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Original Article

Clinicopathologic insight of synchronous primary urologic cancers

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Abstract: Objective: This study aimed to reveal the clinical and histopathologic characteristics of patients with synchronous primary urologic cancers (SPUC). Methods: A retrospective chart review was performed in a large group of patients with genitourinary cancer in our hospital from 1980 to 2010, and patients with SPUC were mined to conduct the clinical and pathologic characteristics of SPUC. Results: In this work, among 2107 patients with genitourinary cancer, a total of 127 cases were SPUC, with a prevalence rate of 6.0%. While only 102 SPUC patients were enrolled because 25 of them miss follow-up. A total of 204 patients with single primary cancer randomly selected from our hospital were set as control group. Presence of SPUC was associated with family history of cancer, smoking history and drinking history. Moreover, SPUC presented a less differentiated degree relative to control group, and the proportion of tumors in stage T2 and T3 was higher than that in control group. The survival rates were 29.4% and 54.9%, respectively, in study group and control group. Furthermore, the mean interval between diagnosis and death in study group (1.35 years) was significant shorter than that in control group (3.26 years). Conclusion: There were significant differences in several clinical and pathologic characteristics between SPUC and single primary cancer. SPUC was more aggressive with a higher mortality relative to single primary cancer, more attention should be paid to the diagnosis and treatment of SPUC.

Keywords: Synchronous primary urologic cancers, genitourinary cancer, clinical presentation, prognosis

Introduction

Multiple primary cancers (MPC) were defined as two or more cancers that each cancer must present a definite malignant lesion and do not have any subordinate relationships [1]. Subsequently, Moertel et al. [2] proposed a new definition, i.e., MPC diagnosed at the same time or within six months were classified to be synchronous multiple primary cancers (SMPC), otherwise were considered to be metachronous MPC. Owing to the increased longevity and the advanced diagnostic and surgical techniques, an increasing number of SMPC have been discovered recently [3-6], attracting much attention of physicians and investigators.

Multiple documentations have demonstrated that genitourinary system is inclined to develop multiple malignant neoplasm [7-9]. Palou et al. [10] indicated that 46% of synchronous upper urinary tract tumor and superficial bladder tumor were invasive, despite of uncommon occurrence. Thus, the urologist and other specialist should pay more attention to evaluating patients for the initial presenting symptoms of tumors [11]. Although synchronous primary urologic cancer (SPUC) is recognized as a significant entity on clinical and molecular level, its clinical and pathological features and prognosis are still controversial. The difficulties of assessing the characteristics of SPUC might be partly related to its relative low prevalence. Previous studies mainly centered on individual cases with SPUC [7, 12, 13] or just focused on multiple primary urologic cancers [14-16]. Statistical researches of SPUC only have been reported in a few studies with a varied incidence rate decades ago [17, 18].

As available studies on this issue are limited, the objective of this study was to investigate, in

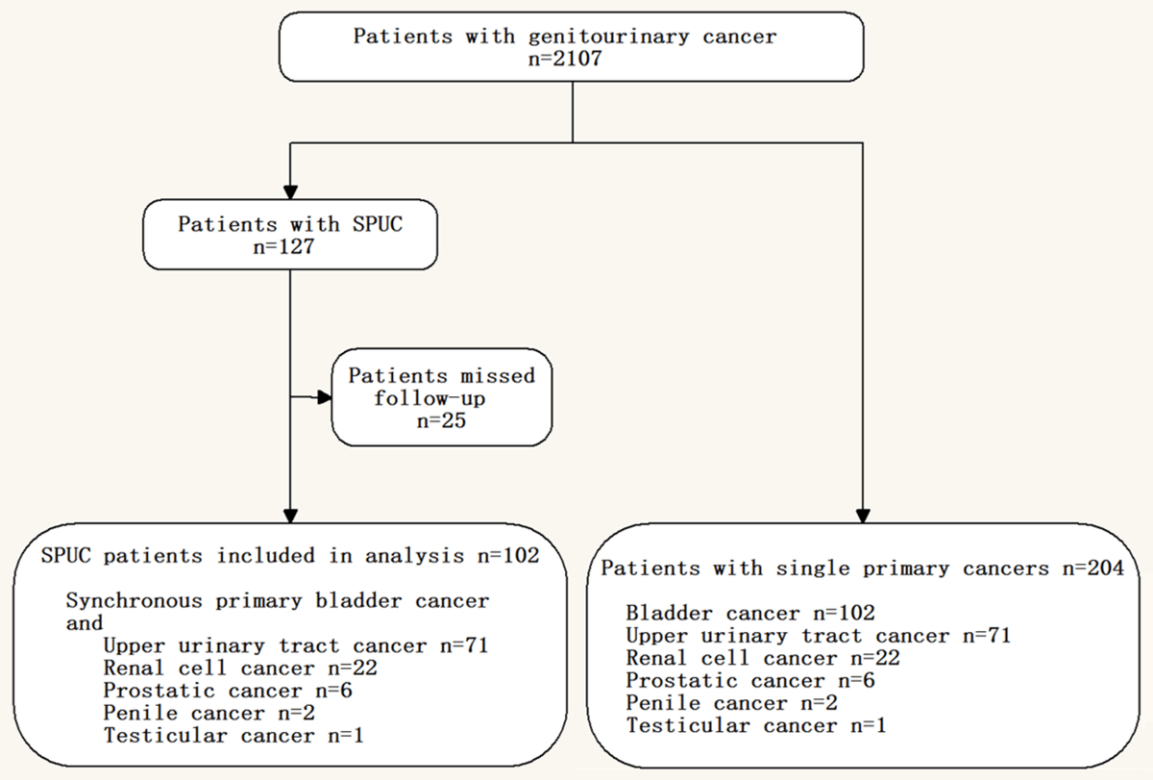

Figure 1. Flow diagram of the study population. SPUC indicates synchronous primary urologic cancer.

depth, the various clinicopathological characteristics of patients with SPUC in a large cohort of patients with long-term follow-up data. This work might lead to a better understanding of the pathogenesis of SPUC, and help us develop more effective methods for the prevention and treatment of neoplastic disease.

Methods

In our study, among 2107 patients who were diagnosed with genitourinary cancer and received surgical treatment at First Affiliated Hospital of Dalian Medical University from 1980 to 2010, a total of 127 patients showed SPUC. While, there were 25 SPUC patients who missed the follow-up. Finally, only 102 SPUC patients were enrolled in our study. The flow diagram of the study population was shown in **Figure 1**. Of these 102 SPUC patients, the first primary malignance was diagnosed as bladder cancer, and second primary malignances were, respectively, diagnosed as upper urinary tract cancer (n=71), renal cell cancer (n=22), prostatic cancer (n=6), penile cancer (n=2) and testicular cancer (n=1). Synchronous cancers in this study met the criteria of synchronous multiple primary cancers described by Moertel et al. [2]. Recurrent bladder cancer, metastatic of primary urologic malignances and metachronous tumors were excluded from our study.

The 102 patients were all diagnosed as synchronous two primary urologic cancers. In this study, these 102 patients were set as SPUC group, and 204 patients with corresponding single primary cancers were randomly selected from 2107 patients with genitourinary cancer as control group. The study was approved by the institutional ethical committee and review board of our hospital, and written informed consent was obtained from patients who agreed to participate in this study. Pathologic characteristics such as age, gender, ABO blood group, familial history of cancer, history of smoking and drinking, notable manifestation, anatomical distribution, pathological pattern, tumor stage, differentiation degrees, and operation method for study group and control group were collected from surgical medical reports. The follow-up information was collected by interviews when patients underwent return visits to the outpatient clinics. For patients who could not make return visits, the follow-up data were achieved by telephone interviews. Statistical analysis was performed using SPSS

Table 1. Basic characteristics of the study population

	Study group, n (%) (102 patients: 204 tumors)	Control group, n (%) (204 patients: 204 tumors)	*P* value
Age at diagnosis	68 (47-85)	68.5 (47-85)	0.496
Male	68.5 (50-85)	67 (58-85)	0.356
Female	68 (47-80)	70 (47-81)	0.608
Gender, n (%)			
Male	76 (74.5)	143 (70.1)	0.420
Female	26 (25.5)	61 (29.9)	
Blood group, n (%)			
A	21 (20.6)	62 (30.4)	0.069
B	35 (34.3)	58 (28.4)	0.292
O	27 (26.5)	36 (17.6)	0.072
AB	19 (18.6)	48 (23.5)	0.328
Chief complaints, n (%)			
Hematuresis	56 (54.9)	99 (48.5)	0.293
Waist/abdominal pain	34 (33.3)	33 (16.2)	0.001
Irritation sign of bladder	5 (4.9)	16 (7.8)	0.337
Dysuresia	7 (6.7)	10 (4.9)	0.480
Physical examinations	16 (15.7)	46 (22.5)	0.159
Familial history of cancer, n (%)			
Positive	54 (52.9)	72 (35.3)	0.003
Negative	48 (47.1)	132 (64.7)	
Smoking history, n (%)			
Positive	71 (69.6)	86 (42.2)	< 0.001
Negative	31 (30.4)	118 (57.8)	
Drinking history, n (%)			
Positive	66 (64.7)	96 (47.0)	0.004
Negative	36 (35.3)	108 (53.0)	

13.0 (SPSS Inc, Chicago, IL, USA). Categorical data were analyzed by χ^2 test. Continuous variables were expressed as median or mean ± standard deviation (SD) and were compared using Student's t-test. Kaplan-Meier method was used to calculate the survival rate of patients and Log-rank was used to assess statistical significance. A difference with $P < 0.05$ was considered statistically significant.

Result

Among the 2107 patients diagnosed with urologic cancer in our hospital from 1980 to 2010, the prevalence rate of SPUC was 6.0% (127/2107). A total of 102 SPUC patients were enrolled in our study.

The basic characteristics of the study population were shown in **Table 1**. Among the study population, no significant differences were existed in age, gender and blood groups between SPUC group and control group ($P > 0.05$). While, patients with smoking and drinking history, and family history of cancer had a significant tendency to suffer from SPUC ($P < 0.05$). Among the chief complaints, waist/abdominal pain showed a higher proportion in SPUC group relative to that in control group ($P < 0.05$).

The anatomical distribution of SPUC was shown in **Table 2**. Compared with patients with single bladder cancer, 60.8% of bladder cancers in SPUC group tend to occur at the fundus of bladder, including trigone, which was significantly different with control group with the percentage of 40.2 ($P < 0.05$). Moreover, only 4.9% of bladder cancers occurred at the apex of bladder in SPUC group compared with 14.7% in control group ($P < 0.05$). In renal cell cancers, 50% occurred at lower pole in SPUC group while only 18.2% in control group ($P < 0.05$). Most of renal cell cancers (59.1%) occurred at upper pole in control group. No significant difference existed in anatomical distribution of other cancers between two groups.

The pathological categories of SPUC were summarized in **Table 3**. Generally, there was no significant difference in the pathological patterns in all cancers between two groups ($P > 0.05$).

The differentiation degrees of SPUC were listed in **Table 4**. In SPUC group, 22.5% of bladder cancers and 21.1% of upper urinary tract cancers were pathologically diagnosed to be poorly differentiated, which were significantly higher than that in control group (10.8% and 5.6%, respectively; $P < 0.05$). While, no significant difference was found in differentiation degrees of

Table 2. Anatomical distribution of synchronous primary urologic cancers

	Study group, n (%) (102 patients: 204 tumors)	Control group, n (%) (204 patients: 204 tumors)	*P* value
Bladder cancer (N=102)			
Fundus (including trigone)	62 (60.8)	41 (40.2)	0.003
Body	32 (31.4)	41 (40.2)	0.189
Apex	5 (4.9)	15 (14.7)	0.019
Neck	3 (2.9)	5 (4.9)	0.471
Upper urinary tract cancer (N=71)			
Calix or pelvis	29 (40.8)	29 (40.8)	1.000
Upper ureter	9 (12.7)	14 (19.7)	0.255
Middle ureter	12 (16.9)	13 (18.3)	0.828
Lower ureter	21 (29.6)	15 (21.1)	0.247
Renal cell cancer (N=22)			
Upper pole	7 (31.2)	13 (59.1)	0.069
Middle pole	4 (18.2)	5 (22.7)	0.709
Lower pole	11 (50)	4 (18.2)	0.026
Prostatic cancer (N=6)			
Peripheral zone	6 (100)	6 (100)	1.000
Penile cancer (N=2)			
Glans	1 (50)	2 (100)	0.248
Body	1 (50)	0 (0)	
Testicular cancer (N=1)			
Left testis	1 (100)	1 (100)	1.000

other cancers between two groups (P > 0.05). Interestingly, compared with control group, the ratio of poor differentiation in each cancer, except for penile cancer and testicular cancer, was obviously increased in SPUC group.

The tumor stages of SPUC were summarized in **Table 5**. In general, the percentage of each cancer in stage T2 and T3 became greater in SPUC group than that in control group. While, no statistical significance existed between two groups (P > 0.05), except for bladder cancers. Compared with control group, the proportion of bladder cancers in stage T2 was significantly higher in SPUC group, and significantly lower in stage T1 in SPUC group (P < 0.05). Moreover, in two groups, the majority of bladder cancers and renal cell cancers were in stage T1, while the majority of upper urinary tract cancers were in stage T2 and T3.

Treatment methods of SPUC were listed in **Table 6**. Most of the patients with bladder cancers received transurethral resection in both groups (70.6% in SPUC group and 84.3% in control group), there was significant difference between two groups (P < 0.05). The proportion of patients with bladder cancers who received partial cystectomy in SPUC group was significantly higher than that in control group (P < 0.05). For upper urinary tract cancers, 63.4% in SPUC group and 76.1% in control group received radical nephroureterectomy, others received radical nephroureterectomy plus bladder cuff shape excision. Meanwhile, 45.5% of renal cell cancers in SPUC group and 72.7% in control group received nephron sparing surgery, others received radical nephrectomy.

The mean follow-up period was 2.68 years in SPUC group and 2.65 years in control group. During the follow-up, 29.4% of patients survived in SPUC group, while 54.9% survived in control group. The average interval between the time of diagnosis and the time of death or alive was 1.35 years in SPUC group and 3.26 years in control group, respectively. Kaplan-Meier estimates for cumulative event-free rate of patients with SPUC and single primary cancers were presented in **Figure 2**. There was a significant difference in survival rate between two groups; the SPUC group had an obviously lower survival rate than control group (P < 0.05).

Discussion

According to our results, we found that family history of cancer, smoking history and drinking history all had influences on the occurrence of SPUC. Besides, there were differences in anatomical distribution, pathological patterns, differentiation degrees, tumor stages and treatment methods between SPUC group and control group to some extent.

The presence of SMPC was once regarded as rare, but is a very frequent situation currently. However, reports on SPUC are scarce, most are

Table 3. Pathological patterns of synchronous primary urologic cancers

	Study group, n (%) (102 patients: 204 tumors)	Control group, n (%) (204 patients: 204 tumors)	*P* value
Bladder cancer (N=102)			
Transitional cell carcinoma	95 (93.1)	100 (98.0)	0.088
Squamous carcinoma	5 (4.9)	1 (1.0)	0.097
Adenocarcinoma	2 (2.0)	1 (1.0)	0.561
Upper urinary tract cancer (N=71)			
Transitional cell carcinoma	65 (91.5)	70 (98.6)	0.053
Squamous carcinoma	2 (2.8)	0 (0)	0.154
Adenocarcinoma	4 (5.6)	1 (1.4)	0.172
Renal cell cancer (N=22)			
Clear cell carcinoma	19 (86.4)	20 (91.0)	0.635
Papillary adenocarcinoma	2 (9.1)	1 (4.5)	0.550
Chromophobe cell carcinoma	1 (4.5)	1 (4.5)	1.000
Prostatic cancer (N=6)			
Adenocarcinoma	6 (100)	6 (100)	1.000
Penile cancer (N=2)			
Squamous carcinoma	2 (100)	2 (100)	1.000
Testicular cancer (N=1)			
Spermatocytoma	1 (100)	1 (100)	1.000

Table 4. Differentiation degrees of synchronous primary urologic cancers

	Study group, n (%) (102 patients: 204 tumors)	Control group, n (%) (204 patients: 204 tumors)	*P* value
Bladder cancer (N=102)			
Poor	23 (22.5)	11 (10.8)	0.024
Moderate	59 (57.9)	65 (63.7)	0.390
Well	20 (19.6)	26 (25.5)	0.315
Upper urinary tract cancer (N=71)			
Poor	15 (21.1)	4 (5.6)	0.007
Moderate	36 (50.7)	46 (64.8)	0.089
Well	20 (28.2)	21 (29.6)	0.853
Renal cell cancer (N=22)			
Poor	6 (27.3)	3 (13.6)	0.262
Moderate	13 (59.1)	15 (68.2)	0.531
Well	3 (13.6)	4 (18.2)	0.680
Prostatic cancer (N=6)			
Poor	1 (16.7)	0 (0)	0.296
Moderate	5 (83.3)	6 (100)	
Penile cancer (N=2)			
Moderate	2 (100)	2 (100)	1.000
Testicular cancer (N=1)			
Moderate	1 (100)	1 (100)	1.000

case reports or case series focused on MPC. Previously, Wegner [17] reported that the prevalence of MPC among patients with urologic cancer was 3.3% in Berlin (1969 to 1988), of which the incidence of synchronous cancer was 23.4% in female and 48.3% in male patients. Another report by Nakata et al. [18] presented that, of 765 patients with urologic cancer in Japan, 12.3% had MPC (1972-1995), of which 11% in female and 27% in male patients were identified as synchronous cancers. In our study, the prevalence of SPUC was 6% in China (1980-2010). This difference in frequency might be due partly to the aging population and the advances in medical technologies, especially in diagnostic techniques and cancer treatment modalities.

In our survey, no significant difference was observed in the average age, sex ratio and ABO blood group between two groups. However, the average age of male SPUC patients was higher than that in control group at the diagnosis of urologic cancers, mainly because the frequency of testis cancer, which developed at a younger age compared with that of other cancers, was lower in SPUC group. According to the study of Inci et al. [19], the ratio of men to women among patients with urologic cancer was 9:1, while the ratio was 5:1 among patients with multiple primary urologic cancers. In our

Table 5. Tumor stages of synchronous primary urologic cancers

	Study group, n (%) (102 patients: 204 tumors)	Control group, n (%) (204 patients: 204 tumors)	*P* value
Bladder cancer (N=102)			
T_1	74 (72.5)	89 (87.3)	0.007
T_2	23 (22.5)	10 (9.8)	0.013
T_3	5 (5.0)	3 (2.9)	0.471
Upper urinary tract cancer (N=71)			
T_1	9 (12.7)	11 (15.5)	0.638
T_2	35 (49.3)	43 (60.6)	0.249
T_3	27 (38)	17 (23.9)	0.089
Renal cell cancer (N=22)			
T_1	12 (54.5)	17 (77.3)	0.361
T_2	8 (36.4)	4 (18.2)	0.243
T_3	2 (9.1)	1 (4.5)	0.561
Prostatic cancer (N=6)			
T_1	2 (33.3)	3 (50)	0.558
T_2	4 (66.7)	3 (50)	
Penile cancer (N=2)			
T_1	2 (100)	2 (100)	1.000
Testicular cancer (N=1)			
T_1	1 (100)	1 (100)	1.000

work, the ratio of men to women was about 3:1 in SPUC group, this might due to the decreased occurrence in male-specific cancers including prostatic, penile and testicular cancer in SPUC group. Compared with a study of Nakata et al. [18], there was no significant difference in our paper between SPUC group and single primary cancer group in the distribution of ABO blood group. Nevertheless the percentage of type B blood and type O blood in SPUC group were larger than that in control group, indicating that patients with type B blood and type O blood might have more tendencies to suffer SPUC.

With regard to the clinical symptoms of patients with SPUC, there was no significant difference in the chief complaints of hematuresis, irritation sign of bladder and dysuresia between two groups, except for waist or abdominal pain. The overall percentage of patients with waist or abdominal pain in SPUC group was significantly higher than that in control group. This may indicate that patients with waist or abdominal pain should be paid more attention to the risk of SPUC.

Family history of cancer has been reported to influence on the formation and progression of multiple malignancies in many documents. In USA, Uccella et al. [20] found that endometrial cancer patients with a family history of hereditary nonpolyposis colorectal cancer-related cancers had a great tendency of developing colorectal cancer within 5 years after endometrial cancer treatment. In Asian, Bai et al. [21] showed that 68.8% patients with synchronous upper gastrointestinal malignancies had a family history of cancer. In our study, we noted that a positive family history of cancer was also more prevalent in SPUC group (52.9%), which was significantly higher than that in control group (35.3%). The results showed that family history of cancer had a significant effect on the occurrence of SPUC, thus regular physical examination was recommended for people who had family history of cancer.

Numerous investigators have noted a high incidence of secondary primary cancer in patients with continuation of smoking and drinking habits. Although smoking is a very strong risk factor for various kinds of cancers [22, 23], a study of Setiawan et al. demonstrated that tobacco use was an independent risk factor for renal cell cancer in males and females [24]. Moreover, Wynder et al. [25] proved that continued consumption of tobacco increased the risk of developing a secondary primary cancer after the diagnosis of the index cancer. Similarly, Druesne-Pecollo et al. [26] indicated that in upper aerodigestive tract (UADT) cancer survivors, alcohol drinking patients had a more than 2-fold increased risk of second UADT cancers than that not drinking alcohol. In our study, we found that 69.6% patients in SPUC group had a history of tobacco use and 64.7% patients had a history of alcohol use, which were significantly higher than that in the single cancer group (42.2% and 47.0%, respectively). As the continued use of tobacco and alcohol gave rise to the

Table 6. Treatment methods of synchronous primary urologic cancers

	Study group, n (%) (102 patients: 204 tumors)	Control group, n (%) (204 patients: 204 tumors)	*P* value
Bladder cancer (N=102)			
Transurethral resection	72 (70.6)	86 (84.3)	0.019
Partial cystectomy	25 (24.5)	12 (11.8)	0.018
Radical cystectomy	5 (4.9)	4 (3.9)	0.733
Upper urinary tract cancer (N=71)			
Radical nephroureterectomy	45 (63.4)	54 (76.1)	0.100
Radical nephroureterectomy plus bladder cuff shape excision	26 (36.6)	17 (23.9)	
Renal cell cancer (N=22)			
Nephron sparing surgery	10 (45.5)	16 (72.7)	0.066
Radical nephrectomy	12 (54.5)	6 (27.3)	
Prostatic cancer (N=6)			
Radical prostatectomy	2 (33.3)	3 (50)	0.558
Transurethral resection plus double testicular castration	4 (66.7)	3 (50)	
Penile cancer (N=2)			
Partial resection	2 (100)	2 (100)	1.000
Testicular cancer (N=1)			
Inguinal probe plus radical orchiectomy	1 (100)	1 (100)	1.000

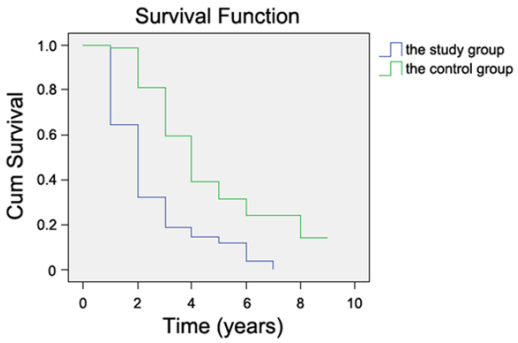

Figure 2. The survival rate of patients in the study group and the control group.

risk of second primary malignancies and affected the survival rates adversely, it may be vital for patients to limit the tobacco and alcohol use after the primary urologic cancers treatment to expect better prognoses by preventing additional secondary urologic cancers.

Previously, renal cell carcinoma and prostatic cancer have frequently been reported to be associated with primary bladder cancer [12, 27, 28]. While, only 21.6% of patients were synchronous bladder and renal cell cancers, and 6% of patients were synchronous bladder and prostatic cancers in the present study. A large percentage of patients were synchronous bladder and upper urinary tract cancers, which accounted for 69.6% in SPUC group. This may attribute to the similar origin between upper urothelium and bladder. In both two groups, the predilection site of bladder cancers was at the fundus of bladder, however, it should be pointed that the proportion in SPUC group was significantly higher than that in control group. Another significant difference in anatomical distribution of cancers between two groups was renal cell cancer. The majority of renal cell cancers located at lower pole in SPUC group while at upper pole in the control group. Concerning the pathological patterns, no significant difference was found between two groups.

In this study, the degree of tumor differentiation was also measured [29]. The differentiation degree of cancer usually divided from very well differentiation to very poorly differentiation. Usually, a tumor whose structure was well differentiated will probably had a biological behavior relatively close to normal, i.e., not very aggressively malignant. In our study, the proportion of poorly differentiated bladder cancer and upper urinary tract cancer were significantly higher in SPUC group than that in control group. Besides, accurate staging of cancer is also critical for patient management. The pri-

mary tumors were staged according to the 2002 TNM system (T1: limited to the lamina propria, T2: invading the muscularis, T3: invasion beyond the muscularis, T4: invading other organ structures) [29]. In this work, the percentage of cancers in stage T2 and T3 was higher in SPUC group than that in control group, while no significant difference existed except for bladder cancers. Moreover, according to our report, there was a remarkably lower 5-year survival rate in SPUC group. This might attribute to two reasons: first, SPUC exhibited more aggressive tumors because they were diagnosed as a much poor differentiation and a higher tumor stage in a large proportion; second, a national screening program for SPUC is still inadequate in China.

To our best knowledge, the present report was the largest case series on SPUC at present. However, there were also some limitations in the present study. First, this is a monocentric study only based on our hospital and lack of information of patients managed at outside institutions. Second, although we have collected all patients with synchronous cancers in our hospital, the sample size is still relatively small. Third, the information was provided to the physicians relying on statistical considerations and did not specify how to individualize patients' management. Thus parts of routine procedure, including abdominal computed tomography, cystoscope, digital rectal examination, and serum PSA, should be undertaken for bladder cancer patients and futurer studies need to further reveal the pathophysiology of SPUC.

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Disclosure of conflict of interest

None.

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