Prognostic Significance of Incidental Prostate Cancer at Radical Cystoprostatectomy for Bladder Cancer

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Abstract

Objective: The aim of the study was to evaluate the impact of the clinical significance of incidental prostate cancer (PC) on overall survival (OS) after radical cystoprostatectomy (RC) for bladder cancer (BC). **Methods:** A total of 822 consecutive men underwent RC in 3 academic centers between 1996 and 2011. The clinical significance of incidental PC was determined according to the Epstein criteria. The Kaplan–Meier analysis with log-rank was used to investigate the impact of PC on OS and univariate and multivariate Cox regression analyses for risk factors of OS. The median follow-up was 36 months (interquartile range 10–49). **Results:** Of the 822 men, 117 (14.2%) had clinically significant, 243 (29.6%) insignificant and 462 (56.2) no PC at RC. Men with PC were at higher risk for lymphovascular invasion (LVI) of BC compared to men without PC (p < 0.001). The 5-year OS for men with clinically significant, insignificant and no PC was 33.3, 51.3 and 51.5%, respectively (p = 0.050). In the subgroup of pN0 patients (n = 601), clinically significant PC was significantly associated with inferior OS (p = 0.044) but not in multivariable analysis (p = 0.46). **Conclusions:** We did not find the clinical significance of incidental PC to be an independent predictor. However, the positive correlation between incidental PC and LVI of BC deserves further investigation.

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Introduction

Radical cystectomy (RC) represents the mainstay of treatment for muscle-invasive bladder cancer (BC) [1, 2]. Advanced pathological tumor and nodal stage as well as positive soft-tissue surgical margins (STSMs) are the main pathologic determinants of survival after RC [3]. Since outcomes of patients can vary considerably inter-individually [4], it is essential to individualize treatment based on patient-centered risk factors in order to selectively advocate the use of adjuvant modalities after RC.

Incidental prostate cancer (PC) is not an uncommon finding in RC specimens after BC surgery [5]. The reported rates of detection vary considerably (2–58%), which is mainly due to different sampling techniques [6, 7]. While

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there are reports in literature that biochemical recurrence does not significantly impact on survival after RC [8], there is evidence that supports the assumption that the presence of incidental PC represents an indicator of aggressive BC biology [6]. In light of recent studies reporting on the altered androgen sensitivity of BC in advanced stages [9, 10], the question arises whether the presence and clinical significance of incidental PC is an indicator for adverse outcomes of patients with invasive BC. In order to evaluate this hypothesis, we assembled a multi-institutional collaborative with the aim of determining the prognostic impact of incidental PC and its clinical significance on survival after RC.

Patients and Methods

This is a retrospective study representing data from 3 prospectively maintained databases of 3 German tertiary care centers. This study was conducted according to the provisions of the local ethics committee on each study site and conforms to the provisions of the Declaration of Helsinki. A common database was generated. Through regular communications, all data inconsistencies were solved prior to final analysis.

A total of 822 consecutive men treated with RC for BC between 1996 and 2011 were included. None of these patients received neo-adjuvant treatment. In all centers, RC included the removal of the tumor-bearing bladder, prostate, seminal vesicles and bilateral pelvic lymph nodes. Adjuvant and palliative chemotherapy for BC was administered at the discretion of the treating physician based on the findings of histopathologic analysis and follow-up investigations.

For BC, the following clinical and pathologic parameters were assessed: age at RC, Eastern Cooperative Oncology Group (ECOG) performance status, pathologic tumor and nodal stage, STSMs, lymphovascular invasion (LVI), performance of postoperative (adjuvant and/or palliative) chemotherapy and histological subtype.

For incidental PC, the following clinical and pathologic parameters were evaluated: preoperative digital rectal examination (DRE), preoperative prostate-specific antigen (PSA) level, prostate volume, prior transurethral resection of the prostate (TURP), any prostate biopsy prior to RC, pathologic tumor and nodal stage, STSMs, lymphatic invasion, vascular invasion, Gleason-Score and tumor volume.

Histologic Assessment
The histologic assessment was performed at the center-specific pathology department by dedicated genitourinary pathologists and was based on the 1973 WHO grading system and TNM classification as approved by the AJCC [11]. The pathological macro- and microscopic evaluation of cystoprostatectomy specimens included cross-sectioning of the entire prostate at 4–5-mm intervals with immunohistochemical staining to identify the presence of bladder [12] and PC [13]. Prostate specimens were processed according to the Stanford protocol [13]. Clinically significant PC was defined as a tumor with Gleason 4 or 5 pattern, stage ≥pT3a, PC lymph node metastasis, positive STSM or tumor volume >0.5 cm^3 [14].

Positive STSMs were defined as the microscopic presence of malignant cells at the resection margins. LVI was defined as the microscopic presence of malignant cells within an endothelial cell line [15] and was separately reported for bladder and PC stage based on immunohistochemical analysis.

Follow-Up
Electronic hospital charts and physician records were reviewed to determine clinical outcomes. In all participating centers, patients generally were seen postoperatively every 3–4 months for the first year, semi-annually for the second and third years and annually thereafter. For determining overall survival (OS), clinical outcomes were measured from the date of RC to the date of death as determined by death certificates or hospital charts or the date of last follow-up when the patient had not experienced death [16]. The median follow-up was 36 months (interquartile range (IQR) 10–52).

Statistical Analysis and Model Development
For univariate analysis, the chi-square test/Fisher exact test was used for nominal data and the Student's t test for scaled data. The Kaplan–Meier plots were used to estimate OS using log-rank testing. For univariate and multivariate analyses, Cox-proportional hazard analysis was carried out to evaluate risk factors for death. p values are 2-sided and $p < 0.05$ was considered significant. Statistical analysis was performed using JMP® 11.0. Values are given as mean ± SEM for all normally distributed variables or as median (range) for non-normally distributed variables.

Results

The clinical and pathologic characteristics of the 822 patients are listed in table 1. Positive lymph nodes (all from BC) were histologically confirmed in 218 of the 822 patients (26.5%; 90 with pN1, 122 with pN2 and 6 with pN3). The median number of retrieved lymph nodes at RC was 18 (IQR 10–25).

Of the 822 patients, 360 (43.7%) were diagnosed with incidental PC at RC. The rates of incidental PC between the 3 centers were 47.6, 44.8 and 35.1%. Of the 360 patients with incidental PC, 243 (67.5%) had clinically insignificant and 117 (32.5%) clinically significant PC. The rates of clinically significant PC were not different across centers (center I: 14.7%, center II: 14.4% and center III: 13.3%, p = 0.54).

Patients with significant PC were of higher age compared to patients with insignificant PC and without PC ($p < 0.001$ between the 3 groups). Compared to the group of patients with insignificant and without PC, patients with significant PC had a positive DRE at RC ($p < 0.001$ between groups), a history of prostate biopsy prior to RC (p = 0.015/p = 0.006) and higher preoperative PSA levels (available data on 477 patients; p = 0.002/p < 0.001).

Table 1. Univariate Pearson chi-square/Fisher exact test for clinical and pathological parameters in the 822 patients with BC according to the presence and significance of incidental PC at RC (bold values indicate a statistically significant difference)

	BC and PC			BC without PC	p value
	insignificant PC	significant PC	p value		
Number of patients, %	243 (29.6)	117 (14.2)		462 (56.2)	
Age at RC, years					
Median	68	71	**<0.001**	66	**<0.001**
IQR	60–73	67–74		57–71	
ECOG performance status (at RC)					
Mean	0.7	0.8		0.9	
Median	1	1	0.58	1	
IQR	0–1	0–1		0–1	0.20
Preoperative DRE					
Positive	76 (31.3)	56 (47.9)	**0.002**	5 (1.1)	**<0.001**
Negative	167 (68.7)	61 (52.1)		457 (98.9)	
Preoperative PSA (n = 477), ng/ml					
Mean	3.5	6.7	**0.020**	1.7	
Median	2.5	3.2		1.0	**<0.001**
IQR	1.0–4.0	1.9–5.4		0.5–2	
Prostate volume, ml					
Mean	22	25	0.40	21	0.97
Median	19	27		24	
IQR	5–33	15–33		8–34	
TURP in history without malignancy					
Yes	3 (1.2)	3 (2.6)	0.39	20 (4.3)	**0.043**
No	240 (98.8)	114 (97.4)		442 (95.7)	
Prostate biopsy prior to RC					
Yes	1 (0.4)	5 (4.3)	**0.015**	0 (0)	**0.006**
No	242 (99.6)	112 (95.7)		462 (100)	
Number of retrieved lymph nodes at RC					
Median	17	18	0.49	18	0.80
Mean	16.4	18.1		17.4	
IQR	7–25	10–26		10–25	
BC					
pT-stage (BC)					
pTX	1 (0.4)	0 (0)	0.19	1 (0.2)	0.42
pT0	25 (10.3)	11 (9.4)		47 (10.2)	
pTa	5 (2.1)	5 (4.3)		18 (3.9)	
pTis	16 (6.6)	12 (10.3)		38 (8.2)	
pT1	32 (13.2)	14 (12.0)		59 (12.8)	
pT2a	39 (16.1)	12 (10.3)		59 (12.8)	
pT2b	14 (5.8)	15 (12.8)		36 (7.8)	
pT3a	43 (17.7)	13 (11.1)		80 (17.3)	
pT3b	33 (13.6)	14 (12.0)		48 (10.4)	
pT4a	32 (13.2)	18 (15.4)		63 (13.6)	
pT4b	3 (1.2)	3 (2.6)		13 (2.8)	
≤pT2b	132 (54.3)	69 (58.2)	0.42	258 (55.8)	0.94
≥pT3a	111 (45.7)	48 (41.8)		204 (44.2)	
pN-stage (BC)					
pNX	0 (0)	0 (0)	0.16	0 (0)	0.88
pN0	179 (73.7)	88 (75.2)		337 (72.9)	
pN1	30 (12.3)	11 (9.4)		49 (10.6)	
pN2	34 (14.0)	16 (13.7)		72 (15.6)	
pN3	0 (0)	2 (1.7)		4 (0.9)	
STSM (BC)					
pRX	1 (0.4)	0 (0)	0.44	3 (0.6)	0.96
pR0	219 (90.1)	102 (87.2)		411 (89.0)	
pR1	22 (9.1)	15 (12.8)		46 (10.0)	
pR2	1 (0.4)	0 (0)		2 (0.4)	

Table 1. (continued)

	BC and PC			BC without PC	p value
	insignificant PC	significant PC	p value		
LVI (BC)					
LV0	100 (41.2)	55 (47.0)	0.99	237 (51.3)	**<0.001**
LVI	95 (39.1)	52 (44.4)		107 (23.2)	
LVX	48 (19.8)	10 (5.5)		118 (25.5)	
Histology					
Pure UC	208 (85.6)	99 (84.6)	0.23	358 (77.5)	0.17
Pure SCC	4 (1.7)	3 (2.6)		8 (1.7)	
Pure AC	1 (0.4)	0 (0)		2 (0.4)	
UC + SCC	10 (4.1)	4 (3.4)		9 (2.0)	
Small cell	3 (1.2)	2 (1.7)		1 (0.2)	
SCC + UC	0 (0)	3 (2.6)		7 (1.5)	
Sarcomatoid + UC	3 (1.2)	0 (0)		2 (0.4)	
UC + sarcomatoid	1 (0.4)	0 (0)		6 (1.3)	
UC + AC	0 (0)	0 (0)		2 (0.4)	
UC + small cell + sarcomatoid	0 (0)	1 (0.9)		0 (0)	
Pure sarcomatoid	1 (0.4)	0 (0)		0 (0)	
UC + SCC + AC	0 (0)	0 (0)		1 (0.2)	
Clear-cell + SCC	0 (0)	0 (0)		0 (0)	
Plasmozytoid	2 (0.8)	0 (0)		1 (0.2)	
Micropapillary	0 (0)	0 (0)		3 (0.7)	
Nested	0 (0)	0 (0)		1 (0.2)	
Lymphoepithelioma-like	0 (0)	0 (0)		0 (0)	
Unclassified/unknown	10 (4.1)	5 (4.3)		61 (13.2)	
Postoperative chemotherapy (BC) (adjuvant + palliative)					
Received	46 (18.9)	14 (12.0)	0.13	89 (19.3)	0.31
Adjuvant	22 (9.1)	6 (5.1)		26 (56.3)	
Palliative	16 (6.6)	6 (5.1)		51 (11.0)	
Adjuvant plus palliative	8 (3.3)	2 (1.7)		12 (2.6)	
Not received	197 (81.1)	103 (88.0)		373 (80.7)	
PC					
pT-stage (PC)					
pT2a	145 (59.7)	28 (23.9)	**<0.001**		
pT2b	18 (7.4)	8 (6.8)			
pT2c	68 (28.0)	49 (41.9)			
pT3a	4 (1.7)	21 (18.0)			
pT3b	0 (0)	6 (5.1)			
pT4	0 (0)	5 (4.3)			
Not assessed	8 (3.3)	0 (0)			
STSM (PC)					
pRX	2 (0.8)	1 (0.9)	**<0.001**		
pR0	229 (94.2)	95 (1.2)			
pR1	3 (1.2)	20 (17.1)			
Not assessed	9 (3.7)	1 (0.9)			
Lymphatic invasion (PC)					
LX	4 (1.7)	0 (0)	**<0.001**		
L0	222 (91.4)	92 (78.6)			
L1	3 (2.6)	21 (18.0)			
Not assessed	14 (5.8)	4 (3.4)			
Vascular invasion (PC)					
VX	5 (2.1)	0 (0)	**<0.001**		
V0	223 (91.8)	108 (92.3)			
V1	0 (0)	5 (4.3)			
Not assessed	15 (61.7)	4 (3.4)			
Gleason score					
4	24 (9.9)	1 (0.9)	**<0.001**		
5	35 (14.4)	2 (1.7)			

Table 1. (continued)

	BC and PC			BC without PC	p value
	insignificant PC	significant PC	p value		
6	184 (75.7)	8 (6.8)			
7	0 (0)	91 (77.8)			
8	0 (0)	7 (6.0)			
9	0 (0)	8 (6.8)			
10	0 (0)	0 (0)			
Tumor volume (PC), mm^3					
Mean	6	11	**<0.001**		
Median	5	12			
IQR	3–10	6–15			

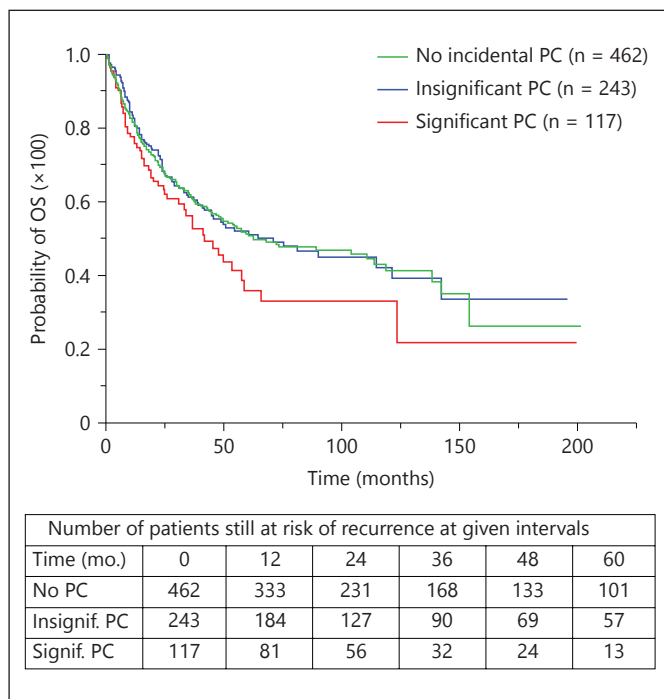AC = Adenocarcinoma; SCC = squamous cell carcinoma; UC = urothelial carcinoma.

Fig. 1. Kaplan–Meier analysis for OS according to the presence and significance of incidental PC at RC for BC (insignif. = insignificant; mo. = months; signif. = significant; p = 0.06 for significant vs. insignificant/no incidental PC).

Patients with PC were at higher risk for LVI of BC compared to patients without PC (p < 0.001). Conversely, patients without PC had undergone significantly more likely a TURP (for benign prostatic syndrome without evidence of malignancy) in their history (p = 0.043).

Compared to the group of patients with insignificant PC, men with significant PC exhibited higher PC tumor stages at RC, higher PC tumor volumes, higher Gleason-Scores, a higher risk of positive STSMs (from PC) as well as lymphatic and vascular invasion by PC cells (all p < 0.001).

In the entire cohort, the 5-year OS was 50.1%. The 5-year OS for patients with significant, insignificant and no PC was 33.3, 51.3 and 51.5%, respectively (p = 0.050; fig. 1).

For the entire cohort (n = 822) of patients, inferior OS was significantly associated with advanced age (p < 0.001), histologic advanced BC tumor stage (p < 0.001), pathologically confirmed lymph node tumor involvement of BC (pN+ vs. pN0 and pN2–3 vs. pN1; both p < 0.001), positive STSMs of BC (p < 0.001), LVI of BC cells (p < 0.001), receipt of postoperative chemotherapy (p < 0.001) and a trend toward significance for patients with significant PC versus insignificant/no PC (p = 0.050; table 2). Sub-analyzed for pN0-staged patients (n = 604), the presence of clinically significant PC correlated with inferior OS compared to insignificant PC/no PC (p = 0.044).

On multivariate analysis, adjusted for all significant variables of univariate analysis, histologically confirmed advanced BC stage (p < 0.001), node-positive disease (p < 0.001), positive STSMs (p < 0.001), presence of LVI (p < 0.001) and advanced age at RC (p < 0.001) were associated with inferior OS (table 2) whereas the clinical significance of PC (p = 0.46) as well as the receipt of postoperative systemic chemotherapy were not (p = 0.79).

Discussion

In the present study, we investigated the impact of incidental PC and its clinical significance on mortality in patients treated with RC for BC. Previous smaller

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Table 2. Univariate and multivariate Cox regression analyses of risk factors for death after RC in patients with BC (bold values indicate a statistically significant difference)

Parameter	Univariable OS		Multivariable OS	
	RR (95% CI)	p value	RR (95% CI)	p value
Significant vs. insignificant PC/no PC	**1.32 (1.00–1.75)**	**0.050**	1.12 (0.82–1.51)	0.45
≥pT3a vs. ≤pT2b (BC)	**3.74 (3.00–4.68)**	**<0.001**	**2.52 (1.93–3.29)**	**<0.001**
Pathologic nodal stage				
pN + vs. pN0	**2.63 (2.11–3.27)**	**<0.001**	**1.53 (1.19–1.98)**	**<0.001**
Positive vs. negative STSMs (BC)	**4.45 (3.35–5.82)**	**<0.001**	**2.50 (1.85–3.33)**	**<0.001**
LVI vs. LV0 (BC)	**2.60 (2.04–3.32)**	**<0.001**	**1.39 (1.07–1.82)**	**<0.001**
Receipt of postoperative chemotherapy				
(no vs. yes)	**2.14 (1.68–2.72)**	**<0.001**	1.05 (0.79–1.40)	0.79
Age, years				
(continuously, total range of risk)	**5.42 (2.96–10.06)**	**<0.001**	**4.41 (2.38–8.29)**	**<0.001**
>66 vs. ≤66	**1.68 (1.35–2.09)**	**<0.001**		
ECOG performance status (at RC)				
(continuously, total range of risk)	3.04 (0.84–10.78)	0.08	–	–
ECOG ≥1 vs. 0	1.11 (0.62–2.08)	0.74		
Preoperative PSA level, ng/ml				
(continuously, total range of risk)	2.38 (0.27–10.43)	0.38	–	–
>4 vs. ≤4, ng/ml	1.13 (0.79–1.59)	0.47		

RR = Relative risk.

studies have suggested that the presence of incidental PC at RC impacts on OS [17]. In this series, the rate of incidental PC was relatively high (43.7%). In prior series, a high variation in the rates of incidental PC at RC ranging between 2 and 58% have been reported [6, 7, 18, 19].

In order to define the clinical significance of incidental PC, we used the Epstein criteria as outlined above [14]. These parameters have been consistently used in other series evaluating the clinical significance of incidental PC at RC [7]. In the present study, the rate of clinically significant PC was similar between centers (13–14%). This suggests that the histopathologic evaluation of PC foci was conducted in the same way in the 3 participating centers over the study period of 15 years.

In order to better characterize each of the 3 groups, we conducted further analyses. We found that the presence and clinical significance of PC correlated with the performance of any prostate biopsy prior to RC, positive DRE, higher age at RC and higher preoperative PSA values. As in our centers the diagnostic work-up with PSA and DRE was usually done a few days prior to RC, the treatment approach did not change for patients with suspicious findings. However, with regard to studies advocating prostate-sparing techniques to improve functional outcomes after RC [7, 20], our findings confirm the current

clinical practice to use these parameters in order to rule out the presence of significant PC at RC.

In this study, mortality was significantly associated with age, advanced pathologic tumor and nodal stage, STSM, LVI and delivery of postoperative chemotherapy. These data underpin that the present cohort is comparable to similar larger series in terms of its primary tumor characteristics [3, 4].

We also found that node-negative patients with clinically significant PC were at higher risk for death compared to patients with insignificant or no PC. However, on multivariate analysis, only the classic pathological risk factors and age were associated with OS whereas clinically significant PC was not.

Nonetheless, an interesting, albeit surprising find of the present study was that LVI by BC cells as determined by immunohistochemistry was strongly associated with the presence of incidental PC. Of note, the rate of locally advanced BC and number of retrieved lymph nodes was not significantly different between the 3 groups. Thus, the question arises whether and how the presence of incidental PC might facilitate lymphovascular invasion of BC cells. This hypothetical question cannot to be adequately addressed based on the available retrospective data but deserves further basic research investigation. As recent data suggest an influence of the

androgen pathway during the development and progression of muscle-invasive BC [9, 10], this may represent a possible molecular link for the development of significant PC foci during progression of invasive BC cells.

This study has limitations inherent to its retrospective and multicenter nature. One limitation of this study is that our multicenter database did not contain data for recurrence-free and cancer-specific survival of all centers. Interestingly, we found that approximately 48% of significant PCs were palpable on DRE which may also be due to BC invasion as approximately 15% had pT4a BC. Conversely, the question arises whether transrectal biopsy in case of a positive DRE may be helpful in selecting patients who should be offered neoadjuvant treatment [1]. Despite the fact that the rate of clinically significant PC was very similar between centers, one cannot rule out an interobserver variability in the pathological assessment of RC specimens. Although we report on the number of retrieved lymph nodes as a surrogate marker for the meticulousness of pelvic LND, its association to the anatomical extent of LND is limited [21]. However, all patients were treated in academic centers by surgeons dedicated to the management of patients with muscle-invasive BC. Nonetheless, owing to these limitations, the results of this study await external validation.

Conclusions

Although node-negative patients with clinically significant PC exhibited inferior OS in univariate analysis, this series did not find the clinical significance of incidental PC to be an independent predictor for OS after RC for BC. However, the positive correlation between incidental PC and LVI of BC deserves further investigation.

Acknowledgments

Disclosure Statement

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