Title: The influence of the presence of intraductal carcinoma of the prostate on the grade group system's prognostic performance

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Abstract

Background: Although the presence of intraductal carcinoma of the prostate (IDC-P) influences biochemical failure in radical prostatectomy patients, no data are available regarding the impact of its integration into the classification grade group system. Thus, the aim of this study was to enhance the utility of the grade group system by integrating the presence of IDC-P.

Methods: This study was a retrospective evaluation of 1019 patients with prostate cancer who underwent radical prostatectomy between 2005 and 2013 without neoadjuvant or adjuvant therapy. Data on age, prostate-specific antigen (PSA) level at diagnosis, pathological T stage (pT), presence of Gleason pattern 5 (GP5), presence of IDC-P, and surgical margin status were analyzed to predict PSA recurrence after prostatectomy.

Results: The median patient age was 67 (range, 45–80) years and the median initial PSA level was 6.8 (range, 0.4–82) ng/ml. The median follow-up period was 82 (range, 0.7–148) months. IDC-P was detected in 157 patients (15.4%). Among these patients, the increase in the positive rate of IDC-P correlated with tumor upgrading. The grade groups (GGs) were as follows: GG1 without IDC-P, 16.0% (n=163); GG2 without IDC-P, 46.1% (n=470); GG3 without IDC-P, 15.7% (n=160); GG4 without IDC-P, 2.6% (n=27); GG5 without IDC-P, 4.1% (n=42); any GG with IDC-P, 15.4% [n=157; GG 2 (n=29); GG3 (n=60); GG4 (n=13); GG5 (n=55)]. Any grade Group with IDC-P showed a significantly worse prognosis than any other group without IDC-P ($p< 0.0001$). In a multivariate analysis,

integration of the IDC-P into the Grade Groups, the PSA level at diagnosis, and the surgical margin status were significant prognostic predictors (P < 0.0001, < 0.0001 and < 0.0001 respectively).

Conclusions: Integrating the presence of IDC-P into the grade group system will result in more accurate predictions of patient outcome.

Key Words: prostate cancer, prostatectomy, IDC-P, the grade group system

INTRODUCTION

Tumor grading was reported using Grade Groups first proposed by authors at Johns Hopkins Hospital led by Dr. Epstein [1], validated in a large multi-institutional study [2], and subsequently endorsed by the 2014 International Society of Urological Pathology Consensus Conference [3], whereby GG1 (Grade Group 1) = Gleason score ≤6, GG2 = Gleason score 3+4=7, GG3 = Gleason score 4+3=7, GG4 = Gleason score 8, and GG5 = Gleason score 9-10 [1-3]. Next, World Health Organization (WHO) 2016 classifications also proposed a grade group system for prostate cancer [4]. At the same time, intraductal carcinoma of the prostate (IDC-P) was first recognized at these consensus meetings. The resulting common understanding, besides the recognition of IDC-P, is the strong association of IDC-P with high-grade and high-volume invasive prostate cancer (PCa). Previous studies have associated IDC-P with a poor prognosis and shorter biochemical-recurrence-free survival [5-11]. Our group reported that

IDC-P is an adverse prognostic factor for patients with high-risk or metastatic PCa patients [6-8]. A recent paper pointed out the higher tendency of distant metastasis rather than local recurrence in IDC-P-positive patients at the first clinical detection of recurrence and that it influenced cancer-specific survival [12]. Molecular evidence also supports the association of a TMPRESS2-ERG genomic change and the heterozygosity of RB1 and TP53 in patients with IDC-P [13, 14]. These findings have led some organizations that officially recommended reporting IDC-P [15].

The ability of IDC-P to predict prognosis after local therapy (radical prostatectomy or radiation therapy) has been determined in studies of a small number patients; the diagnosis of IDC-P was based on the pre-2005 or 2005 ISUP grading criteria [16-20]. Although the presence of IDC-P influences biochemical recurrence (BCR) in radical prostatectomy patients, its inclusion is not recommended in grade determination according to the latest WHO classification. The utility of integrating the presence of IDC-P into the grade group system has also not been examined. Thus, the aim of this study, conducted with a large cohort of patients, was to improve the prediction of BCR after radical prostatectomy by integrating IDC-P into the grade group system.

MATERIALS AND METHODS

This study was a retrospective evaluation of patients treated with radical prostatectomy between 2005 and 2013 at Nagoya University Hospital, Japanese Red Cross Nagoya Daini Hospital, JCHO

Chukyo Hospital, and Komaki City Hospital. All patients had been diagnosed with localized PCa and had undergone radical prostatectomy. Patients with missing data or slides, were excluded, such that 1019 patients were finally enrolled in the study. The choice of lymphadenectomy and operative (open, laparoscopic, or robotic) approach was left to each institution. The clinical T (cT) of each tumor was re-assessed based on the 2016 UICC TNM classification system [21]. All prostatectomy specimens were serially sliced at 3- or 5- mm intervals and paraffin embedded. The slides were reviewed by a single genitourinary pathologist (T.T.) according to the ISUP 2014 criteria.

IDC-P was defined according to the criteria of McNeal. Details on the definition of IDC-P were described previously [8, 22]. In brief, IDC-P is well-circumscribed lesions bound by an intact basal cell distended by overtly malignant-appearing epithelial populations. These lumen spanning lesions are found almost exclusively in close proximity to invasive cancer.

Complete baseline and follow-up data were available for all 1019 patients. Prostate-specific antigen (PSA) level were measured every 3 months over the first 2 years after surgery and every 6 months thereafter. BCR following radical prostatectomy was defined according to European Association of Urology guidelines as a continuously rising PSA level > 0.2 ng/ml [23]. The primary endpoint of this study was BCR-free survival, defined as the time from prostatectomy to BCR. Cumulative incidence curves were used in a competing-risks setting to calculate the probabilities of BCR, with clinical progression and death treated as competing risks [24]. The cumulative incidence

curves for BCR-free survival within each group were compared using Gray's test [25]. The influence of prognostic factors for BCR- free survival was evaluated using Fine and Gray's model [26]. Data on age, PSA level at diagnosis, pathological T stage, the presence of Gleason pattern 5, the presence of IDC-P, and surgical margin status were analyzed to predict BCR after prostatectomy. A P-value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS software (ver. 9.3; SAS Institute, Cary, NC, USA). This retrospective study was approved by the Institutional Review Board of Nagoya University Graduate School of Medicine.

RESULTS

Tabe1 lists the patient demographics. The median age at diagnosis was 67 (range 45–80) years and the median serum PSA level was 6.8 (range 0.4–82) ng/mL. The median follow-up period was 82 (range 0.7–148) months. Pathological T (pT) occurred in 199 patients with pT2a, 114 patients with pT2b, 430 patients with pT2c, 234 patients with pT3a, and 42 patients with pT3b (Table 1). PSA progression occurred in 293 patients (28.8%) and clinical disease progression in 16 (1.6%). Further 3 patients died of the disease (0.3 %), and 46 (4.5%) patients died of other causes during follow-up.

IDC-P was detected in 157 patients (15.4%). The grade groups (GGs) were as follows: GG 1 without IDC-P, 16.0% (n=163); GG 2 without IDC-P, 46.1% (n=470); GG 3 without IDC-P, 15.7% (n=160); GG 4 without IDC-P, 2.6% (n=27); GG 5 without IDC-P, 4.1% (n=42); any GG with IDC-

P, 15.4% [n=157; GG 2 (n=29); GG3 (n=60); GG4 (n=13); GG5 (n=55)]. Any grade Group with IDC-P showed a significantly worse prognosis than any other groups without IDC-P (p< 0.0001). (Table 1). Among these patients, the IDC-P positive rate increased with tumor upgrading (GG 1:0%, GG 2: 5.8%, GG 3: 27.3%, GG 4: 32.5%, and GG5: 56.7%) (Table 1). BCR-free survival differed significantly among the five groups (grade groups 1-5; p < 0.0001; Figure 1 and Table 2). Any grade Group with IDC-P showed a significantly worse prognosis than any other group without IDC-P (p< 0.0001; Fig. 2). GGs 3, 4, and 5 with IDC-P had a significantly worse prognosis than any other groups without IDC-P and GG 2 with IDC-P showed similar prognosis with GG 4 or GG 5 without IDC-P (supplement 1). Within each Grade Group, GGs 2-5 with IDC-P were associated with a worse prognosis than the corresponding GGs 2-5 without IDC-P.

In a multivariate analysis, the integration of IDC-P into the Grade Groups, the PSA level at diagnosis, and the surgical margin status significantly predicted the prognosis (P < 0.0001, < 0.0001 and < 0.0001 respectively). The presence of Gleason pattern 5 was not significant after IDC-P was integrated into the grade group system (Table 3).

DISCUSSION

The basis of this study was our proposal that integrating the presence of IDC-P into the grade group

system would improve the accuracy of patient outcome predictions. Never, in grade group system has a Gleason score for intraductal carcinoma been assigned and no data are available regarding the significance of IDC-P in the current classification system.

IDC-P is characterized by a retrograde spreading pattern in which carcinoma cells invade benign glandular structures [14, 22, 27, 28]. McNeal and Yemoto [16] were the first to report that patients with PCa characterized by an IDC-P component had a significantly worse prognosis than those with PCa that did not include an IDC-P component. Subsequent multivariate analyses have shown that the presence of IDC-P in radical prostatectomy specimens is an independent adverse prognostic factor in the prediction of PSA-free survival [16-20] . Van der Kwast et al. [29] recommended the presence of IDC-P in a needle biopsy as a predictive factor for patients with intermediate- and high-risk PCa treated by radiotherapy. Moreover, we previously reported that the presence of IDC-P was the only prognostic factor for progression free survival, cancer-specific survival, and overall survival; those results were obtained from a multivariate analysis of patients who underwent radical prostatectomy [8] and had a distant metastasis at their initial presentation [7]. As these studies make clear, IDC-P correlates with increased stage and prognosis [3]. Because the latest WHO classification does not recommend grading the presence of IDC-P [4], we propose integrating IDC-P into the grade group system based on the results of the present study, in which patients in any grade group with IDC-P had the worst prognosis. Especially, GGs 3, 4, and 5 with IDC-P had a significantly worse prognosis

to the same extent, and GG 2 with IDC-P showed similar prognosis with GG 4 or GG 5 without IDC-P. Whereas in previous studies the number of patients was relatively small, except in meta-analyses [30], our study had the advantage of a large cohort comprising > 1000 cases of PCa with IDC-P. Moreover, the pathology specimens were viewed by a single genitourinary pathologist who standardized their pathological evaluation.

The incidence of IDC-P is thought to depend on the grade and stage of prostatic adenocarcinoma but is typically in the range from 20-40% of radical prostatectomy cases [16, 17, 31]. According to a review article the frequency of IDC-P ranges between 10 and 40% in biopsies and between 20 and 60% in prostatectomies among patients in the intermediate-risk subgroup [32]. A recent meta-analysis of 7279 specimens obtained from patients with localized and metastatic disease showed that 20.9% were positive for IDC-P [30]. Compared to the low-risk category, the prevalence of IDC-P as seen on biopsy samples was significantly higher in patients with high-risk or recurrent/metastatic disease [30]. The IDC-P prevalence increased from 2.1% in low-risk patients to 23.1%, 36.7%, and 56.0% in patients with a moderate-risk, high-risk, or risk of metastatic/ recurrent disease, respectively [6]. In our series, the group of patients with localized prostate cancer had an IDC-P-positivity rate of 15.1% based on the prostatectomy specimens [7] This rate increased as upgrading in the grade group (GG 1: 0%, GG 2: 5.8%, GG 3: 27.3%, GG 4: 32.5%, and GG 5: 56.7%). We previously reported that the IDC-P-positivity rate was 36.3% in high-risk patients and 66.7% in patients with de novo metastatic disease,

as determined from biopsy samples [7]. The IDC-P detection rate was lower in biopsy samples than in prostatectomy specimens, but this was likely due to sampling errors, as our study population probably did not differ from those of previously reported studies.

A recent study demonstrates that the type and extent of IDC-P can influence on prognosis [33]. However, there is little consensus to separate IDC-P by morphology. In addition, the precise distinction among high grade PIN, atypical ductal hyperplasia, and IDC-P, even if immunohistochemical staining were performed [34]. Therefore, we performed neither the characterization nor quantification of IDC-P in this study.

IDC-P is usually intrinsically resistant to systemic therapy, and novel treatment-intensification protocols may be required to improve the outcomes in patients with IDC-P [32]. The occurrence and aggression of IDC-P may be caused by a series of genomic and epigenomic alterations in the prostate gland during tumorigenesis [32]. In IDC-P, PTEN loss and ERG expression is common, whereas PTEN loss is rare and ERG expression is uncommon in high-grade prostatic intraepithelial neoplasia [28, 35]. BRCA2-mutant PCa harboring IDC-P is reported to be related with genomic and epigenomic dysregulation of the MED12L/MED 12 axis [36]. These tumors may be responsive to treatment with PARP inhibitors, based on genetic synthetic lethality [36]. A recent paper proposed a nomogram including IDC-P to predict both the incidence of castration-resistant PCa and overall survival for patients with de novo metastatic PCa.[37]. We also demonstrated that patients with PCa characterized

by IDC-P had a worse clinical outcome despite docetaxel therapy [38].

The present study had several limitations. First, it had a nonrandomized retrospective design and was conducted at three different centers, without centralized regulation. Second, the statistical difference between GG 4 and GG 5 patients and patients in the other grade groups was relatively small because at the participating institutions patients with high-risk and very high-risk disease underwent one-time neoadjuvant therapy. Therefore, only a limited number of GG 5 cases could be regarded as involving clinically localized disease, which may have improved the prognosis of this cohort. In our opinion, this selection bias for high GG cases did not significantly impact our conclusions. Third, the surgical approach including lymph node dissection was not uniform because of the different approaches at the participating institutions, which included robot-assisted radical prostatectomy and laparoscopic radical prostatectomy. Nevertheless, we believe that these limitations had little influence on the results of this study. Finally, we didn't perform immunohistochemical staining for basal cells to confirm the presence of IDC-P. Theoretically, confirming the presence of basal cells are essential to diagnose IDC-P. Some papers also mentioned that immunohistochemical staining could be an objective method to identify IDC-P [33, 37]. However, staining all surgical specimen by basal cell markers, such as p63, high molecular weight cytokeratin etc. is mostly impossible because both of high costs and heavy pathologists' labor in daily practice. Furthermore, interobserver reproducibility issues with identifying IDC-P using immunohistochemical staining have

not been verified. Therefore, H&E staining based practice is desirable to utilized IDC-P in daily service.

CONCLUSIONS

Integrating the presence of IDC-P into the grade group system can improve the accuracy of BCR predictions. Thus, in choosing the best route of patient management, pathologists and urologists should be aware of the implications of the presence of IDC-P.

Disclosure/ conflict of interest

The authors declare no conflict of interest.

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Figure legends

Figure 1: Cumulative incidence curves for prostate specific antigen (PSA) progressive survival after prostatectomy according to the grade group system ($P < 0.0001$).

Figure 2: Cumulative incidence curves for prostate specific antigen (PSA) progressive survival after prostatectomy. The grade group system integrating the presence of intraductal carcinoma of the prostate (IDC-P) was used ($P < 0.0001$).

Table 1: Clinical and pathological characteristics (n = 1019)

Table 2: Biochemical-recurrence-free survival and variables related to the grade group (n = 1019)

Table 3: Biochemical-recurrence-free survival and variables related to the grade group after the integration of intraductal carcinoma of the prostate (IDC-P) (n = 1019)

Supplement 1: Cumulative incidence curves for prostate specific antigen (PSA) progressive survival after prostatectomy. The each grade group integrating the presence of intraductal carcinoma of the prostate (IDC-P) was used ($P < 0.0001$).

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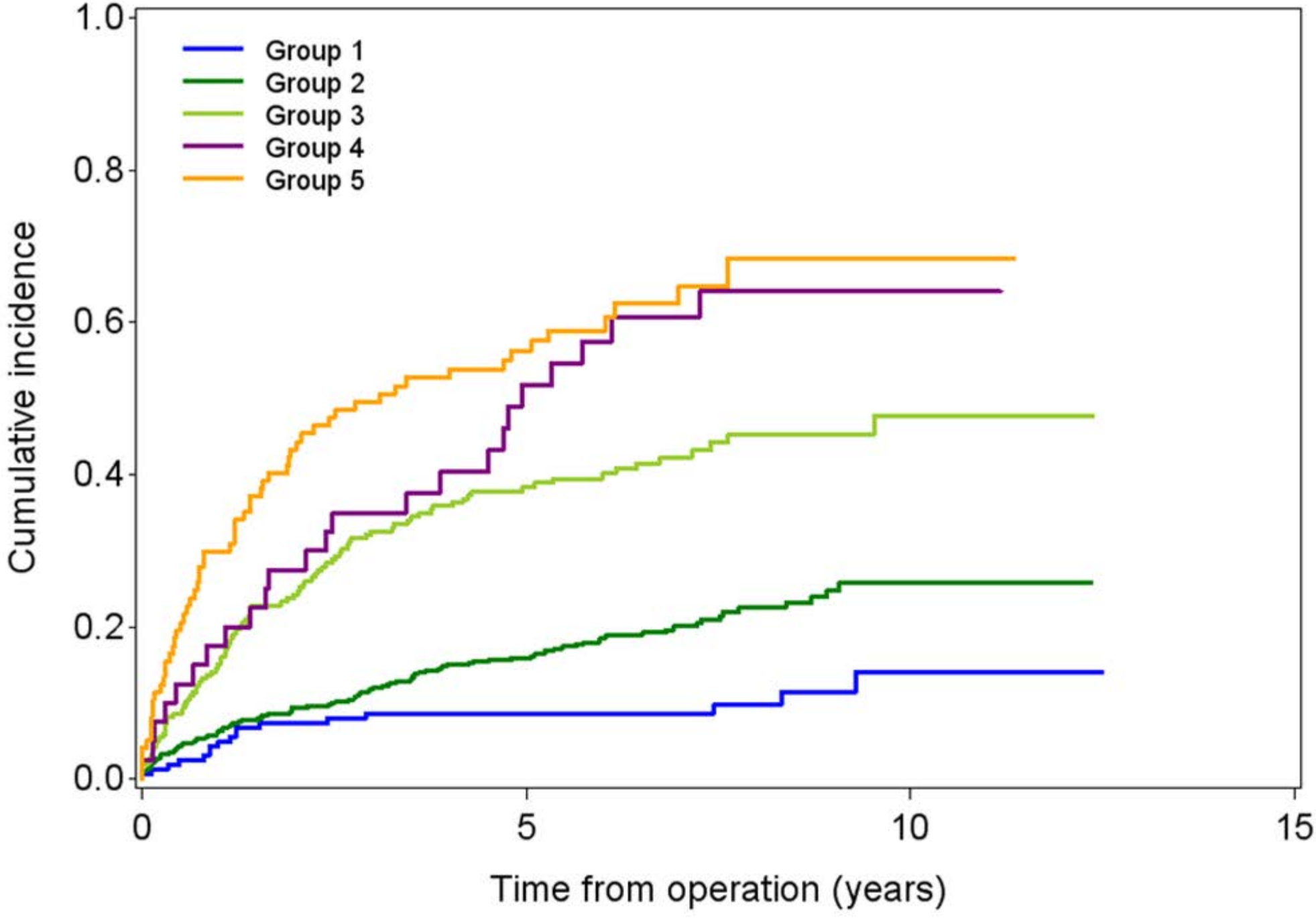

Group 1
Group 2
Group 3
Group 4
Group 5
1.0
0.8
0.6
0.4
0.2
0.0
Cumulative incidence
0
5
10
15
Time from operation (years)

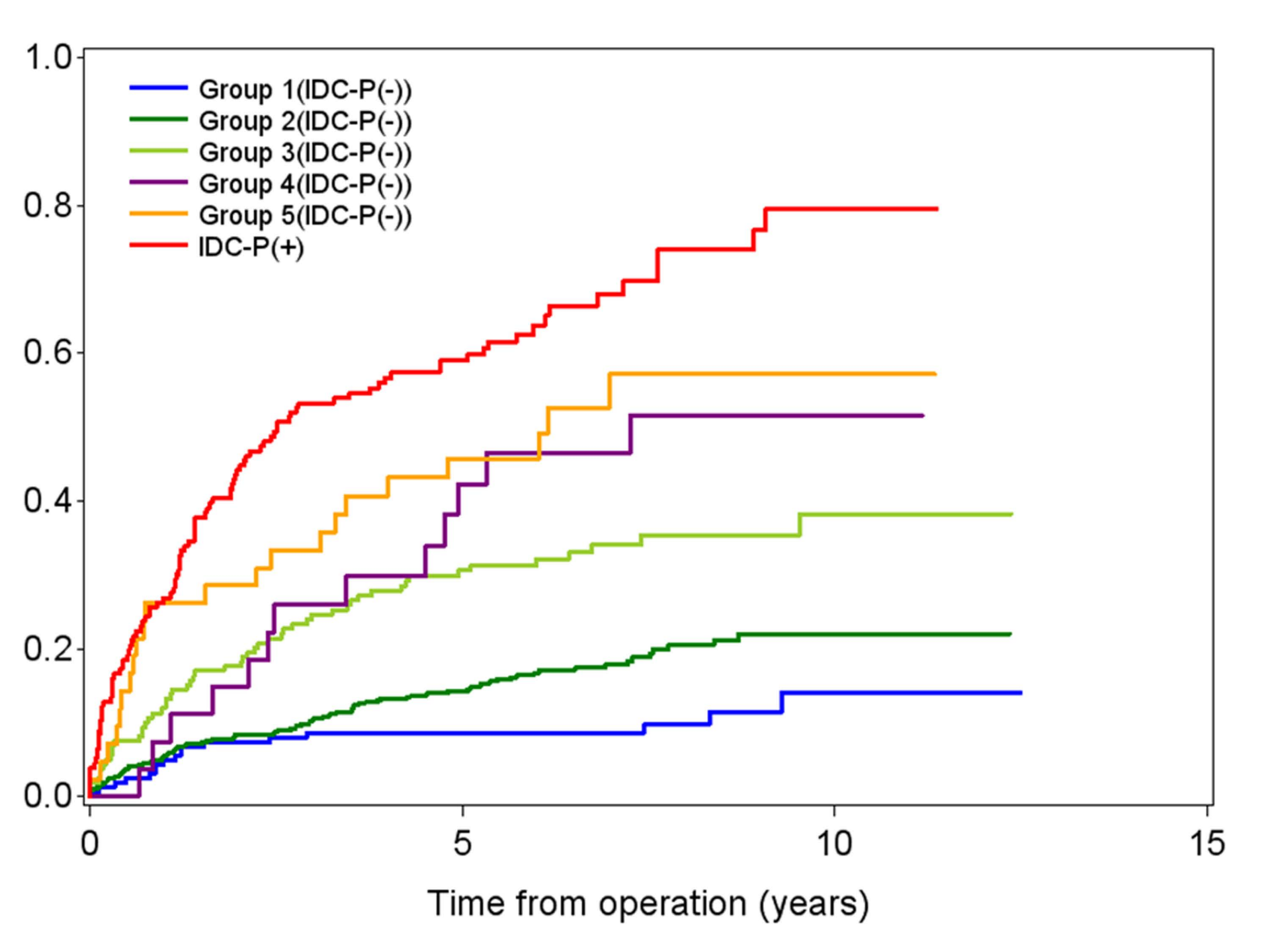

Group 1(IDC-P(-))
Group 2(IDC-P(-))
Group 3(IDC-P(-))
Group 4(IDC-P(-))
Group 5(IDC-P(-))
IDC-P(+)
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
Time from operation (years)

Table 1: Clinical and pathological characteristics (n = 1019)

Grade Group		**1**	**2**	**3**	**4**	**5**
		N=163	N=499	N=220	N=40	N=97
Age		67	67	68	67	69
		(46-77)	(45-79)	(50-80)	(56-77)	(48-77)
Follow up period	months	90	80.7	81.8	92.4	76.9
		(4.9-148)	(0.7-146)	(4.6-146)	(6.6-136)	(23.3-134)
PSA	ng/ml	5.7	6.6	8	7	8.3
		(1.1－19.5)	(0.4-50.9)	(3.1-81)	(2.5-17)	(4-82)
Clinical T	cT1c, cT2	163	484	212	37	92
	cT3a		15	7	2	5
	cT3b			1	1	
Pathological T	pT2a	71	82	33	6	7
	pT2b	20	59	25	5	5
	pT2c	70	249	71	14	26
	pT3a	2	100	78	12	42
	pT3b		9	13	3	17
Margin status	positive	25/163	202/499	108	10	43
		(15%)	(40%)	(49%)	(33%)	(44%)
IDC-P positive rate		0/163	29/499	60/220	13/40	55/97
		(0%)	(5.8%)	(27%)	(33%)	(57%)

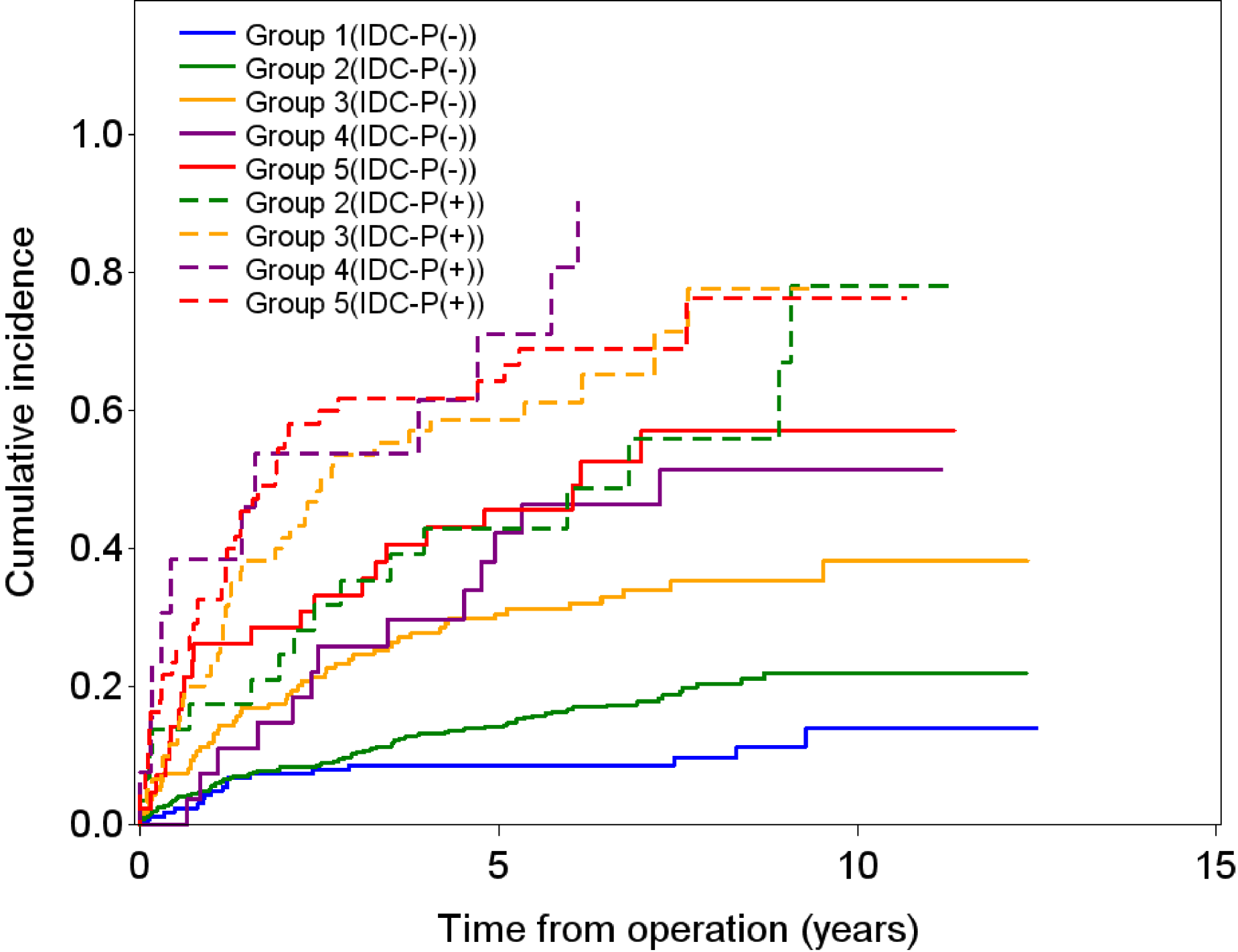
Table 2;

Biochemical-recurrence-free survival and variables related to the grade group (n=1019)

		Multivariate			
Variables	**Category**	**Hazard ratio**	**95% Lower**	**95% Upper**	**P-value**
Grade Group (GG)	GG 1	1			
	GG 2	1.371	0.813	2.314	0.2369
	GG 3	2.443	1.414	4.221	0.0014
	GG 4	7.848	4.162	14.798	<.0001
	GG 5	11.599	4.61	29.183	<.0001
Age	Continuous	1.001	0.98	1.022	0.9374
Pathological T	pT2	1			
	pT3,4	1.116	0.843	1.478	0.4432
Margin status	Negative	1			
	Positive	3.066	2.35	4	<.0001
PSA	Continuous	1.022	1.012	1.032	<.0001
Gleason pattern 5	Negative	1			
	Positive	0.336	0.158	0.713	0.0045
IDC-P	Negative	1			
	Positive	2.172	1.583	2.981	<.0001

Table 3; Biochemical-recurrence-free survival and variables related to the grade group after the integration of IDC-P (n=1019)

		Multivariate			
Variables	**Category**	**Hazard ratio**	**95% Lower**	**95% Upper**	**P-value**
Grade Group (GG)	GG 1 IDC-P(-)	1			
	GG 2 IDC-P(-)	1.301	0.765	2.221	0.3315
	GG 3 IDC-P(-)	2.461	1.402	4.317	0.0017
	GG 4 IDC-P(-)	5.391	2.709	10.728	<.0001
	GG 5 IDC-P(-)	4.209	1.968	9.002	0.0002
	IDC-P(+)	5.381	3.029	9.559	<.0001
Age	Continuous	1.005	0.984	1.026	0.6632
Pathological T	pT2	1			
	pT3	1.139	0.866	1.498	0.3531
Margin status	Negative	1			
	Positive	2.975	2.27	3.899	<.0001
PSA(ng/ml)	Continuous	1.022	1.013	1.032	<.0001
Gleason pattern 5	Negative	1			
	Positive	1.22	0.831	1.792	0.3109


Group 1(IDC-P(-))
Group 2(IDC-P(-))
Group 3(IDC-P(-))
Group 4(IDC-P(-))
Group 5(IDC-P(-))
Group 2(IDC-P(+))
Group 3(IDC-P(+))
Group 4(IDC-P(+))
Group 5(IDC-P(+))
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
Time from operation (years)