Long-Term Management of Incidental Bladder Cancer Detected in Patients Undergoing Prostatectomy for Prostate Cancer

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Key Words

Incidental bladder cancer • Prostate cancer

Abstract

Introduction: At our institution, screening for incidental bladder cancer is routinely performed to avoid tumor cell dissemination caused by surgery in patients undergoing prostatectomy for prostate cancer (PCa). Here, we report the long-term clinical results in patients with incidental bladder cancer detected by routine screening prior to prostatectomy. **Materials and Methods:** Between January 2003 and December 2013, 430 patients undergoing prostatectomy for resection of PCa were enrolled in this cohort study. All patients underwent screening with cystoscopy, urinary sediment analysis, and urinary cytology to detect incidental bladder cancer. The clinical outcomes of cases with incidental bladder cancer were evaluated. **Results:** The incidence of incidental bladder cancer was 2.1% (9/430). All tumors were single papillary tumors located around the urinary orifice or lateral side and were diagnosed as urothelial cancer (UC). No significant findings were detected by urinary sediment analysis or urinary cytology. Pathological results of transurethral resections revealed 5 cases of pTa with Grade 1 UC and 4 cases of pTa with Grade 2 UC. Androgen-deprivation therapy was administered to 8/9 patients. During the observation period (average of 7.2 years), UC recurrence was detected in 2 cases (2 and 7.3 years). However, transurethral resection successfully removed the tumor completely. After an average of 19.6 months (12–25 months) without UC recurrence,

7 patients (77.8%) underwent prostatectomy, and 2 patients received radiation or androgen-deprivation therapy. Prostatectomy was carried out without dissemination of UC during the observation period. **Conclusion:** Incidental UC was detected in 2.1% of prostatectomy candidates. Preoperative routine screening with flexible cystoscopy was useful to detect early incidental UC.

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Introduction

Prostatectomy is the treatment of choice for prostate cancer (PCa). During preparation for surgery, information on the condition of the prostatic urethra and seminal vesicles, including the location of the urinary orifice, is indispensable, since prostatectomy itself requires dissection between the prostate and the urinary bladder and vesicle anastomosis with the urethra.

With regard to how the condition of the vesicles affects surgery, 1.4–2.2% of cases with a coincident rate of bladder tumor (BT) and PCa have been reported [1–4]. However, since screening with routine cystoscopy could detect simultaneous BT and PCa with only a relatively low incidence (0.4–0.9%) [5, 6], justification of the use of routine cystoscopy has been uncertain.

According to our institutional policy, screening for incidental BT with routine flexible cystoscopy is performed in patients undergoing prostatectomy for resection of PCa. However, if incidental BT is detected, an optimal

Table 1. Baseline characteristics of incidental bladder cancer in patients with PCa

Patient demography (bladder cancer)	Values
Number	9/430 (2.1%)
Papillary/non-papillary	9/0
Single/multiple	9/0
Size, mm	5.7 ± 3.8 (3.0–15.0)
Location: around orifice/lateral wall	7/2
cTa/over cT1	9/0
Microscopic hematuria : (+)/(-)	0/9
Cytology: positive/negative	0/9
Pathological results	
pTa/over pT1	9/0
G1/G2 and G3	9/0

Table 2. Baseline characteristics of PCa in patients with incidental bladder cancer

Patient demography	Values
Number	9/430 (2.1%)
Age, years (range)	61.6 ± 6.09 (58–69)
Prostate specific antigen, ng/ml (range)	7.0 ± 3.0 (4.7–13.6)
Gleason score	
6	7 (77.8%)
7	1 (11.1%)
8	1 (11.8%)
Clinical T stage	
1c	3 (33.3%)
2	6 (66.4%)
Risk classification	
Low	1 (11.8%)
Intermediate	7 (77.8%)
High	1 (11.8%)

treatment strategy for PCa without dissemination of BT has not been established due to insufficient knowledge of the long-term history of patients with simultaneous incidental BT and PCa.

To assess the information required to design an optimal treatment strategy for PCa with incidental urothelial cancer (UC), we analyzed the long-term clinical results of incidental BT detected by routine screening of prostatectomy candidates.

Materials and Methods

A total of 430 patients undergoing prostatectomy for resection of PCa between January 2003 and December 2013 were enrolled in this prospective cohort study. As part of the preoperative work-

up, all patients underwent routine screening with cystoscopy, urinary sediment analysis, and urinary cytology in an outpatient setting to detect incidental BT, followed by systemic screening consisting of computed tomography, pelvic magnetic resonance imaging and bone scintigraphy. Routine cystoscopy was performed 1 month prior to the date of surgery. If incidental BT was detected, patients underwent transurethral resection of BT, and the prostatectomy was immediately cancelled. After BT resection, patients underwent additional routine cystoscopy with urinary sediment examination, and urinary cytology every 3 months for the first year, every 4 months for the second year, every 6 months between 3 and 4 years, and annually after 5 years.

Our criterion for administration of curative treatment for PCa, consisting of prostatectomy or radiation, was ≥ 1 year free of recurrence of BT. The clinical outcomes of patients with incidental BT associated with PCa were evaluated.

Statistical Analysis

The chi-square test was used to compare the incidences of incidental BT. Differences with p-values < 0.05 were considered statistically significant. All statistical analyses were performed with SPSS version 15 software (SPSS, Chicago, IL, USA).

Results

The incidence of incidental BT was 2.1% (9/430). All tumors were single papillary tumors located around the urinary orifice in 7 cases (77.8%) and the lateral wall in 2 cases (22.2%). The mean tumor size was 5.7 mm, and the clinical T stages were cTa. No significant findings were detected by urinary sediment analysis or urinary cytology.

Transurethral resections were performed, and the pathological results revealed pTa Grade 1 or Grade 2 UC. Additional transurethral resections were carried out for Case 3 and Case 9, and the pathological results were the same as the previous results, pTa Grade 1 (table 1).

The clinical characteristics of PCa are summarized in table 2. The average age of the patients was 61.6 years, the average prostate specific antigen was 7.0 ng/ml, and a high incidence (77.8%) of a Gleason score of 6 was revealed. Androgen-deprivation therapy (ADT) was administered to all patients except Case 4. The average observation period was 7.2 years, during which UC recurrence was detected in 2 cases (7.3 years and 12.1 years in Case 3 and 2 years in Case 9). However, transurethral resection successfully removed the tumor completely.

In terms of the treatment strategy for PCa, after at least 1 year and an average of 19.6 months (12–25 months) without UC recurrence, 7 patients (77.8%) underwent prostatectomy, and 2 patients received radiation or ADT. Prostatectomy did not appear to cause UC dissemination during the observation period (fig. 1).

Fig. 1. Course of incidental bladder cancer in patients undergoing prostatectomy for PCa (TUR-BT= transurethral resection of bladder cancer; RT = radiation therapy; RP = radical prostatectomy).

Discussion

In an early study of second primary cancers detected in patients with PCa, the incidence of bladder cancer and malignant lymphoma was significantly higher than expected [2]. A subsequent study determined that the BT rate in patients with PCa is 18 times higher than expected [4]. To detect BT in the early stage, cystoscopy is indispensable; however, the efficacy of routine cystoscopy for the detection of incidental BT is uncertain, and a standard strategy for the management of PCa associated with incidental BT has not been established, due to insufficient evaluation of routine cystoscopy and lack of long-term observations of outcomes of patients with incidental BT.

In our clinical practice, we have continued to use routine cystoscopy for candidates for prostatectomy, under our institutional policy. In addition, as a treatment strategy for PCa, definitive treatment, prostatectomy or radiation, was administered with a ≥ 1 -year recurrence-free interval after resection of BT. With this strategy, we were able to manage both PCa and BT successfully, without dissemination of BT.

To determine the incidence of simultaneous presentation of BT and PCa, we reviewed the literature, focusing on the incidence of BT, the indication for cystoscopy, and the strategy of treatment for PCa after treatment for BT

(table 3) [1–10]. In summary, simultaneous presentation of BT and PCa was defined as one cancer being diagnosed at the same time as the other, or within the same 6-month period, or when one carcinoma is diagnosed during work-up for the other [3]. The incidence of simultaneous presentation of BT and PCa was 0.4–6.6%.

According to our results, the incidence of simultaneous presentation of BT in candidates for prostatectomy for PCa was 2.1%, which is in the middle of that range. Since the criteria for cystoscopy may affect the reported incidence, we reviewed the criteria for cystoscopy in these reports. Most of the indications for cystoscopy were urological symptoms, consisting of hematuria or dysuria [3, 4, 7–9]. Evaluation for this indication was reported in only 3 studies, including our report [5, 6]. The incidence in cases with urological symptoms tended to be higher (2.2–6.6%) compared with the others (0.4–2.1%).

In terms of the effectiveness of routine cystoscopy, evaluation of its benefit was difficult, since cystoscopy may provide many types of benefits in addition to information for prostatectomy and screening for BT. Therefore, we focused our evaluation on the incidence of and benefits for BT.

In general, to obtain crucial information related to the condition of the prostate, urethra and vesicles, preoperative cystoscopy was thought to be beneficial, except for

Table 3. Summary of reported cases of simultaneous presentation of bladder cancer and PCa

Report	Year	Simultaneous incidence before treatment (cases)	Indication of cystoscopy	Interval until treatment for PCa
Androulakakia et al. [1]	1986	2.0% (12)	unknown	radiotherapy after 2 years
Liskow et al. [2]	1987	1.4% (14)	unknown	unknown
Konski [3]	1991	2.2% (22)	hematuria, symptom	unknown
Kim et al. [5]	1994	0.9% (4)	76% of cases	unknown
Schwartz et al. [7]	1996	4.0%(4)	hematuria, symptom	2 years
Ranparia et al. [8]	1996	6.6% (6)	urological history, hematuria	unknown
Chun et al. [4]	1997	3.2% (18)	hematuria, symptom	unknown
Mor et al. [6]	2001	0.4% (1)	routine	immediately
Singh et al. [9]	2005	3.1%(21)	hematuria, symptom	unknown
Boorjian et al. [10]	2007	0.4% (42) ^a	unknown	unknown
Present study	2018	2.1% (9)	routine	1 year

^aWithin 30 days after treatment.

the screening of BT. Actually, cystoscopy may provide information regarding prostatic anatomy, such as the median lobe position of ureteric orifice [7], pre-existing urethral pathologic conditions, and tumor encroachment on the urethra [5]. Thus, outpatients undergoing radical prostatectomy should be assessed with preoperative cystoscopy to screen for possible bladder cancer and to evaluate the lower urinary tract [5, 7], which can be done at low cost with minimal morbidity [7].

In contrast, in another study, pre-operative rigid cystoscopy detected BT in less than 0.4% (1/225) of patients; thus, routine cystoscopy before prostatectomy was considered unjustified, due to lack of cost effectiveness [6].

In addition, in the robotic-assisted prostatectomy era, for the first step in the anterograde approach, dissection between the prostate and the urinary bladder is needed, with wide visibility of the inside of the vesical membrane; thus, information about the condition of the urethra and vesicles will be indispensable. We have continued to evaluate routine cystoscopy, for the future, in the robotic-assisted prostatectomy era.

The incidence of incidental BT in our population tended to be higher (2.1%) compared with those in previous reports that used routine cystoscopy (0.4–0.9%) [5, 6]. The reason for this difference is likely the difference in patient background. Characteristics such as older age, white, low income and education, and smoking were independent risk factors for BT and PCa [10]. In another study, initial treatment with prostatectomy for PCa led to a delay in bladder cancer diagnosis, affected by treatment history [4]; thus, routine cystoscopy may provide a benefit for BT management. In our study, no urological signs, such as microscopic hematuria and dysuria or pos-

itive urinary cytology were demonstrated in any of the 9 cases with incidental BT; thus, we do not agree with the indication of cystoscopy only for patients with urological symptoms.

In terms of the optimal interval between treatment for bladder cancer and prostatectomy, radical prostatectomy should not be attempted to prohibit BT implantation into the surgical field during manipulation of the urinary tract, until the patient is free from recurrence of BT. In general, noninvasive BT is not a contraindication for radical treatment of the prostatic primary cancer alone [11]. Unfortunately, the optimal interval between treatment for bladder cancer and prostatectomy has been uncertain. According to a previous report, 3 of 4 cases with transitional cell carcinoma undergoing prostatectomy for localized PCa, were free of disease 2 years after diagnosis [7]. In contrast, in another study, it was recommended that prostatectomy should be carried out immediately, without assessment of BT [6]. In addition, during the observation period, additional ADT should be administered for PCa until complete of staging of the incidental BT [7]. In our study, we delayed curative treatment for PCa until patients were free of BT recurrence for ≥ 1 year after transurethral resection followed by ADT in 88.8% of cases (8/9). Additional resection for BT was needed at 23 months in only 1 case (Case 9); fortunately, we succeeded in managing both PCa and BT with this strategy. According to these results, we suggest that a 1-year interval would be acceptable with appropriate clinical findings.

How long should examination by cystoscopy be continued? To determine the appropriate period of cystoscopy, the risk of BT should be evaluated. Patients with

BT should undergo surveillance after resection [7], since BT was detected after initial primary PCa [2, 10]. With regard to secondary BT, an increased risk has been observed after radiation therapy for PCa [12, 13]. Patients with localized PCa treated with radiotherapy have a higher risk of BT [10, 14]. In contrast, there is no evidence of an increased risk of BT after external beam radiation therapy [15, 16] or brachytherapy for PCa, compared with prostatectomy [17]. Even though an increased risk of BT after radiation therapy is uncertain, we observed BT with routine cystoscopy over 5 years. BT was detected within 2 years of resection in Case 9 and over 7

years in Case 3. Thus, we suggest that routine cystoscopy should be continued for over 5 years, especially after radiation therapy.

The limitation of this study is its limited number of cases. However, incidental bladder cancer was detected with routine cystoscopy in 2.1% of prostatectomy candidates, which is a relatively high incidence compared with previous reports [6, 7]. In addition, with over 5 years of observations, routine work-up with detection of incidental BT by routine screening and curative treatment for PCa, after strict observation for BT recurrence over at least 12 months. This information should be useful for designing a strategy for candidates for prostatectomy.

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