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Assessment of 5-year overall survival in bladder cancer patients with incidental prostate cancer identified at radical cystoprostatectomy

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Abstract

Objective To investigate the oncological impact of incidental prostate cancer (iPCa) found during radical cystoprostatectomy (RCP) on overall survival (OS) prognosis of urothelial carcinoma of the bladder (BCa).

Patients and methods A total of 122 RCP cases resected between 2002 and 2012 at our center were included for study. Survival of BCa patient was compared using the Kaplan–Meier method and the log-rank test. Cox proportional hazards regression models were used to analyze the impact of iPCa on the 5-year overall mortality of BCa patients after RCP.

Results Among the 122 BCa cases that underwent RCP, 38 cases (31.1%) had iPCa, in which, 17 cases (44.7%) were identified as clinically significant iPCa (csPCa). BCa patients with iPCa were older (71 vs 64 years, $p=0.004$) and had higher preoperative PSA level (3.1 ng/mL vs 1.4 ng/mL, $p=0.017$) when compared to those without iPCa. Cases with iPCa showed a more favorable 5-year OS than cases without iPCa, although this difference did not reach statistical significance ($p=0.219$). When excluding the higher risk cases with Gleason score (GS) $\geq 4+3$ and/or preoperative PSA >10 ng/mL, BCa patients with iPCa showed a significantly longer OS than cases without iPCa on univariate analysis ($p=0.044$), but not on multivariate analysis ($p=0.125$).

Conclusion Our results demonstrated that the frequent findings of low-risk iPCa in BCa patients could indicate the potential possibility of shared pathogenesis pathways between iPCa and BCa. Future study with a larger cohort is warranted to validate this result.

Keywords Bladder cancer · Incidental prostate cancer · Cystoprostatectomy · Prognosis · Androgen receptor

Abbreviations

BCa	Urothelial carcinoma of the bladder
MIBC	Muscle-invasive bladder cancer
NMIBC	Non-MIBC
RCP	Cystoprostatectomy
iPCa	Incidental prostate cancer
csPCa	Clinical significant iPCa
cisPCa	Clinical insignificant iPCa
PSA	Prostate-specific antigen
DRE	Digital rectal examination
GS	Gleason score
LVI	Lymphovascular invasion
PNI	Perineural invasion
STSM	Soft-tissue surgical margin
AR	Androgen receptor
ADT	Androgen deprivation therapy
IQR	Interquartile range

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Introduction

Bladder cancer (BCa) is the fourth most common cancer in men, which is three to four times more prevalent in men than in women in the United States [1]. Radical

cystoprostatectomy (RCP), which involves removal of the bladder, prostate, seminal vesicles, and regional lymph nodes, is the standard treatment for male patients with muscle-invasive bladder cancer (MIBC) or refractory high risk non-MIBC (NMIBC) [2]. Incidental prostate cancer (iPCa) is not an uncommon finding in RCP specimens with an overall incidence rate of 24.4% [3]. Its incidence varies markedly among different ethnic groups and is dependent on the completeness of histopathologic evaluation of the RCP specimen [3]. Wolters et al. [4] previously showed that PCa cases detected by PSA-screening and treated with radical prostatectomy (RP) had more aggressive clinicopathological features than iPCa cases, as they were often multifocal, larger in volume, more advanced in tumor stage and with a higher Gleason score (GS). Extensive investigations have been performed on iPCa regarding the method of prostate specimen processing, prevalence, pathologic characteristics, and clinical significance [3, 5]. iPCa was, therefore, subsequently categorized into clinical significant iPCa (csPCa) and clinical insignificant iPCa (cisPCa), where the former is generally defined as a tumor with a Gleason 4 or 5 pattern, pT stage ≥ pT3a, lymph node involvement, positive surgical margin, or tumor volume > 0.5 cm^3 [6]. In the previous studies, when the iPCa associated BCa prognosis was analyzed, inconsistent results were observed with some of them reported that cases with iPCa had a significantly worse overall survival (OS) than cases without iPCa [7–10]. A significantly worse OS in patients with csPCa was also reported when comparing it in patients with cisPCa [9]. However, other studies concluded that iPCa showed no impact on BCa OS [5, 11–15].

Previously, Singh et al. [16] had proposed a common carcinogenesis pathway between BCa and PCa based on the clinical finding that patients with PCa had higher incidence of BCa and those with BCa had a higher incidence of PCa. Recent studies showed that BCa was correlated with androgen and androgen receptor (AR) sensitivity [17]. We also demonstrated that aromatase, which is the key enzyme catalyzing the conversion of androgens to estrogens, was involved in BCa progression [18]. An increasing body of clinical evidence showed that 5α-reductase inhibitor administration could decrease BCa risk [19–21], and androgen deprivation therapy (ADT) could prevent BCa recurrence [22]. Most recently, Makela et al. [23]. reported that the use of 5α-reductase inhibitor before BCa diagnosis was associated with lowered risk of BCa death in 10,720 Finnish men with newly diagnosed BCa. In this study, we aimed to evaluate whether iPCa is associated with BCa progression and OS following RCP.

Materials and methods

Study population

Following Institutional Review Board approval, using a BCa database of the Departments of Urology and Pathology of Massachusetts general hospital, a total of 128 patients who underwent RCP for localized BCa between 2002 and 2012 were selected. Six cases with the previous positive biopsy diagnosis of PCa were excluded from further analysis (GS 3 + 3: 4, GS 3 + 4: 1, GS 4 + 4: 1). Clinicopathologic characteristics including the age at RCP, year of RCP, pT, pN, histologic grade, soft-tissue surgical margins (STSM), lymphovascular invasion (LVI), perineural invasion (PNI), metastasis, and postoperative treatment were extracted for BCa. For iPCa, preoperative PSA, GS, pT, PNI, tumor volume, and surgical margin were extracted. Preoperative digital rectal examination (DRE) was not included for analysis, because data were not available for most of the patients.

Pathological assessment

All surgical specimens were processed according to routine pathologic procedures used in our hospital. The bladder and prostate specimens were surface inked and fixed for 24 h in 4% neutral buffered formalin. Prostate specimens were processed by either complete protocol according to the Stanford protocol with serial step sections at 3 mm in 21 cases (17.2%), or by partial protocol which sampled four-to- eight sections for whole prostate in 101 cases (82.8%).

Follow-up

Follow-up was performed according to institutional protocols. Postoperatively, patients were generally seen in clinic every 3 months in the first year, every 6 months in the second year, and annually thereafter. Follow-up visits consisted of physical examination, serum routine blood tests and diagnostic imaging. Metastasis was defined as demonstrable disease recurrence on diagnostic imaging or on biopsies. Information on death was taken from death certificates, patient charts, and physician correspondence. OS was measured from the date of RCP to the date of death or the date of last follow-up if the patient was still living.

Statistical analysis

Descriptive statistics of categorical variables focused on frequencies and proportions. Medians and interquartile range (IQR) were reported for continuous variables. Statistical analysis was performed using the Kruskal–Wallis *H* test

for continuous variables and Pearson's Chi-squared test or Fisher's exact test for categorical variables. Kaplan–Meier survival analysis was performed to estimate probability of OS. Comparison of survival distributions was performed with the log-rank test. Univariate Cox proportional hazards models, as well as multivariate models fitted with variables showed significance on univariate analysis were created to compute hazard ratios for predictors of OS. All tests were two sided with statistical significance set at $p < 0.05$. All statistical analyses were performed with Stata14 (College Station, TX, USA).

Results

Patient characteristics

The clinical and pathological characteristics of the 122 men who underwent RCP are summarized in Table 1. Median age at RCP was 66 years (IQR 56–74), median preoperative PSA was 2.0 ng/mL (IQR 1.0–3.3), median prostate volume was 25 cm^3 (IQR 18–36), and median BMI was 27 (IQR 24–31). Pathologic assessment of RCP specimens showed MIBC in 81 cases (66.4%). Thirty-three patients (27.1%) had lymph node involvement by BCa. High-grade BCa was present in the majority of cases (82.0%). LVI was found in 43 (35.2%) cases. Forty-two cases (34.4%) showed prostatic involvement by BCa and 38 patients (31.1%) had iPCa. Fifty-six cases (45.9%) received adjuvant treatment, 48 cases (39.3%) had metastasis, and 53 cases (43.4%) died within the follow-up period.

Patients with iPCa were older (median 71 years) when compared with patients without iPCa (median 64 years) ($p = 0.004$). Patients with iPCa showed a significantly higher preoperative PSA (median 3.1 ng/mL) than those without iPCa (median 1.4 ng/mL) ($p = 0.017$) [PSA data were available from 47 patients (38.5%)]. There was no difference in prostate volume or body mass index (BMI) between patient groups with or without iPCa. Moreover, there was no significant difference in BCa-related pathologic factors including pT, pN, histology grade, LVI, PNI, STSM, prostatic involvement, adjuvant treatment, or metastasis status between patient groups with or without iPCa.

Of the 38 cases with iPCa, 17 cases (44.7%) were csPCa, and the other 21 cases (55.3%) were cisPCa. When compared with the cisPCa group, the csPCa group showed a significantly higher pN rate for BCa ($p = 0.023$). Although it failed to reach any statistical significance, cases with csPCa showed a trend of higher preoperative PSA (5.3 vs 2.1 ng/mL, $p = 0.068$) and higher frequency of MIBC (82.3% vs 57.1%, $p = 0.096$) as well as PCa-PNI (23.5% vs 4.8%, $p = 0.089$).

The prognostic role of iPCa for predicting 5-year overall survival for BCa

During the follow-up period (median 40 months, IQR 19–64), 53 patients from the cohort died (43.4%) and the 5-year OS rate was 54.3%. As shown in Fig. 1a, the Kaplan–Meier survival curve was stratified by cases with or without iPCa. Although the log-rank comparison test did not show statistical significance ($p = 0.219$), there was a trend toward better OS survival in patients with iPCa (5-year OS survival rate 57.5%) when compared to patients without iPCa (5-year OS survival rate 53.3%). Upon further stratification of iPCa into csPCa group and cisPCa group (Fig. 1b, $p = 0.448$), BCa patients with cisPCa showed a better survival (5-year survival rate 60.1%) than those with csPCa (5-year survival rate 56.1%) ($p = 0.691$, data not shown). There was no OS difference between the cisPCa group and the group without iPCa ($p = 0.441$, data not shown). When iPCa was subcategorized into groups of GS = 3 + 3 ($n = 27$), GS = 3 + 4 ($n = 6$), and GS ≥ 4 + 3 ($n = 3$) or any GS with PSA > 10 ($n = 2$, both GS = 3 + 3), we found, except the five cases of GS ≥ 4 + 3 or any GS with PSA > 10 which had a markedly worse prognosis than other groups ($p = 0.009$), patients with GS = 3 + 4 had a similar overall survival to that of group GS 3 + 3 with a low PSA (Fig. 1c). Therefore, these patients were designated as low-risk iPCa group. Interestingly, we found that this low-risk iPCa group showed a significant better 5-year overall survival than the group of BCa without iPCa ($p = 0.044$) (Fig. 1d). On univariate analysis, poor 5-year OS was significantly associated with MIBC ($p = 0.012$), positive pN ($p = 0.013$), LVI by BCa ($p < 0.001$), and STSM ($p < 0.001$). On the other hand, low-risk iPCa status and the year of surgery were significantly associated with longer 5-year OS (HR: 0.46, 95% CI 0.21–0.99, $p = 0.049$; HR: 0.82, 95% CI 0.75–0.91, $p < 0.001$, respectively) (Table 2). On multivariate analysis, after adjusting for all significant variables on univariate analysis, positive STSMs ($p = 0.001$) and the year of surgery ($p = 0.002$) remained as significant independent prognostic factors (Table 2), whereas low-risk iPCa status ($p = 0.125$), MIBC ($p = 0.127$), and positive pN of BCa ($p = 0.412$) lost their statistical significance.

Discussion

It is known that iPCa is a common finding in RCP for male patients with BCa [3, 5]. However, the prognostic impact of iPCa on OS has not been conclusively determined. A majority of the previous studies demonstrated that iPCa had no impact on BCa OS [5, 11–15], while some other studies reported that BCa cases with iPCa had a significantly worse OS than those without iPCa [7–10].

Table 1 Clinicopathological characteristics of 122 patients underwent radical cystoprostatectomy between 2002 and 2012 for localized bladder urothelial carcinoma

	Total	BCa with iPCa	*cisPCa*	*csPCa*	*p*	BCa without iPCa	p
Number of patients, no. %	122 (100)	38 (31.1)	*21 (55.3)*	*17 (44.7)*		84 (68.9)	
Age at RCP (IQR)	66, 56–74	71, 64–79	*71, 63–75*	*71, 66–80*	*0.403*	64, 56–71	**0.004**
PSA ($n=47$), ng/ml (IQR)	2, 1–3.3	3.1, 1.2–7.6	*2.1, 0.9–3.4*	*5.3, 3.0–12.5*	*0.068*	1.4, 0.7–2.1	**0.017**
Prostate volume (cm^3) (IQR)	25, 18–36	22, 16–36	*21, 15–31*	*23, 19–38*	*0.151*	25, 19–36	0.419
BMI (IQR)	27, 24–31	26, 23–29	*26, 24–29*	*27, 23–31*	*0.692*	28, 25–31	0.173
pT (BCa)-1, no. %					*0.312*		0.747
pT0	14 (11.5)	4 (10.5)	*4 (19.0)*	*0 (0)*		10 (11.9)	
pTa	4 (3.3)	2 (5.3)	*1 (4.8)*	*1 (5.9)*		2 (2.5)	
pTis	8 (6.6)	1 (2.6)	*1 (4.8)*	*0 (0)*		7 (8.3)	
pT1	15 (12.3)	5 (13.2)	*3 (14.3)*	*2 (11.7)*		10 (11.9)	
pT2	16 (13.0)	7 (18.4)	*4 (19.0)*	*3 (17.7)*		9 (10.7)	
pT3	40 (32.8)	11 (29.0)	*6 (28.6)*	*5 (29.4)*		29 (34.5)	
pT4	25 (20.5)	8 (21.0)	*2 (9.5)*	*6 (35.3)*		17 (20.2)	
pT (BCa)-2, no. %					*0.096*		0.750
Non-muscle invasive	41 (33.6)	12 (31.6)	*9 (42.9)*	*3 (17.7)*		29 (34.5)	
Muscle invasive	81 (66.4)	26 (68.4)	*12 (57.1)*	*14 (82.3)*		55 (65.5)	
pN (BCa), no. %					***0.023***		0.902
pN−	89 (72.9)	28 (73.7)	*19 (90.5)*	*9 (52.9)*		61 (72.6)	
pN+	33 (27.1)	10 (26.3)	*2 (9.5)*	*8(47.1)*		23 (27.4)	
Histology grade (BCa), no. %					*0.164*		0.489
No tumor	14 (11.4)	4 (10.5)	*4 (19.1)*	*0 (0)*		10 (11.9)	
Low grade	8 (6.6)	4 (10.5)	*2 (9.5)*	*2 (11.8)*		4 (4.8)	
High grade	100 (82.0)	30 (79.0)	*15 (71.4)*	*15 (88.2)*		70 (83.3)	
LVI (BCa), no. %					*0.240*		0.840
LVI−	79 (64.8)	24 (63.2)	*15 (71.4)*	*9 (52.9)*		55 (65.5)	
LVI+	43 (35.2)	14 (36.8)	*6 (28.6)*	*8 (47.1)*		29 (34.5)	
PNI (BCa), no. %					*0.239*		0.561
PNI−	99 (81.1)	32 (84.2)	*19(90.5)*	*13(76.5)*		67 (79.8)	
PNI+	23 (18.9)	6 (15.8)	*2(9.5)*	*4(23.5)*		13 (20.2)	
STSM (BCa), no. %					–		0.171
Margin−	118 (96.7)	38 (100)	*21 (100)*	*17 (100)*		80 (95.2)	
Margin+	4 (3.3)	0 (0)	*0 (0)*	*0 (0)*		4 (4.8)	
BCa involved prostate, no. %					*0.126*		0.430
Involve−	80 (65.6)	23 (60.5)	*15 (71.4)*	*8 (47.1)*		57 (67.9)	

Table 1 (continued)

	Total	BCa with iPCa	*cisPCa*	*csPCa*	*p*	BCa without iPCa	p
Involve+	42 (34.4)	15 (39.5)	*6 (28.6)*	*9 (52.9)*		27 (32.1)	
Adjuvant treatment, no. %					*0.254*		0.338
Adjuvant−	66 (54.1)	23 (60.5)	*11 (52.4)*	*12 (70.6)*		43 (51.2)	
Adjuvant+	56 (45.9)	15 (39.5)	*10 (47.6)*	*5 (29.4)*		41 (48.8)	
Metastasis (BCa) no. %					*0.899*		0.435
Mets−	74 (60.7)	25 (65.8)	*14 (66.7)*	*11 (64.7)*		49 (58.3)	
Mets+	48 (39.3)	13 (34.2)	*7 (33.3)*	*6 (35.3)*		35 (41.7)	
Gleason score, no. %					***< 0.001***		
≤ 6		29 (76.3)	*21 (100)*	*8 (47.1)*			
3 + 4		6 (15.8)	*0 (0)*	*6 (35.2)*			
4 + 3		2 (5.3)	*0 (0)*	*2 (11.8)*			
≥ 8		1 (2.6)	*0 (0)*	*1 (5.9)*			
pT(PCa), no. %					***0.045***		
≤ pT2		35 (92.1)	*21 (100)*	*14 (82.4)*			
≥ pT3		3 (7.9)	*0 (0)*	*3 (17.6)*			
Margin (PCa), no. %					***0.019***		
Margin−		34 (89.5)	*21 (100)*	*13 (76.5)*			
Margin +		4 (10.5)	*0 (0)*	*4 (23.5)*			
Tumor volume (PCa), cm^3					***< 0.001***		
≤ 0.5		25 (65.9)	*21 (100)*	*4 (23.5)*			
> 0.5		13 (34.1)	*0 (0)*	*13 (76.5)*			
PNI (PCa), no. %					*0.089*		
PNI−		35 (92.1)	*20 (95.2)*	*13 (76.5)*			
PNI +		3 (7.9)	*1 (4.8)*	*4 (23.5)*			

RCP radical cystoprostatectomy, *BCa* bladder urothelial carcinoma, *iPCa* incidental prostate cancer, *cisPCa* clinical insignificant iPCa, *csPCa* clinical significant iPCa, *IQR* interquartile range, *BMI* body mass index, *LVI* lymphovascular invasion, *PNI* perineural invasion, *STSM* soft-tissue surgical margin

In our current retrospective BCa study, after excluding 6 cases with the previous biopsy proven PCa, we observed an overall iPCa rate of 31.1%, which is comparable to data presented in the previous studies [3]. Surprisingly, we found that cases with iPCa showed a trend toward more favorable 5-year OS when compared with those without iPCa. After excluding the high-risk iPCa cases, we found that the remaining low-risk iPCa cases showed a significantly better prognosis for 5-year OS on univariate analysis than those without iPCa, but this significance was lost on multivariate analysis. Previously, studies had shown that iPCa was identified more often in older patients [3], and advanced age was associated with worse BCa outcome [24]. In this study, we found that BCa patients with iPCa were significantly older (71 vs 64 years, $p = 0.004$) and showed better 5-year OS when compared with those without iPCa. It is possible that our observation of better survival in BCa patients with iPCa is not coincident, but the result of underlining mechanism regulating BCa progression.

To better understand our findings, we carefully reviewed the previous studies that examined the impact of iPCa on BCa patients' oncological outcomes. Interestingly, some studies concluded that the OS was not significantly different between cases with or without iPCa. In addition, in fact, some BCa cases with iPCa showed a more favorable 5-year OS than cases without iPCa [8, 13–15]. For example, in a previous study from Italy with a cohort of 893 RCP cases including 319 cases (36%) with iPCa, Moschini et al. [15] reported that the cisPCa group had a higher 3-year survival rate (64% vs 60%) and an identical 5-year survival rate (54%) when compared with the group without iPCa. The csPCa group also showed a similar 5-year survival rate

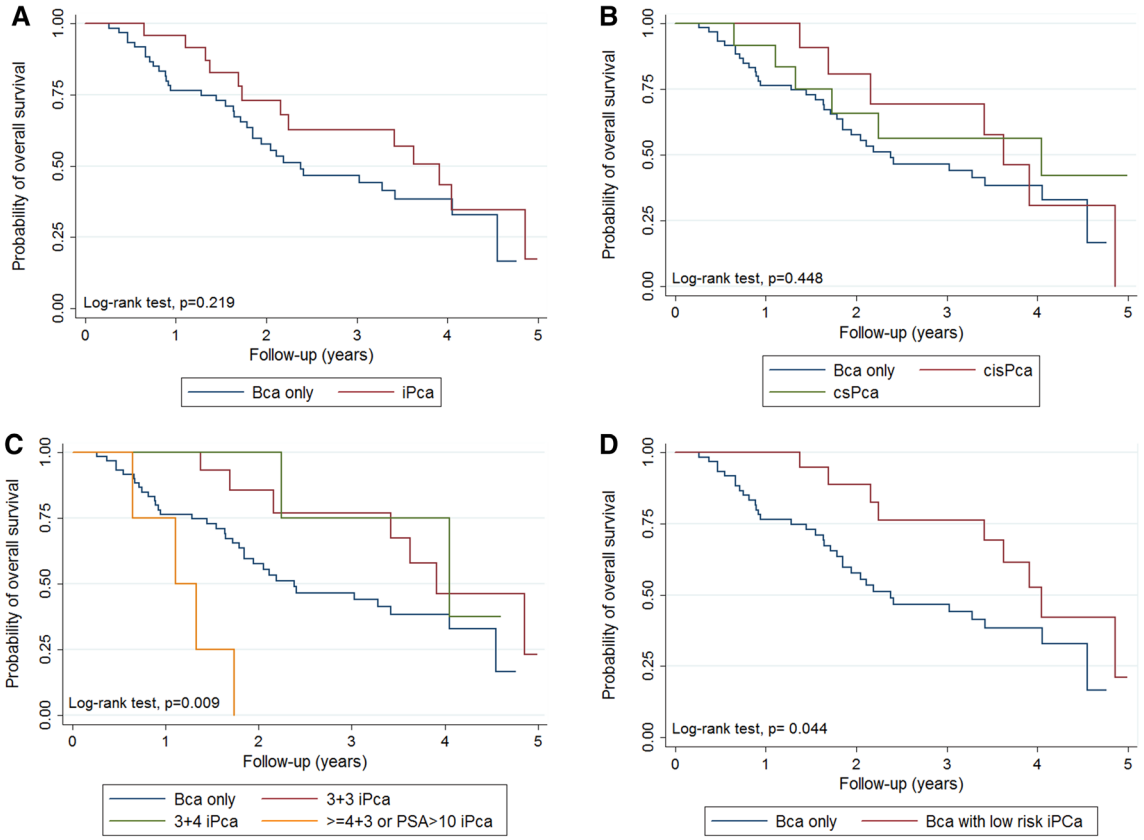

Fig. 1 Kaplan–Meier curve showing overall survival within 5-year stratified by: **a** with iPCa or without iPCa; **b** with csPCa, cisPCa or without iPCa; **c** with GS3 + 3 iPCa, GS 3 + 4 iPCa, iPCa with GS ≥ 4 + 3 and/or PSA > 10 or without iPCa; **d** with low-risk iPCa or without iPCa

(55% vs 54%) when compared with patients without iPCa. In a study with a cohort of 945 RCP cases from Germany, Thomas et al. [8] reported that 237 cases (25.1%) had iPCa. In this study, the group with GS ≥ 7 iPCa had the worst OS ($n = 81$, median OS: 37.9 months); however, the group with GS < 7 iPCa ($n = 146$, median OS: 101.6 months) showed a better OS when compared with the group without iPCa ($n = 655$, median OS: 75.9 months). In their iPCa cases, 64 cases (27.0%) were GS = 7 and 18 cases (7.6%) were GS ≥ 8. However, no detailed information regarding GS = 7 (GS3 + 4 or GS4 + 3) was provided. Results from these studies were consistent with our finding that low-risk iPCa may be associated with longer survival in BCa patients post-RCP.

In contrast to our findings, three previous studies found that the OS of patients with iPCa was significantly decreased when compared with those without iPCa [7, 9, 10]. In a study from Germany which included 822 RCP cases, Gakis et al. [9] reported that 117 cases (14.2%) had csPCa, 243 cases (29.6%) had cisPCa, and 462 cases (56.2%) were without iPCa. They found that the cases with csPCa showed a trend toward worse 5-year OS in comparison with cases with cisPCa and cases without iPCa over the entire cohort ($p = 0.06$) and were significantly worse in a pN (BCa) negative subgroup ($p = 0.044$) on univariate analysis, but lost significance on multivariate analysis ($p = 0.46$). In addition, in another Germany study which included 1122 RCP from six academic institutions, Buse et al. [7] reported that iPCa was detected in 17.8% ($n = 200$) cases. They showed that iPCa was associated with worse OS on both univariate analysis (HR 1.45, 95% CI 1.18–1.79, $p < 0.01$) and multivariate analysis (HR 1.27, 95% CI 1.02–1.58, $p < 0.05$). However, in this cohort, only 106 iPCa patients (53%) had available GS data. One more study which from Lithuania with a total of 81 RCP cases reported a worse OS in BCa patients with iPCa. In this study, 27 patients (33.3%) had iPCa, 7 of these cases (25.9%) had GS7, and 1 case (3.7%) had GS ≥ 8 PCa. Sruogis et al. [10] showed that BCa patients with iPCa had shorter survival than patients without iPCa (28.1 ± 27.5 and 45.5 ± 35.40 months, $p = 0.03$).

There are several possible contributing factors for the observed discrepancy. The most likely explanation is the differences in iPCa cases included for analyses from different studies. For example, pre-diagnosed PCa cases were excluded in our study but not in the studies of Buse et al. [7] or Gakis et al. [9]. Another possible explanation is the

Table 2 Univariate analysis of clinicopathologic factors with 5 year overall survival

	Univariate			Multivariate		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age	0.99	0.97–1.02	0.631	–	–	–
PSA (ng/mL)	1.10	0.96–1.26	0.184	–	–	–
Prostate volume (cm^3)	0.99	0.97–1.02	0.627	–	–	–
Year of surgery	0.82	0.75–0.91	**< 0.001**	0.82	0.72–0.92	**0.001**
Low-risk iPCa[#]						
Without	1.00	–	–	1.00	–	–
With	0.46	0.21–0.99	**0.049**	0.52	0.22–1.20	0.125
Clinical significance (iPCa)				–	–	–
cisPca	1.00	–	–	–	–	–
csPca	0.24	0.05–1.24	0.088	–	–	–
pT (BCa)*						
NMIBC	1.00	–	–	1.00	–	–
MIBC	2.48	1.22–5.02	**0.012**	1.97	0.83–4.68	0.127
pN (BCa)						
pN−	1.00	–	–	1.00	–	-
pN+	2.18	1.18–6.03	**0.013**	1.34	0.67–2.69	0.412
LVI (BCa)						
Negative	1.00	–	–	1.00	–	–
Positive	2.59	1.39–4.80	**0.003**	2.08	0.98–4.38	0.055
PNI (BCa)						
Negative	1.00	–	–	–	–	–
Positive	1.54	0.73–3.26	0.257	–	–	–
STSM (BCa)						
Negative	1.00	–	–	1.00	–	–
Positive	14.8	4.49–48.8	**< 0.001**	8.52	2.27–32.0	**0.002**
BCa prostatic involvement						
Negative	1.00	–	–	–	–	–
Positive	1.56	0.84–2.89	0.161	–	–	–

Multivariate Cox regression models fitted with factors that showed significance in univariate analysis

**MIBC* muscle-invasive bladder cancer, *NMIBC* non-MIBC

[#]Low-risk iPCa: iPca excluded GS more than 4 + 3 and/or with PSA more than 10 ng/ml

differences in the percentage of iPCa cases with GS ≥ 4 + 3. For example, cases with GS7 were not further subgrouped into GS3 + 4 or GS4 + 3 in some of the previous studies [7, 9, 10]. Finally, iPCa with preoperative PSA higher than 10 ng/ml has been considered as an increased risk factor for PCa outcome; however, this was not emphasized in the previous studies [25].

In our current study, cases with iPCa showed decreased frequencies of pN positivity, high histologic grade, PNI, and distant metastasis for BCa when compared with cases without iPCa, even though these differences were not statistically significant. In agreement with our findings, in a large international cohort with 2114 RCP cases, Malte et al. [11] reported that cases with iPCa had a lower frequency of MIBC ($p = 0.03$), high histology grade for BCa ($p = 0.04$), and LN involvement by BCa ($p = 0.09$). Thomas et al. [8] also found that cases with iPCa had a lower frequency of high histology grade (80.0% vs 82.5%) and LN metastasis (22.8% vs 25.2%) by BCa. These findings indicate that better OS observed in BCa patients with iPCa could be the result of the pathological characteristics rather than the presence of iPCa.

The close relationship of BCa and PCa has been established by the previous studies [5, 16]. Molecular evidence has indicated that the AR-signaling pathway promotes bladder carcinogenesis as well as cancer progression [26]. Chang et al. [27] demonstrated that AR plays different roles in metastatic PCa and BCa, as AR could suppress PCa metastasis, but might also stimulate BCa metastasis. Epidemiologically, patients with PCa are known to have a higher risk of coincidental BCa (3.4%) than patients in a non-PCa control population [28]; patients with BCa are reported to have a 19-fold higher prevalence of coincidental PCa than controls [29]. Clinically, Morales et al. [21] reported that finasteride

(5α-reductase inhibitor) administered for benign prostatic hyperplasia (BPH) can reduce the risk of BCa in a large screening study. In addition, Izumi et al. [22] reported clinical evidence, indicating that androgen deprivation therapy (ADT) prevented BCa recurrence in a Japanese cohort. Most recently, Makela et al. [23] reported that the administration of 5α-reductase inhibitor prior to BCa diagnosis resulted in a better disease-specific survival for BCa. In our study, cases with iPCa had a lower BCa metastasis rate than cases without iPCa (34.2% vs 41.7%), and cases with iPCa had a lower rate of BCa LN metastasis (26.3% vs 27.4%). These data suggest that AR signaling might be involved in BCa carcinogenesis and disease progression.

In this study, the year of surgery also showed as an independent indicator of prognosis, and we consider that the increasing application of neoadjuvant chemotherapy may improve the OS prognosis of the later patients.

Currently, the selection of prostate-sparing cystectomy vs partial prostatectomy, which protects sexual function and better maintains continence, is suitable only for a highly selected population, whose BCa were neither with prostatic urethra involvement nor with iPCa [30]. Our findings indicate that if no PCa is identified by a systemic prostate biopsy or transurethral resection of the prostate before surgery for BCa, a more limited surgery for BCa may be selected for these patients.

Our study is limited by several factors. First, it is retrospective and non-randomized, which may lead to selection bias. In addition, given the increased cases treated with bladder-preserving tri-modality therapy for patients with MIBC [31], our cohort was with limited samples for analysis. Future studies with a larger cohort to validate the current results and to directly examine the expressions of AR and its related molecules are warranted.

Conclusion

In summary, our results indicated that older age and increased PSA were associated with iPCa and BCa patients with low-risk iPCa identified at RCP could impact BCa disease progression. Once results from this work can be confirmed in further studies, additional therapy may be considered as a strategy to treat a subgroup of BCa patients and to improve their survival outcomes.

Compliance with ethical standards

Conflict of interest All the authors declare that there is no conflict of interest.

Ethical approval All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards.

References

1. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics. CA Cancer J Clin 66(1):7–30. https://doi.org/10.3322/caac.21332
2. Gakis G, Efstathiou J, Lerner SP, Cookson MS, Keegan KA, Guru KA, Shipley WU, Heidenreich A, Schoenberg MP, Sagaloswky AI, Soloway MS, Stenzl A, International Consultation on Urologic Disease-European Association of Urology Consultation on Bladder C (2013) ICUD-EAU International consultation on bladder cancer 2012: radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. Eur Urol 63(1):45–57. https://doi.org/10.1016/j.eururo.2012.08.009
3. Fahmy O, Khairul-Asri MG, Schubert T, Renninger M, Stenzl A, Gakis G (2017) Clinicopathological features and prognostic value of incidental prostatic adenocarcinoma in radical cystoprostatectomy specimens: a systematic review and meta-analysis of 13,140 patients. J Urol 197(2):385–390. https://doi.org/10.1016/j.juro.2016.08.088
4. Wolters T, Montironi R, Mazzucchelli R, Scarpelli M, Roobol MJ, van den Bergh RC, van Leeuwen PJ, Hoedemaeker RF, van Leenders GJ, Schroder FH, van der Kwast TH (2012) Comparison of incidentally detected prostate cancer with screen-detected prostate cancer treated by prostatectomy. Prostate 72(1):108–115. https://doi.org/10.1002/pros.21415
5. Lopez-Beltran A, Cheng L, Montorsi F, Scarpelli M, Raspollini MR, Montironi R (2017) Concomitant bladder cancer and prostate cancer: challenges and controversies. Nat Rev Urol 14(10):620–629. https://doi.org/10.1038/nrurol.2017.124
6. Epstein JI, Walsh PC, Carmichael M, Brendler CB (1994) Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 271(5):368–374
7. Buse S, Hofner T, Muller SC, Hermann E, Wieland WF, May M, Stief CG, Bastian PJ, Hohenfellner M, Haferkamp A (2013) Characterization and risk stratification of prostate cancer in patients undergoing radical cystoprostatectomy. Int J Urol 20(9):866–871. https://doi.org/10.1111/iju.12073
8. Thomas C, Giesswein A, Hainz M, Stein R, Rubenwolf P, Roos FC, Neisius A, Nestler S, Hampel C, Jager W, Wiesner C, Thuroff JW (2015) Concomitant Gleason Score %3e/= 7 prostate cancer is an independent prognosticator for poor survival in nonmetastatic bladder cancer patients undergoing radical cystoprostatectomy. Int Urol Nephrol 47(11):1789–1796. https://doi.org/10.1007/s11255-015-1110-1
9. Gakis G, Rink M, Fritsche HM, Graefen M, Schubert T, Hassan F, Chun FK, Brummeisl W, Fisch M, Burger M, Stenzl A, Renninger M (2016) Prognostic significance of incidental prostate cancer at radical cystoprostatectomy for bladder cancer. Urol Int 97(1):42–48. https://doi.org/10.1159/000443239
10. Sruogis A, Ulys A, Smailyte G, Kardelis Z, Kulboka A, Anglickiene G, Samalavicius N, Anglickis M (2012) Incidentally found prostate cancer and influence on overall survival after radical cystoprostatectomy. Prostate Cancer 2012:690210. https://doi.org/10.1155/2012/690210
11. Malte R, Kluth LA, Kaushik D, Boorjian SA, Abufaraj M, Foerster B, Rink M, Gust K, Roghmann F, Noldus J, Vordos D, Hagiwara M, Kikuchi E, Ikeda M, Matsumoto K, Karakiewicz PI, Roupret M, Briganti A, Scherr DS, Shariat SF, Seebacher V (2017) Frequency and prognostic significance of incidental prostate cancer at radical cystectomy: Results from an international

retrospective study. Eur J Surg Oncol 43(11):2193–2199. https://doi.org/10.1016/j.ejso.2017.08.013
12. Kaelberer JB, O'Donnell MA, Mitchell DL, Snow AN, Mott SL, Buatti JM, Smith MC, Watkins JM (2016) Incidental prostate cancer diagnosed at radical cystoprostatectomy for bladder cancer: disease-specific outcomes and survival. Prostate Int 4(3):107–112. https://doi.org/10.1016/j.prnil.2016.06.002
13. Cho IC, Kim JE, Kim SH, Joung JY, Seo HK, Chung J, Park WS, Lee KH (2015) Oncologic aspects of long-term followed incidental prostate cancer detected by cystoprostatectomy in Korean patients. Prostate Int 3(2):56–61. https://doi.org/10.1016/j.prnil.2015.03.006
14. Pan J, Xue W, Sha J, Yang H, Xu F, Xuan H, Li D, Huang Y (2014) Incidental prostate cancer at the time of cystectomy: the incidence and clinicopathological features in Chinese patients. PLoS ONE 9(4):e94490. https://doi.org/10.1371/journal.pone.0094490
15. Moschini M, Shariat SF, Freschi M, Soria F, Abufaraj M, Gandaglia G, Dell'Oglio P, Mattei A, Damiano R, Salonia A, Montorsi F, Briganti A, Gallina A, Colombo R (2017) Impact of prostate involvement on outcomes in patients treated with radical cystoprostatectomy for bladder cancer. Urol Int 98(3):290–297. https://doi.org/10.1159/000454736
16. Singh A, Kinoshita Y, Rovito PM Jr, Landas S, Silberstein J, Nsouli I, Wang CY, Haas GP (2008) Higher than expected association of clinical prostate and bladder cancers. J Urol 179(5 Suppl):S2–5. https://doi.org/10.1016/j.juro.2008.03.130
17. Gakis G, Stenzl A, Renninger M (2013) Evolution of the concept of androgen-sensitive bladder cancer. Scand J Urol 47(3):173–178. https://doi.org/10.3109/00365599.2012.756929
18. Wu S, Ye J, Wang Z, Lin SX, Lu M, Liang Y, Zhu X, Olumi AF, Zhong WD, Wu CL (2018) Expression of aromatase in tumor related stroma is associated with human bladder cancer progression. Cancer Biol Ther 19(3):175–180. https://doi.org/10.1080/15384047.2017.1414762
19. Chen CC, Huang CP, Tsai YT, Hseih TF, Shyr CR (2017) The genomic alterations of 5alpha-reductases and their inhibitor finasteride's effect in bladder cancer. Anticancer Res 37(12):6893–6898. https://doi.org/10.21873/anticanres.12152
20. Shiota M, Kiyoshima K, Yokomizo A, Takeuchi A, Kashiwagi E, Dejima T, Takahashi R, Inokuchi J, Tatsugami K, Eto M (2017) Suppressed recurrent bladder cancer after androgen suppression with androgen deprivation therapy or 5alpha-reductase inhibitor. J Urol 197(2):308–313. https://doi.org/10.1016/j.juro.2016.08.006
21. Morales EE, Grill S, Svatek RS, Kaushik D, Thompson IM Jr, Ankerst DP, Liss MA (2016) Finasteride reduces risk of bladder cancer in a large prospective screening study. Eur Urol 69(3):407–410. https://doi.org/10.1016/j.eururo.2015.08.029
22. Izumi K, Taguri M, Miyamoto H, Hara Y, Kishida T, Chiba K, Murai T, Hirai K, Suzuki K, Fujinami K, Ueki T, Udagawa K, Kitami K, Moriyama M, Miyoshi Y, Tsuchiya F, Ikeda I, Kobayashi K, Sato M, Morita S, Noguchi K, Uemura H (2014) Androgen deprivation therapy prevents bladder cancer recurrence. Oncotarget 5(24):12665–12674. https://doi.org/10.18632/oncotarget.2851
23. Makela VJ, Kotsar A, Tammela TL, Murtola TJ (2018) Bladder cancer survival in men using 5-alpha-reductase inhibitors. J Urol. https://doi.org/10.1016/j.juro.2018.04.082
24. Taylor JA 3rd, Kuchel GA (2009) Bladder cancer in the elderly: clinical outcomes, basic mechanisms, and future research direction. Nat Clin Pract Urol 6(3):135–144. https://doi.org/10.1038/ncpuro1315
25. D'Amico AV (2011) Risk-based management of prostate cancer. N Engl J Med 365(2):169–171. https://doi.org/10.1056/NEJMe1103829
26. Miyamoto H, Yang Z, Chen YT, Ishiguro H, Uemura H, Kubota Y, Nagashima Y, Chang YJ, Hu YC, Tsai MY, Yeh S, Messing EM, Chang C (2007) Promotion of bladder cancer development and progression by androgen receptor signals. J Natl Cancer Inst 99(7):558–568. https://doi.org/10.1093/jnci/djk113
27. Chang C, Lee SO, Yeh S, Chang TM (2014) Androgen receptor (AR) differential roles in hormone-related tumors including prostate, bladder, kidney, lung, breast and liver. Oncogene 33(25):3225–3234. https://doi.org/10.1038/onc.2013.274
28. Kinoshita Y, Singh A, Rovito PM Jr, Wang CY, Haas GP (2004) Double primary cancers of the prostate and bladder: a literature review. Clin Prostate Cancer 3(2):83–86
29. Chun TY (1997) Coincidence of bladder and prostate cancer. J Urol 157(1):65–67
30. Vallancien G, Abou El Fettouh H, Cathelineau X, Baumert H, Fromont G, Guillonneau B (2002) Cystectomy with prostate sparing for bladder cancer in 100 patients: 10-year experience. J Urol 168(6):2413–2417. https://doi.org/10.1097/01.ju.0000036521.21034.ec
31. Giacalone NJ, Shipley WU, Clayman RH, Niemierko A, Drumm M, Heney NM, Michaelson MD, Lee RJ, Saylor PJ, Wszolek MF, Feldman AS, Dahl DM, Zietman AL, Efstathiou JA (2017) Long-term outcomes after bladder-preserving tri-modality therapy for patients with muscle-invasive bladder cancer: an updated analysis of the Massachusetts general hospital experience. Eur Urol 71(6):952–960. https://doi.org/10.1016/j.eururo.2016.12.020