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Incidence of Bladder Cancer Discovered by Urethrocystoscopy at Prostate Biopsy: Extraordinary High Incidence of Tiny Bladder Cancer in Elderly Males

HIROSHI OKAZAKI, KOICHI SUZUKI, TAKANORI SUZUKI, KOHEI KUROKAWA,[1] KAZUTO ITO,[1] KAZUHIRO SUZUKI[1] and HIDETOSHI YAMANAKA[1]

Department of Urology, Gunma Cancer Center, Ota 373-8550,
[1]Department of Urology, Gunma University School of Medicine, Maebashi 371-8511

OKAZAKI, H., SUZUKI, K., SUZUKI, T., KUROKAWA, K., ITO, K., SUZUKI, K. and YAMANAKA, H. *Incidence of Bladder Cancer Discovered by Urethrocystoscopy at Prostate Biopsy: Extraordinary High Incidence of Tiny Bladder Cancer in Elderly Males*. Tohoku J. Exp. Med., 2004, **203** (1), 31-36 —— In order to clarify the incidence of bladder cancer with and without prostate cancer, we investigated bladder cancer discovered incidentally by urethrocystoscopy at prostate biopsy. Between April 1997 and December 2003, 498 patients who were suspected prostate cancer were performed prostate biopsy and urethrocystoscopy simultaneously. We investigate possible invasion of prostate cancer into the urethra or bladder mucosa as well as bladder cancer, including other benign lesions of the bladder by urethrocystoscopy. Prostate cancer was confirmed in 175 (35.1%) of the 498 patients histologically, and bladder cancer was discovered incidentally in 12 patients (2.4 %). The incidence of bladder cancer in patients with prostate cancer of 2.3% (4/175) was not significantly different from that in patients without prostate cancer, which was 2.5% (8/323). Superficial and those with a size less than 1 cm were noted in 11 patients (92%) and 10 patients (83%) respectively. High incidence rate of bladder cancer with prostate cancer was reported previously, however, there was no study to compare the incidence rate of bladder cancer between cases with and without prostate cancer. The present study suggests that asymptomatic tiny bladder cancer may be present at an unexpectedly high incidence rate in elderly males. ——— prostate biopsy; bladder cancer; urethrocystoscopy; incidence; clinically significant tumor

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Present address for Hiroshi Okazaki, Department of Urology, Tatebayashi Kosei Hospital, 262-1, Narushima-machi, Tatebayashi, Gunma 374-8533, Japan.
E-mail: h-okakky@tohgoku.or.jp

For reprints request, contact H. Okazaki at the address above.

The pathogenesis of prostate cancer and bladder cancer is thought to be similar and the incidence rate of prostate cancer may be high in patients with bladder cancer (Montie et al. 1989; Tashiro et al. 1999; Kurokawa et al. 2002). Similarly, the incidence rate of bladder cancer may be high in patients with prostate cancer (Chun 1997).

Both bladder cancer and prostate cancer are frequently diagnosed in elderly. In Japanese, the mean age at the onset of bladder cancer is about 70 years (Nakao et al. 1989; Okazaki et al. 1998), which is similar to that of prostate cancer (Watanabe 2000). Several clinical studies demonstrated that the incidence rate of bladder cancer might be high in patients with prostate cancer, however, there was no study to compare incidence of bladder cancer between cases with and without prostate cancer.

In the present study, we compared difference in the incidence rate of bladder cancer between men who were diagnosed with prostate cancer and were those without prostate cancer.

Materials and Methods

Prostate biopsy was performed in 505 consecutive patients with increased prostate-specific antigen (PSA) levels, and abnormal findings on digital rectal examination (DRE)/transrectal ultrasonography (TRUS) in the Department of Urology at Gunma Cancer Center between April 1997 and December 2003. Majority of patients were visited our outpatient clinic to undergo detailed examination for PSA screening and remaining patients having lower urinary symptoms were introduced to rule out prostate cancer. Seven patients were excluded from this study, in whom prostate biopsy was performed under local anesthesia. No patients had past history of transitional cell carcinoma of the bladder or ureter. The study was performed according to the institutional review board guideline and written informed consent was obtained from all patients with respect to urethrocystoscopy at biopsy. TRUS-guided age-specific and prostate volume-adjusted prostate biopsy (Ito et al. 2002) was performed transrectally at 8 to 20 sites under spinal block. Urethrocystoscopy was performed on the operating table just before the prostate biopsy and investigated possible invasion of prostate cancer into the urethra or bladder mucosa as well as bladder cancer, including other benign lesions of the bladder. When abnormalities needing treatment were observed, endoscopic treatment was performed simultaneously. When bladder cancer was detected, transurethral resection of the tumor (TUR-BT) was performed, and histopathological evaluation was carried out. Prostate biopsy was performed several times in 37 patients of 498, only first urethrocystoscopic finding was evaluated in these cases.

We evaluated the incidence rate of bladder cancer between men who were diagnosed with prostate cancer and those without prostate cancer and the clinicopathological features of detected tumors.

Differences were considered significant when p was <0.05 using Mann-Whitney's U-test, the χ^2 test or Fisher's exact test if the expectation on χ^2 test was 5 or less.

Results

The mean age of 498 consecutive patients who underwent prostate biopsy was 70.3±8.0 years (mean±S.D.). The median serum PSA level (Tandem-R kit, SRL Inc., Tokyo) was 7.4 ng/ml and ranged from 0.4 to 4370 ng/ml (45.3±231.2 ng/ml; mean±S.D.). According to the distribution of serum PSA levels, 28 patients were PSA levels less than 2.1 ng/ml with abnormal DRE and/or TRUS, 36 were 2.1 to 4.0 ng/ml, 262 were 4.1 to 10 ng/ml, and 172 were greater than 10 ng/ml, respectively. In 175 patients, prostate cancer was confirmed histopathologically (CaP group), and the age ranged from 46 to 91 years (71.9±7.4). The age of the remaining 323 patients (Non-CaP group) ranged from 39 to 88 years (69.4±8.2). In the age distribution between the CaP and Non-CaP groups, CaP group was significantly older than Non-CaP ($p<0.01$, Table 1). In

TABLE 1. *Comparison of clinical characteristics in patients with and without prostate cancer*

Variables	CaP group	Non-CaP group	Statistical significance
No. of patients	175	323	
Age (years old)			
Mean±S.D.	71.9±7.4	69.4±8.2	
Median	72.3	70.2	$p<0.01$[1]
Range	46-91	39-88	
No. of patients with bladder cancer	4	8	N.S.[2]
% of patients with bladder cancer	2.3%	2.5%	
Age (years old)			
Mean±S.D.	76.0±9.1	73.2±10.4	
Median	78.5	75	N.S.[1]
Range	63-84	50-83	
Tumor shape			
papillary, pedunculated	3	7	N.S.[2]
papillary, broad based	1	1	
No. of tumor			
Single	3	6	N.S.[2]
Miltiple	1	2	
Tumor diameter (cm)			
<1	4	6	N.S.[2]
1 to 3	0	2	
pT category			
pTa/pT1	4	7	N.S.[2]
pT2	0	1	
Histological grade			
G1	3	5	N.S.[2]
G2	1	3	

CaP, prostate cancer; Non-Cap, non-prostate cancer; PSA, prostate specific antigen; N.S., not significant.

[1] Results were compared by Mann-Whitney's U-test.

[2] Results were compared by χ^2 test or Fisher's exact test if the expectation on χ^2 test was 5 or less.

12 patients (12/498, 2.4%), bladder cancer was detected by urethrocystoscopy and confirmed histologically, the age ranged from 50 to 84 years (74.2±9.7). Age, reason for prostate biopsy, PSA level, microhematuria, tumor number, shape, and histopathological findings are shown in Table 2. Four patients out of 498 (4/498, 0.8%) had prostate cancer and bladder cancer simultaneously. Of these 4 double cancers, 3 (3/4, 75%) patients had advanced stage prostate cancer with low stage bladder cancer.

Invasion into the urethra or bladder mucosa was observed in 7 patients out of the 175 prostate cancers. As for other benign findings, bladder stone was observed in 1 patient, transitional papilloma in 5 patients, and bladder mucosal cysts in 1 patient. And none of these was thought to be clinically serious.

Bladder cancer was concurrently detected in 4 patients out of the 175 prostate cancers, at an

TABLE 2. *Patient characteristics of bllader cancer diagnosed at prostate biopsy*

No.	Age	Reason for prostate biopsy	Microhematuria	PSA (ng/ml)	Tumor shape	Number	Size	BT histology	pT	Prostate histology, stage
1	83	Abnormal DRE	(–)	4.6	Papillary broadbased	Multiple	<1 cm	TCC G1	a	Non-CaP
2	84	Pollakisuria	(–)	87.8	Papillary broadbased	Multiple	<1 cm	TCC G1	1	CaP, wel, T3N0M0
3	63	Pollakisuria	(–)	180.0	Papillary pedunculated	Single	<1 cm	TCC G1	1	CaP, mod, T3N0M0
4	70	Pollakisuria	(–)	4.5	Papillary pedunculated	Multiple	1<3 cm	TCC G2	2	Non-CaP
5	75	Prostate disease screening	(–)	5.0	Papillary pedunculated	Single	<1 cm	TCC G2	1	Non-CaP
6	83	Abnormal DRE	(–)	2.8	Papillary pedunculated	Single	1<3 cm	TCC G1	1	Non-CaP
7	76	PSA elevation	(–)	6.3	Papillary pedunculated	Single	<1 cm	TCC G1	a	Non-CaP
8	75	PSA elevation	(–)	10.2	Papillary pedunculated	Single	<1 cm	TCC G1	a	Non-CaP
9	77	Prostate disease screening	(–)	5.3	Papillary pedunculated	Single	<1 cm	TCC G2	a	CaP, mod, T2b0M0
10	80	Nocturia	(–)	410.0	Papillary pedunculated	Single	<1 cm	TCC G1	a	CaP, mod, T3N0M0
11	50	PSA elevation	(–)	2.7	Papillary pedunculated	Single	<1 cm	TCC G2	a	Non-CaP
12	74	Dysuria	(–)	3.1	Papillary pedunculated	Single	<1 cm	TCC G2	1	Non-CaP

DRE, digital rectal examination; TCC, transitional cell carcinoma; BT, bladder tumor; CaP, prostate cancer; mod, moderately differentiated adenocarcinoma; wel, well differentiated adenocarcinoma.

incidence of 2.3% (4/175, CaP group), and the bladder cancer incidence of the non-prostate cancer patients was 2.5% (8/323, Non-CaP group). Therefore, incident of bladder cancer in each group was not different significantly. The clinicopathologic features of the tumors between the 2 groups were not also different significantly. Muscle-invasive bladder cancer (pT2) of G2 transitional cancer was found only 1 patient without prostate cancer.

Discussion

Recent studies have suggested that the tumorigenesis of both prostate and bladder cancer is similar in part. Singh et al. (1999) reported that the tumor suppressor genes p53 and Rb play a crucial role in the development of those two cancers. Amara et al. (2001) reported that the prostate stem cell antigen, which is expressed in the majority of human prostate cancers, was also over-expressed in human transitional cell carcinoma.

Several clinical studies have demonstrated that the incidence of bladder cancer might be high in patients with prostate cancer. Since the diagnostic bias can occur when the presence of one genitourinary cancer leads to a greater likelihood of evaluations that result in incidental diagnosis of another genitourinary cancer, the high incidence of bladder cancer in patients with prostate cancer might partly be attributed to diagnostic bias. To evaluated this diagnostic bias, there have been some studies concerning the usefulness of urethrocystoscopy for prostate cancer. Some studies have asserted the usefulness of urethrocystoscopy prior to radical prostatectomy in finding bladder cancer (Kim and Ignatoff 1994; Schwartz et al. 1996), however, recently Mor et al. (2001) reported routine urethrocystoscopy before radical prostatectomy was not useful. In this report, nonmalignant bladder lesions ranged from 1.2% to 7.7% and incidence of concurrent bladder cancer ranged from 0.4% to 6.6% (Kim and Ignatoff 1994; Ranparia et al. 1996; Schwartz et al. 1996; Mor et al. 2001). Woehr et al. (2000) reported that invasive cancer was concurrently detected in 1.0% (10/966). In short summary, these studies strongly suggest that the incidence rate of bladder cancer concurrent in patients with prostate cancer may be high, but the clinical significance of detected tumors is still controversial.

From the perspective of the prevalence of bladder cancer in the elderly, there have scarcely been any reports. We performed urethrocystoscopy in patients undergoing prostate biopsy and detected 12 cases of incidental bladder cancer. The incidence of concurrent bladder cancer in the CaP group was 2.3% (4/175), which was almost similar to that of the above-mentioned reports. Furthermore we found that the incidence of bladder cancer in the Non-CaP group of 2.5% (8/323), which was extraordinary high.

In the literature, it has been reported that the incidence rate of bladder cancer is 15.8/100 000 in Japanese males, 53.9/100 000 in the 65 to 69-year age group, and 80.7/100 000 in the 70 to 74-year age group (Tsukuma 2003). In comparing this incidence and our results, the incidence in our study is 28 times higher. In the 12 patients in our study, the tumors were tiny, superficial and might to be detected only by urethrocystoscopy that provided a direct and augmented visual field.

Concerning latent prostate and bladder cancer, it is generally known that the incidence of prostate cancer detected at autopsy ranges from 14 to 34% (Rich 1935; Franks 1954; Yatani et al. 1988).

However, none of the previous studies reported the incidence of latent bladder cancer. Our results may suggest that asymptomatic small bladder cancer like latent prostate cancer may be present at an unexpectedly high incidence rate in elderly males.

From a viewpoint of medical cost, urethrocystoscopy is performed on the operating table just before the prostate biopsy under spinal block, expense of cystoscopy procedure (about 80 US $ in a medical insurance of Japan) is added to prostate biopsy. We detected 12 bladder cancer cases and 7 benign findings incidentally and treated si-

multaneously. However, taking into account that almost lesions are thought to be not serious clinically, routine urethrocystoscopy may not be justified for medical cost.

We revealed an extraordinary high incidence of bladder cancer in patients undergoing prostate biopsy for the first time. However, most of the bladder cancer lesions are tiny and superficial, it is unclear whether the detection and treatment of these lesions are clinically significant.

Conclusion

We discovered bladder cancer incidentally by urethrocystoscopy at prostate biopsy and clarified an extraordinarily high incidence of tiny bladder cancer. The incidence rate of bladder cancer in patients without prostate cancer is high as well as with prostate cancer. Our results suggest that asymptomatic tiny bladder cancer may be present at an unexpectedly high incidence in elderly males.

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