



Original Article

Oncologic aspects of long-term followed incidental prostate cancer detected by cystoprostatectomy in Korean patients

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ABSTRACT

Purpose: To determine the incidence and clinical features of incidentally discovered prostate adenocarcinoma in patients undergoing radical cystoprostatectomy (CPT) for bladder cancer.

Methods: Ninety-six consecutive patients scheduled to undergo CPT were prospectively enrolled. The prostates were excised completely during CPT. The CPT specimens were examined, and the clinico-pathologic characteristics of incidental prostate cancer studied. Complete transverse sections of the prostate were taken from the apex to the base at 4-mm intervals and all prostates were examined by a single pathologist.

Results: The mean patient age and prostate-specific antigen level were 66.1 ± 10.0 years and 2.8 ± 5.0 ng/mL, respectively. Of the 96 patients, 35 (36.5%) had prostate cancer (PCa). Of these incidental PCas, 57.1% (20.8% of all patients undergoing CPT) were clinically significant. None of the patients who were age ≤ 50 years had incidental PCa. However, the incidences of PCa in the 51–60 years, 61–70 years, and ≥ 71 years age groups were 27.8% (5/18), 48.7% (19/39), and 35.5% (15/31), respectively, and the difference according to the age subgroup was significant ($P = 0.048$). During the median follow-up of 49 months, 29.2% (28/96) of patients died. There were no PCa-specific deaths, and two patients (2.1%) showed biochemical recurrences.

Conclusion: Incidental PCas were diagnosed in ~40% of CPT specimens, and ~50% of incidental PCas were clinically significant. During radical CPT in patients aged ≥ 60 years, the possibility of the presence of PCa and the potential oncologic risk of partial prostatectomy during CPT should be remembered.

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1. Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy and the second leading cause of cancer-specific deaths in men in Western industrialized countries. In 2012, about 241,740 men were estimated to have been diagnosed with PCa in the USA.¹ Although the incidence of PCa is lower in Korea compared to the USA, it has been increasing in recent years. According to 2010 Cancer Statistics in Korea, prostate is among the five leading primary cancer sites in men, and the mortality rates of PCa have also increased.²

The prevalence of PCa far exceeds that of clinically detected disease. In autopsy studies, the prevalence of silent PCa varies among different ethnic and age-related groups. The majority of incidental prostate tumors is small, organ-confined, and considered clinically insignificant. Many of these tumors will never present with clinical signs during the lifetime of these men.³ Radical cystoprostatectomy (CPT) specimens represent a random sample of prostates from asymptomatic men, and these samples are then subjected to pathological examination and the patients undergo a clinical follow-up. This cohort is similar to that in autopsy studies in terms of randomness. Autopsy studies have revealed that PCas are found incidentally in 30% of 50-year-old men, and in 70% of 80-year-old men in the USA.⁴ Compared with Western countries, fewer studies on incidental PCa have been conducted in Asian countries. Clinical data in Asian countries are sparse because most of the published studies have been performed retrospectively. We

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reported the prevalence and the characteristics of incidental PCa in Korean men about 5 years ago. It was the first prospectively performed study. However, the limitation of that study was the small sample size and short-term follow-up.⁵ Therefore, we performed a larger cohort study with a longer observation period. Our aim was to review the features of incidentally discovered prostate adenocarcinoma in patients with bladder cancer with regard to its incidence, pathologic characteristics, and clinical significance.

2. Methods

2.1. Study population

The study protocol was approved by the Institutional Review Board of the Korean National Cancer Center, Goyang, Korea. One hundred consecutive male patients who were scheduled to undergo CPT and had no history or clinical evidence of PCa before surgery were enrolled into this study between January 2005 and December 2012 at a single institution. Routine preoperative evaluations included abdominal computed tomography, bone scans, digital rectal examination, and serum prostate-specific antigen (PSA) assay. Standard CPT with bilateral pelvic lymphadenectomy was performed in patients with transitional cell carcinoma (TCC) of the bladder. Four patients who underwent pelvic exenteration including CPT for other concomitant malignancies were excluded. Finally, this study was performed in a total of 96 Korean patients with TCC of the bladder or prostatic urethra. For urinary diversion, ileal conduit and orthotopic ileal bladder substitution were performed in 72 (75.0%) and 22 (22.9%) patients, respectively. In two patients (2.1%), partial cystectomy and radical prostatectomy was performed for TCC of the bladder neck or prostatic urethra. After CPT, regular computed tomography scans were performed during follow-up to detect primary tumor recurrence. Patients with incidental PCa were also scheduled for digital rectal examination and serum PSA evaluation at every 3 months for the 1st postoperative year and biannually thereafter. Biochemical recurrence was defined as a sustained PSA level >0.4 ng/mL on two or more consecutive occasions. Patients were evaluated according to age, tumor focality, tumor location, Gleason score, pathological tumor stage, extracapsular extension, seminal vesicle invasion, surgical margin status, tumor volume, and clinical significance. Follow-up data included data for adjuvant treatment, tumor relapse, subsequent medical intervention, and survival status.

2.2. Histopathologic evaluations

CPT specimens were immersed intact in formalin solution. The prostate and seminal vesicles were removed *en bloc* from the bladder, and the entire circumference of each resected prostate gland was inked. Complete transverse sections were taken from the apex to the base at 4-mm intervals. All prostates were examined by a single pathologist (W.S.P.). When adenocarcinoma of the prostate was detected, tumor location and tumor volume were noted {defined as $[0.4(\text{slope of the regression line}) \times \text{length} \times \text{width} \times \text{CPT thickness (number of cross sections} \times \text{sectional thickness)}]}$.⁶ Gleason score, presence of extracapsular extension, and evidence of seminal vesicle invasion were assessed. The 2002 Tumor-Node-Metastasis (TNM) classification was used to determine the pathologic stage, and if needed, immunohistochemical staining was performed using specific antibodies against PSA, prostate-specific membrane antigen, prostate stem cell antigen, α -methylacyl-coenzyme racemase, or p63. Significant PCa was defined as a tumor volume of 0.5 cm³ or larger, a Gleason score ≥ 7 , presence of extraprostatic extension, or a positive surgical margin.⁷

2.3. End points and statistical analyses

In the present study, we determined the prevalence of PCa in CPT specimens and evaluated whether these cancers were clinically significant. Then, we studied the clinical characteristics of these patients and determined the relationships between clinical parameters including age, PSA, and pathologic information. Chi-square analysis (or Fisher's exact test for nonparametric variables) was used to analyze categorical variables and the *t* test (or Mann–Whitney *U* test for nonparametric variables) was used to analyze continuous variables. SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, and two-sided $P < 0.05$ were considered significant.

3. Results

3.1. Patient characteristics

The clinicopathological characteristics of 96 men are summarized in Table 1. Radical CPT with ileal conduit diversion was performed in 72 patients (75.0%), CPT with ileal neobladder substitution in 22 (22.9%), and partial cystectomy and prostatectomy in two patients (2.1%). The mean age and preoperative PSA level of the patients were 66.1 ± 10.0 years and 2.8 ± 5.0 ng/mL. Thirty-nine patients (40.6%) had incidental PCa that was diagnosed after surgery. Of these 39 patients, clinically significant PCa was found in 57.1% (20.8% of all CPT patients; Table 2). The mean age in the 35 patients with incidental PCa was 69.1 ± 8.4 years and in patients without incidental prostate cancer was 64.4 ± 10.5 years, and this difference was significant ($P = 0.025$). Mean serum PSA level in patients with incidental PCa was significantly higher than that in patients without incidental prostate cancer (4.6 ± 7.3 ng/mL and 1.7 ± 2.2 ng/mL, respectively, $P = 0.013$). The incidence of PCa among eight patients who were aged ≤ 50 years was zero. However, the incidences of PCa in patients in the 51–60 years, 61–70 years, and ≥ 71 years age groups were 27.8% (5/18), 48.7% (19/39), and 35.5% (15/31), respectively, and the difference according to the age subgroup was significant ($P = 0.048$; Table 1). The incidences of clinically significant PCa in patients in the 51–60 years, 61–70 years, and ≥ 71 years age groups were 11.1% (2/18), 25.6% (10/39), and 25.8% (8/31), respectively, and the difference according to the age subgroup was insignificant (Table 2). As an adjuvant therapy, 39 patients with bladder TCC received platinum-based combination chemotherapy (e.g., methotrexate, vinblastine, actinomycin, and cisplatin or gemcitabine and cisplatin regimens), and one patient with PCa and lymph node metastasis underwent androgen ablation therapy with gonadotropin-releasing hormone agonists and antiandrogens.

3.2. Histopathologic characteristics

Among all of the patients, 35 (36.5%) had incidental PCa. Among them, high-grade prostatic intraepithelial neoplasia (HGPIN) was detected in 60.0% of patients (21.9% of all CPT patients). Twenty patients (20.8% of all patients) had an HGPIN without adenocarcinoma (data are not shown). The histopathological characteristics are summarized in Table 3. According to the pathologic staging of incidental PCAs, 21 cases (60.0%) were classified as pT2a, seven cases (20.0%) as pT2b, five cases (14.3%) as pT2c, one case (2.9%) as pT3b, and one case (2.9%) as pT4N1M0. Gleason scores ranged from 2 to 4 in four cases (10.2%), from 5 to 6 in 31 cases (79.5%), and from 7 to 10 in four cases (10.2%). Gleason scores from 2 to 4 of pathology were not defined as prostate cancer. Mean tumor volume was 0.9 ± 0.9 cm³, and a tumor volume >0.5 cm³ was identified in 22

Table 1The clinical characteristics of patients who underwent cystoprostatectomy according to the presence of incidental prostate cancer (PCa; $n = 96$).

Variable	Total patients	Patients without incidental PCa	Patients with incidental PCa	<i>P</i>
Patients	96 (100.0)	61 (63.5)	35 (36.5)	–
Age (y)	66.1 ± 10.0	64.4 ± 10.5	69.1 ± 8.4	0.025
PSA level (ng/mL)	2.8 ± 5.0	1.7 ± 2.2	4.6 ± 7.3	0.013
Age subgroup (y)				
≤ 50	8 (100.0)	8 (100.0)	0 (0.0)	0.048
51–60	18 (100.0)	13 (72.2)	5 (27.8)	
61–70	39 (100.0)	20 (51.3)	19 (48.7)	
≥ 71	31 (100.0)	20 (64.5)	15 (35.5)	

Data are presented as n (%) or mean ± SD.
PSA, prostate-specific antigen.

Table 2The clinical characteristics of patients who underwent cystoprostatectomy according to the presence of clinically significant prostate cancer (PCa; $n = 96$).

Variable	Total patients	Patients without significant PCa	Patients with significant PCa	<i>P</i>
Patients	96 (100.0)	76 (79.2)	20 (20.8)	–
Age (y)	66.2 ± 10.1	64.8 ± 10.0	71.4 ± 8.8	0.008
PSA level (ng/mL)	2.9 ± 5.0	1.9 ± 2.3	6.3 ± 9.1	0.001
Age subgroup (y)				
≤ 50	8 (0.0)	8 (100.0)	0 (0.0)	0.290
51–60	18 (100.0)	16 (88.9)	2 (11.1)	
61–70	39 (100.0)	29 (74.4)	10 (25.6)	
≥ 71	31 (100.0)	23 (74.2)	8 (25.8)	

Data are presented as n (%) or mean ± SD.
PSA, prostate-specific antigen.

Table 3Histopathologic characteristics of incidental prostate cancer according to age subgroup ($n = 35$).

Variable	Total patients	Age subgroup (y)			<i>P</i>
		51–60	61–70	≥ 71	
Patients	35 (100.0)	5 (14.3)	19 (54.3)	11 (31.4)	–
PSA level (ng/mL)	4.4 ± 6.9	3.1 ± 4.2	4.6 ± 8.3	4.4 ± 5.7	0.942
Pathologic stage					
Prostate confined	33 (100.0)	5 (15.2)	19 (57.6)	9 (27.3)	0.361
Extraprostatic extension	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	
Lymph node metastasis	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	
Gleason score					
5–6	31 (100.0)	4 (12.9)	17 (54.8)	10 (32.3)	0.796
7–10	4 (100.0)	1 (25.0)	2 (50.0)	1 (25.0)	
Tumor volume (cm ³)	0.9 ± 0.9	0.4 ± 0.2	0.9 ± 0.7	1.1 ± 1.1	0.238
Tumor volume					
>0.5 cm ³	22 (100.0)	2 (9.1)	11 (50.0)	9 (40.9)	0.236
≤0.5 cm ³	13 (100.0)	3 (23.1)	8 (61.5)	2 (15.4)	
Multiplicity					
Present	10 (100.0)	1 (10.0)	4 (40.0)	5 (50.0)	0.316
Absent	24 (100.0)	3 (10.7)	15 (53.6)	6 (25.0)	
Apex involvement					
Present	5 (100.0)	1 (20.0)	3 (60.0)	1 (20.0)	1.000
Absent	30 (100.0)	4 (13.3)	16 (53.3)	10 (33.3)	
Margin status					
Positive	3 (100.0)	0 (0.0)	3 (100.0)	0 (0.0)	0.722
Negative	29 (100.0)	5 (17.2)	15 (51.7)	9 (31.0)	

Data are presented as n (%) or mean ± SD.

BC, bladder cancer; CI, confidence interval; Cis, carcinoma *in situ*; HR, hazard ratio; LA, locally advanced; PSA, prostate-specific antigen; PSCA, prostate stem cell antigen.

patients (56.4%). Tumor involvement of the prostate apex was found in five of the 35 patients (14.3%). Three of the 32 patients (9.4%) had a positive surgical margin. Histopathologic characteristics of incidental PCa between age subgroups showed no significant differences.

3.3. Follow-up

Follow-up data were available for all of the 96 patients who underwent CPT. Median follow-up period was 49.0 months after

CPT (range, 10.0–90.0 months). Twenty-eight deaths had occurred by the time of analysis; 26 patients died of bladder cancer progression; and two patients died of other conditions. However, there were no PCa-specific deaths. The Kaplan–Meier survival curve showed that the presence of PCa (significant or not) was not associated with risk of mortality after CPT (Fig. 1). Except for one patient, almost all of the patients (30/31, 96.8%) with incidental PCa had undetectable serum PSA levels at 3 months after CPT. During the follow-up period, two of the 30 patients experienced a biochemical recurrence.

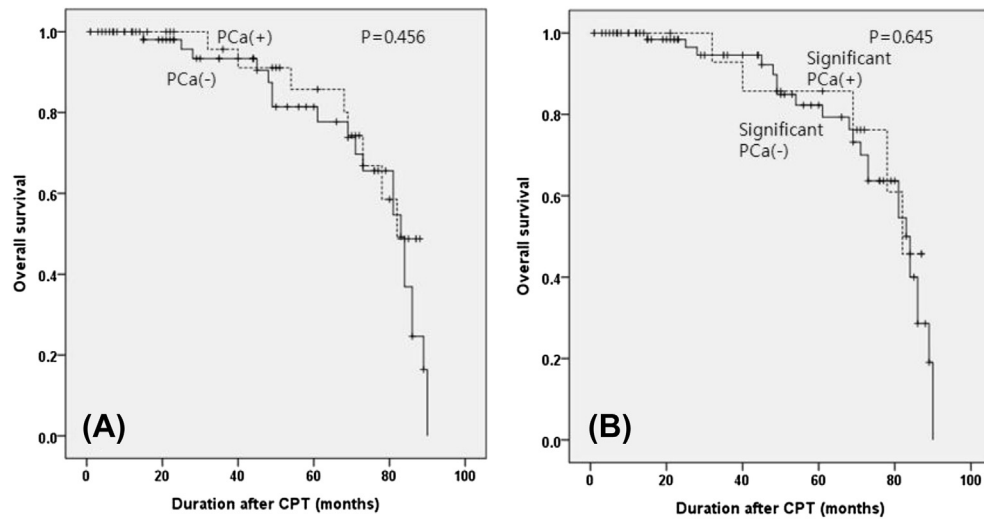


Fig. 1. Overall survival of patients. Patients (A) with or without incidental prostate cancer and (B) with or without clinically significant prostate cancer (PCa) in the cystoprostatectomy specimens. CPT, cystoprostatectomy.

4. Discussion

Several studies have reported incidental PCa detection rates of 14–60% in CPT specimens (Table 4).⁵ These high detection rates may be related to hereditary and exogenous factors, such as food consumption and patterns of sexual behavior. These substantial differences between studies can also be probably explained by the different pathologic evaluation methods used and different patient characteristics. The detailed pathological examination of the excised prostatic tissue specimens may be another important factor for the detection of small cancer.⁸ In this respect, two important issues are the thickness of the slice of the prostate and whether the prostate is totally embedded.⁹ The advantage of complete sampling over partial sampling is that small foci of cancer are seen more frequently. When prostate slices are thicker than 5 mm, small foci of cancer within the slice might be missed. By complete sampling, cancer features, such as extraprostatic extrusion and positive margins, are more accurately evaluated.¹⁰ Some investigators have suggested that the prostatic apex should be preserved to improve the results of continent neobladder substitution.¹¹ According to our literature search, the highest prevalence was reported by Winkler et al.,¹² who reported a rate of 60%, and the lowest prevalence of only 14% was reported by Delongchamps et al.¹³ Among Asian studies, a Taiwanese study reported that only 4% of 248 CPT cases had incidental PCa using a 5-mm section interval.¹⁴ By contrast, in

our previous report, PCa was detected in 18 of 36 patients (50%) who had undergone CPT when prostates were transversely sectioned at 4-mm intervals from the apex to the base.⁵ Another Asian study by Nakagawa et al.¹⁵ demonstrated a prevalence of 27% for incidental PCa among 349 patients, using a 5-mm section. In our present study (*n* = 96), incidental PCa was detected in 36.5% of all the men. Furthermore, HGPIN, a precursor lesion of prostatic adenocarcinoma, has a prevalence ranging from 0.7% to 16.5% in the West according to reports from various institutions. In the present study, HGPIN was found in 60% of PCa patients (21.9% of all CPT patients). Specifically, isolated HGPIN was found in 20 CPT specimens (20.8%) without evidence of PCa, which is a higher prevalence rate than that reported previously in studies on isolated HGPIN.^{16,17} Two major determinants of the PCa detection rate in CPT specimens are the sampled populations in terms of age and ethnicity, and the histopathological work-up of the specimens in terms of the proportion of tissue analyzed (whole mount vs. partial mount) and the width of sections. Mean patient age was the highest in our study than in other Asian studies, and detailed pathological examinations were performed in our study (4-mm whole-mount step sections) than in other Asian studies (5-mm whole mount step section: Taiwanese study, 5-mm section with an unknown sampling technique: Japanese study).

Our updated data showed a prevalence of 36.5% for incidental PCa in 96 CPT cases after sectioning at 4-mm intervals, but 42.8% of

Table 4
Published reports on incidental prostate cancer (PCa) in radical cystectomy specimens.

Study	Years	Country	<i>n</i>	Mean age (y)	Section (mm)	PCa <i>n</i> (%)	Significant PCa, <i>n</i> (%)	G2–4 %	G5 %	G6 %	G7 %	G8–10 %	pT2 %	pT3 %
Pritchett ²⁴	1988	USA	165	NA	NA	45 (27)	NA	—	—	—	—	—	82	18
Abbas ²⁵	1996	USA	40	64.3	2–3	18 (45)	NA	28	<u>67</u>	<u>67</u>	<u>67</u>	5	67	33
Revelo et al. ⁷	2004	USA	121	67.4	2–3.5	50 (41)	24 (48)	80	<u>80</u>	<u>80</u>	16	4	84	16
Delongchamps et al. ¹³	2005	France	141	62	4	20 (14.2)	14 (70)	<u>90</u>	<u>90</u>	<u>90</u>	10	0	90	10
Abdelhady et al. ³	2006	Canada	204	67	NA	58 (28.4)	18 (31)	78	<u>78</u>	<u>78</u>	20	2	90	10
Winkler et al. ¹²	2007	UK	97	NA	2	58 (60)	31 (53)	—	—	—	—	—	—	—
Joung et al. ⁵	2008	Korea	36	66	4	18 (50)	7 (39)	17	<u>67</u>	<u>67</u>	<u>17</u>	<u>17</u>	94.4	5.6
Nakagawa et al. ¹⁵	2009	Japan	349	65	5	91 (26.1)	68 (74.7)	<u>26</u>	<u>26</u>	<u>26</u>	69	4	93.4	6.6
Gakis ²⁶	2010	Germany	95	68	4–5	26 (27)	7 (27)	<u>85</u>	<u>85</u>	<u>85</u>	15	0	100	0
Aytac ²⁷	2011	Turkey	300	62	3–5	60 (20)	40 (66.6)	80	<u>80</u>	<u>80</u>	20	0	90	10
Alsinawi ²⁸	2012	Ireland	110	66	4	35 (32.5)	10 (28.5)	<u>80</u>	<u>80</u>	<u>80</u>	14	6	94	6
Present study	2013	Korea	96	66	4	39 (40.6)	20 (51.3)	10	<u>79</u>	<u>79</u>	<u>10</u>	<u>10</u>	94.9	5.1

G, Gleason score.

Data underlined indicate those spread across different gleason scores.

incidental PCa cases were considered clinically insignificant (tumor volume $\leq 0.5 \text{ cm}^3$, and Gleason score < 7). These results are comparable with the data presented in many Western studies.^{7,12} However, the largest Asian study by Nakagawa et al.¹⁵ demonstrated a low prevalence of incidental PCa (26.1%) and a high prevalence of clinically significant PCa (74.7%). These findings provide strong evidence that the reported prevalence of PCa in the CPT specimens is related to the section size. Significant PCa was relatively broadly defined in the Japanese study than in our study. In addition, racial heterogeneity might have also existed.

In several autopsy studies, the prevalence of silent PCa varies among different ethnic and age-related groups. In autopsy studies, the prevalence of PCa also varies according to the country. The prevalence of incidental PCa is estimated to be 14–70% in the 7th decade, and the highest prevalence rate is seen in African Americans.¹⁸ The incidence rate of PCa in our study (36.5%) is similar to that in the Japanese (32%) and Hungarian (44%) autopsy studies.¹⁸ The prevalence of incidental PCa in this study is much higher than that in the autopsy study conducted in China, which reported a prevalence of incidental PCa of 9.3% in men aged 51–69 years and a prevalence of 25% in men aged ≥ 70 years.¹⁹ There is some preliminary molecular evidence suggesting that the association between TCC and PCa might arise from a congruence in the expression of tumor suppressor genes (p53 and pRb) in both bladder and prostate cancers.²⁰ However, these data were obtained from a small sample of patients presenting with both malignancies ($n = 15$).²⁰ An autopsy study on PCa in age-matched Korean men without bladder cancer is required to assess the additional risk of PCa in men who have bladder cancer. In this study, we showed an incidence of 36.5% for incidental PCa in CPT specimens from the largest cohort of patients undergoing radical CPT in Korea. Our data indicated that the prevalence of PCa in the specimens increased according to age after CPT for bladder cancer. We found that the detection rate of PCa was significantly higher in the ≥ 61 years group (48.5%) than in the age ≤ 60 years group (19.2%). Pettus et al.²¹ demonstrated a significant association between age and concomitant PCa in 235 CPT specimens with a multivariable odds ratio of 1.3 (confidence interval 1.0–1.8; $P = 0.046$) per 10 years increase in age. In addition, Buse et al.²² quantified the increase in the odds ratio of PCa at 2.8% per year in these patients. In our cohort, we also found a significant association between age and the prevalence of occult PCa in the CPT specimens; however, we could not quantify the strength of the association due to the small sample size.

Histological criteria have been developed based on CPT specimens regarding differences between clinically significant versus insignificant PCa.²³ Clinically significant cancers are defined as having a volume $>0.5 \text{ mL}$ or a Gleason grade >6 , or are locally invasive. Tumors that do not meet any of these criteria are thought to represent clinically insignificant, low biological risk tumors that are unlikely to cause risk to the health of the patient. In our study, the prevalence of PCa increased with age. Overall 57.1% (20 of 35) of the tumors were clinically significant according to the histological definition, but two of all the tumors in men younger than 60 years (40%, 2 of 5) were clinically significant. In addition, there was no correlation between age and prevalence of significant PCa. This may be due to the small sample size of our study.

During the median follow-up period of 40 months after CPT, 29.2% (28/96) of patients died. Survival data showed no additional risk according to the presence of PCa. There were no PCa-specific deaths and two patients (2.1%) showed biochemical recurrences, which suggests that the outcome of patients with incidental PCa after CPT depends on the prognosis of the primary tumor. By contrast, in their large cohort study, Buse et al.²² concluded that concomitant PCa is an independent prognostic factor for mortality

after radical CPT for bladder cancer. However, the follow-up period in our study was longer (median, 40 months), and we routinely performed complete excision of the prostate gland during CPT at our institution unlike in the study by Buse et al.²² These differences could have affected the results.

A number of factors may have contributed to the variation between the findings of the current study and earlier studies. First, in the current study, unlike in earlier studies, a relatively homogeneous group of patients was assessed. The study population comprised of native Koreans. Second, this was a prospective, well-designed study with consistency in histopathological work-up of the specimens in terms of the proportion of tissue analyzed and the width of the sections. Third, the follow-up period of this study was the longest among the studies published in the literature to date. Our present study has some limitations that need to be mentioned. It is limited by a small sample size. A larger cohort study is required to determine the overall outcome of Korean patients with incidental PCa. In addition, CPT specimens represent a random sample of prostates from asymptomatic men, which are then subjected to pathological examination and to clinical follow-up. This cohort is similar to autopsy studies in terms of randomness, but differs fundamentally.

In conclusion, incidental PCas were detected in 36% of CPT specimens, with about half of the specimens showing characteristics of clinically significant PCa. Increasing patient age is associated with a high incidence of incidental PCa. During radical CPT in patients aged ≥ 60 years, the possibility of the presence of PCa and the potential oncologic risk of partial prostatectomy during CPT should be remembered.

Conflicts of interest

All authors declare no conflicts of interest.

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