDC-P show better clinicopathological behavior and less frequent biochemical recurrence than patients with regular type IDC-P. Our results suggest that IDC-P does not always represent intraductal spread of preexisting high-grade invasive carcinoma, and at least a subset of IDC-P could account for a precursor lesion of invasive carcinoma, akin to HGPIN.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jae Y Ro, Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Weill Cornell Medical College of Cornell University, 6565 Fannin Street, Suite M227, Houston, TX 77030, USA. Tel: +1-713-441-2263; Fax: +1-713-793-1603; E-mail: jaero@houstonmethodist.org

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