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·Original Article·

Incidental prostate cancer in radical cystoprostatectomy specimens

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Abstract

Aim: To investigate the rates of prostate cancer (PCa) in radical cystoprostatectomy (RCP) specimens for bladder cancer in mainland China. To determine the follow-up outcome of patients with two concurrent cancers and identify whether prostate-specific antigen (PSA) is a useful tool for the detection of PCa prior to surgery. **Methods:** From January 2002 to January 2007, 264 male patients with bladder cancer underwent RCP at our center. All patients underwent digital rectal examination (DRE) and B ultrasound. Serum PSA levels were tested in 168 patients. None of the patients had any evidence of PCa before RCP. Entire prostates were embedded and sectioned at 5 mm intervals. **Results:** Incidental PCa was observed in 37 of 264 (14.0%) RCP specimens. Of these, 12 (32.4%) were clinically significant according to an accepted definition. The PSA levels were not significantly different between patients with PCa and those without PCa, nor between patients with significant PCa and those with insignificant PCa. Thirty-four patients with incidental PCa were followed up. During a mean follow-up period of 26 months, two patients with PSA > 4 ng/mL underwent castration. None of the patients died of PCa. **Conclusion:** The incidence of PCa in RCP specimens in mainland China is lower than that in most developed countries. PSA cannot identify asymptomatic PCa prior to RCP. In line with published reports, incidental PCa does not impact the prognosis of bladder cancer patients undergoing RCP. *(Asian J Androl 2008 Sep; 10: 809–814)*

Keywords: bladder cancer; cystoprostatectomy; incidental; prostate cancer; prostate-specific antigen

1 Introduction

Incidental prostate cancer (PCa) in radical cystoprostatectomy (RCP) specimens is very common in Europe and USA. The highest rate reported was 60% [1]. However, the rate is much lower in Asian countries, and only 4% in Taiwan according to a report by Lee *et al.* [2]. In terms of randomness, the studies on incidental PCa in RCP specimens are similar to autopsy studies. The primarily autopsy studies from mainland China revealed the incidental finding of PCa in Chinese men is significantly lower than that for men in USA; incidental PCa in Chinese men of 51–69 years old was 9.3% and that for men over 69 years old was 25% [3]. However, it has been reported that there was a higher incidence of PCa for men with bladder cancer [4, 5]. There is still no study on the rates of incidental PCa in patients undergo-

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ing RCP in mainland China.

Recently, some authors suggested that prostate-sparing cystectomy (PSC) might be appropriate in selected men to improve postoperative sexual and urinary function [6, 7]. However, PCa in retained prostatic tissue presents a clinical dilemma because the radiation doses recommended for PCa are above the toxic threshold for bowel, and surgery in this setting would likely compromise functional status [8]. Therefore, it is important to find a tool for detecting incidental PCa before operation. The prostate-specific antigen (PSA) value is the most common tool to screen and monitor PCa. Some authors reported that PSA levels were different between significant and insignificant PCa [9, 10], but other investigators did not report the same results [1, 11]. The value of PSA as a useful tool for the detection of PCa before surgery is still uncertain.

We conducted a retrospective investigation of 264 patients with bladder cancer undergoing RCP. We calculated the rates of incidental PCa in RCP specimens, compared the PSA levels between patients with incidental PCa and those without PCa, and analyzed the results of short-term follow-up after surgery in patients with incidental PCa.

2 Materials and methods

2.1 Study subjects

From January 2002 to January 2007, 264 patients with bladder cancer underwent RCP at Department of Urology, The First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China). The age of the patients ranged from 37 to 94 years (mean 65 years). Before RCP, all patients underwent clinical examination including digital rectal examination (DRE), B ultrasound, magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT), and a chest X-ray. Serum PSA levels were tested in 168 patients and 127 patients had emission CT bone scans. Two patients with bladder cancer were diagnosed as synchronous PCa before operation and excluded from the current study.

A standard RCP was carried out for all patients. Urinary diversion consisted of an orthotopic ileal neobladder in 104 cases, a cutaneous ureterostomy in 73 cases, and an ileal conduit in 87 cases. Complete transverse sections of the prostate were obtained at 5 mm intervals from apex to base. Tissue samples of each cross-section were examined under microscope. If adenocarcinoma of prostate was found, cancer volume was estimated from histological tissue using a ruled scale in two dimensions and the number of 5 mm planes involved in the third dimension. Then tumor grade, presence of extracapsular disease, evidence of seminal vesicle invasion, and lymph node metastasis were recorded. The 2002 tumor–node–metastasis classification was used to determine the pathological stage [12]. Clinically significant cancer was defined according to Revelo *et al.* [13] as a tumor volume > 0.5 mL, Gleason pattern ≥ 4, tumor extends through the prostatic capsule (pT3), lymph node metastasis, or positive surgical margins.

2.2 Statistical tests

Descriptive statistics are presented as mean ± SD, median, number, and percentage. The unpaired *t*-test (two-sided) was used for comparison between two groups. $P < 0.05$ was considered statistically significant.

3 Results

According to final pathological results, 250 patients were diagnosed with bladder transitional cell cancer (250/264, 94.7%). The remainder were diagnosed as squamous cell carcinoma (8/264, 3.0%) or adenocacinaoma (6/264, 2.3%). Of these, 37 patients (37/264, 14.0%) had evidence of adenocarcinoma of the prostate with a median age of 70.9 years (range 56–84 years). Incidental PCa in men of 51–69 years old was 10.3% (15/146) and in men older than 69 years it was 18.6% (22/118). Table 1 summarizes the pathological features of 37 patients undergoing RCP with incidental PCa. The median volume of PCa was 0.31 mL (0.04–1.08 mL). Twelve cases were clinically significant according to the definition of Revelo *et al.* [13]. Of these, there was lymph node metastasis in one case and positive surgical margin in one case. The median PSA level of 168 case patients before RCP was 2.2 ng/mL (0.5–9.4 ng/mL), and that for 26 patients with PCa was 2.8 ng/mL (0.6–8.6 ng/mL). There was no significant difference between these two groups. The PSA level between patients with and without clinically significant PCa was not significantly different (Table 2). The mean (range) follow-up of the 34 patients with adenocarcinoma of the prostate was 26 months (9–60 months). Three cases were lost to follow-up, nine patients died of bladder cancer, and four patients died of other diseases. PSA levels did not reach the nadir < 0.2 ng/mL (the cut-off value of biochemical

Table 1. Pathological features of bladder and prostate cancer (PCa) in 37 male patients who underwent radical cystoprostatectomy (RCP).

Bladder cancer		Prostate cancer	
Stage	No. of patients	Stage	No. of patients
pT1-pT2N0M0	28	pT1-pT2N0M0	34
pT3N0M0	3	pT3N0M0	2
pT4N0M0	4	pT3N1M0	1
pT4N1M0	2	pT4N0M0	0
Grade	No. of patients	Gleason score	No. of patients
I	0	2–4	5
II	21	5–7	29
III	16	7–10	3

Table 2. Comparison between clinically significant and insignificant prostate cancer (PCa) in male patients with bladder cancer who underwent radical cystoprostatectomy (RCP). PSA, prostate-specific antigen; TPSA, total PSA level ; FPSA, free PSA level ; F/T, free PSA level/total PSA level.

	Significant PCa		Insignificant PCa		*P* value
	mean ± SD	No. of patients	mean ± SD	No. of patients	
Mean age (years)	69.70 ± 7.90	12	70.90 ± 8.10	25	0.68
TPSA (ng/mL)	3.60 ± 2.60	8	2.40 ± 1.70	18	0.16
F/T (%)	24.80 ± 6.60	8	27.60 ± 10.50	18	0.51
Gleason score	6.10 ± 1.10	12	5.20 ± 0.70	25	0.01
Tumor volume (mL)	0.55 ± 0.17	12	0.20 ± 0.10	25	0.00
Follow-up (months)	22.60 ± 16.50	12	27.90 ± 11.10	22	0.29
Patient outcome	PSA did not reach the nadir < 0.2 ng/mL in four cases. Of these, PSA was > 4 ng/mL and castration was carried out in two cases. No patient died of PCa.	12	PSA did not reach the nadir < 0.2 ng/mL in one case. PSA was < 0.2 ng/mL in other 21 patients. No case had evidence of tumor recurrence.	22	NA

recurrence for PCa) [12] in five cases after surgery. Two of these had a PSA level > 4 ng/mL during the follow-up and underwent castration; the other three patients who had stable PSA levels were treated by watchful waiting. No patient died of PCa.

4 Discussion

The possibility of incidental PCa in RCP specimens is closely related to the incidence of PCa. PCa constitutes approximately 11% of all male cancers in Europe [14]. However, the incidence of PCa in Asia is much lower [15]. Therefore, in developed countries, incidental PCa in RCP specimens is much more common than that in Asian countries. Winkler *et al.* [1] analyzed 97 RCP specimens and incidental PCa was detected in 58 cases (58/97, 60%). Montironi *et al.* [16] found a 42% rate of incidental PCa with slices taken every 5 mm. In Asia, Hosseini *et al.* [17] identified seven PCa cases in 50 RCP specimens (14%) in Iran, a rate very similar to ours [17]. However, a surprisingly low rate was recently reported by a Taiwanese group; Lee *et al.* [2] found only 10 cases in 250 specimens (4%). Besides hereditary and exogenous factors, such as food consumption and patterns of sexual behavior, the detailed pathological examination of the excised prostatic tissue specimens is extremely important for the detection of small cancer. In this respect, two important issues are the thickness of the slice of the prostate and whether the prostate is totally embedded. We believe that the Stanford technique, using slices taken every 2–3 mm, could detect a higher incidence of PCa. However, many investigators still use

Table 3. Prostate cancer (PCa) in cystoprostatectomy specimens: data from published reports.

References	Samples (*n*)	Section (mm)	Sampling	PCa (%)
Montie *et al.* [18]	72	4.0–5.0	Total	46
Revelo *et al.* [13]	121	2.0–3.0, 5.0	Total	41
Moutzouris *et al.* [19]	59	5.0	Total	27
Montironi *et al.* [16]	132	5.0	Total	42
Pettus *et al.* [20]	235	5.0	Total	48
Lee *et al.* [2]	248	5.0	Total	4
Hosseini [17]	50	3.0–5.0	Total	14
Present study	264	5.0	Total	14

a pathologic examination protocol with 5-mm sections (Table 3). In our study using 5-mm sections, a few incidental cancers might have been missed, but the results are more comparable with studies using sections of the same thickness. Furthermore, careful preoperative evaluation to diagnose concurrent PCa is very important. In Winkler's study, the PSA range was 1.055–43.65 ng/mL, which was related to higher incidence. In our center, if the PSA > 4 ng/mL or a palpable nodule is found, a biopsy will be considered. If it is diagnosed as metastatic PCa, RCP will not be carried out. In addition, there were 96 patients without detected PSA levels before operation in this study, which could be a factor of higher incidence. Certainly, compared with Lee's report (from August 1993 to August 2003) [2], our results (from January 2002 to January 2007) could show an increasing trend in the incidence of PCa in Asia.

It has been reported that the possibility of coincidence of PCa is higher in patients with bladder cancer [4, 5]. However, Pritchett *et al.* [21] compared the frequency of incidental PCa in RCP specimens with that of latent PCa in autopsy cases and reported that there was no difference between the two groups. Compared with an autopsy report [3] which showed that the frequency of incidental PCa in 51–69-year-old Chinese men was 9.3% and that in men over 69 years was 25%, our study showed the rate of incidental PCa was 10.3% in 51–69-year-old men and 18.6% in over 69 years old men, respectively, which supports the opinion that patients with bladder cancer are not considered as a risk group for PCa. Furthermore, some patients with PCa had been excluded preoperatively by DRE, PSA and B ultrasound examination, which could explain why the incidence rate of our study is a little lower than that in the autopsy study. However, further studies with larger sample sizes should be carried out to verify whether bladder cancer is a risk factor for PCa.

Although PSA is the most common tool used to screen for PCa, our study showed that static PSA could not detect incidental PCa in patients with bladder cancer. This was also shown by Winkler *et al.* [1] and Ruffion *et al.* [11]. Therefore, the PSA value is confirmed as a poor screening tool that appears to cause a serendipitous detection of PCa. PSA thresholds should be abandoned as a biopsy trigger and better markers of biological aggressiveness should be sought. However, the PSA era and its challenges are not over. There is growing evidence supporting the importance of PSA kinetics, such as PSA velocity and PSA doubling time [22].

Stamey *et al.* [23] first defined the clinically significant adenocarcinoma of PCa in RCP specimens. This definition was modified by other authors [13, 24]. We took the definition used by Revelo *et al.*, [13] that is, a tumor volume > 0.5 mL, Gleason pattern ≥ 4, tumor extends through the prostatic capsule (pT3), lymph node metastasis, or positive surgical margins. According to this definition, the ratio of clinically significant PCa in our study was 32.4% (12/37). Some authors have tried to use PSA as a surrogate maker for tumor volume and incorporate this into predictive models of tumor significance. Although Stamey *et al.* [23] reported that serum PSA had long been associated with cancer volume, our study showed that PSA could not identify patients with clinically significant PCa from clinically insignificant PCa. Winkler *et al.* [1] also reached a similar conclusion, that the correlation between PSA and tumor volume was weak.

The overall survival rate of our group was 64.9% (24/37) and no patient died of PCa. Delongchamps *et al.* [25] reported on 141 patients with invasive bladder cancer.

Twenty patients had incidental PCa. No patients experienced PSA recurrence during the follow-up. The poor survival rate was due to the advanced stage of the bladder tumors seen in the majority patients. Pritchett *et al.* [21] reported no worse survival in patients with both cancers compared with those with bladder cancer alone. In our study, PSA did not reach the nadir < 0.2 ng/mL (considered the cut-off value of biochemical recurrence for PCa) in five patients after RCP. Of these, lymph node metastasis occurred in one case and positive surgical margin in one case. In both cases, PSA levels increased continuously during the follow-up, and castrations were carried out. However, the two patients were still alive. All of these findings show that incidental PCa does not influence prognosis and suggest that the outcome of patients with incidentally discovered PCa after RCP depends on the prognosis of the bladder cancer. However, the follow-up durations of all the studies are too short. Firm conclusions on the survival of patients with both cancers should be drawn by longer follow-ups involving more patients.

Recently, some authors have suggested PSC for bladder cancer to help improve functional recovery, such as sexual function and urinary continence [6, 7]. However, quality-of-life considerations should be balanced against concerns of cancer control. PSC increases the risk for residual cancers. Because PCa and prostatic urothelial carcinoma are common in RCP specimens. Pettus *et al.* [20] analyzed retrospectively 235 consecutive patients undergoing RCP. They identified 113 of 235 (48%) and 77 of 235 (33%) men with PCa and prostatic urothelial carcinoma, respectively. Fortunately, according to one published report [26] and our study, incidental PCa does not impact the prognosis of patients with bladder cancer. A major concern in patients undergoing PSC might be the risk of residual urothelial cancer, but not the risk of PCa. However, it is still necessary to exclude incidental PCa before PSC because PCa in retained prostatic tissue presents a clinical dilemma: the radiation doses recommended for PCa are above the toxic threshold for bowel; and surgery in this setting would likely compromise functional status. PSA levels, in our study, did not correlate either with the overall risk of PCa nor with the risk of clinically significant disease. Therefore, for candidates for PSC, it seems logical to include a routine prostate biopsy in the standard preoperative work-up, even in men with a normal DRE and PSA.

In addition, some studies showed that the preservation of the prostate apex did not improve urinary continence in intestinal bladder substitutes [27]. Therefore, the real impact of prostate-sparing radical cystectomy on functional outcomes requires further investigation.

In conclusion, the incidence of PCa in RCP specimens in mainland China is much lower than that in most developed countries, but is higher than that in Taiwan, China. PSA cannot identify asymptomatic PCa, so there is still no effective tool for the detection of PCa before surgery. In line with published reports, incidental PCa does not impact the prognosis of bladder cancer patients undergoing RCP.

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