Oncological Outcomes of Patients with Concomitant Bladder and Urethral Carcinoma

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Abstract

Introduction: The study aimed to investigate oncological outcomes of patients with concomitant bladder cancer (BC) and urethral carcinoma. ***Methods:*** This is a multicenter series of 110 patients (74 men, 36 women) diagnosed with urethral carcinoma at 10 referral centers between 1993 and 2012. Kaplan–Meier analysis was used to investigate the impact of BC on survival, and Cox regression multivariable analysis was performed to identify predictors of recurrence. ***Results:*** Synchronous BC was diagnosed in 13 (12%) patients, and the median follow-up was 21 months (interquartile range 4–48). Urethral cancers were of higher grade in patients with synchronous BC compared to patients with non-synchronous BC (p = 0.020). Patients with synchronous BC exhibited significantly inferior 3-year recurrence-free survival (RFS) compared to patients with non-synchronous BC (63.2 vs. 34.4%; p = 0.026). In multivariable analysis, inferior RFS was associated with clinically advanced nodal stage (p < 0.001), proximal tumor location (p < 0.001) and synchronous BC (p = 0.020). ***Conclusion:*** The synchronous presence of BC in patients diagnosed with urethral carcinoma has a significant adverse impact on RFS and should be an impetus for a multimodal approach.

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Introduction

According to European cancer registries, urethral carcinoma is a very rare malignancy. It accounts for well under 1% of all malignancies, with an estimated incidence of 650 new cases per year and an age-standardized ratio of approximately 2–5 per million in men and 0.6–2 per million in women [1, 2].

Given the fact that tumors of the lower urinary tract may arise from different locations within the urinary tract, there is currently no data regarding the prognostic significance of concomitant bladder and urethral cancer as compared to those patients with urethral carcinoma only [3]. With regard to the significantly higher incidence of bladder cancer (BC), the question arises as to whether synchronous BC impacts the prognosis of patients with urethral carcinoma [3, 4].

In order to develop tailored treatment pathways and optimize the management of patients with urethral carcinoma [3], the effect of synchronous BC on the prognosis of patients with urethral cancer needs to be better understood. For this reason, we have assembled a multi-institutional collaborative with the aim of determining the prognostic impact of concomitant BC in patients diagnosed with urethral carcinoma.

Patients and Methods

This is a retrospective study representing data from 10 international academic centers. The study was approved by the independent ethics committee at Tübingen (protocol number: 469/2015BO2) and participating sites. A computerized database was generated to combine the different data sets. Through regular communication with all sites, resolution of all identified anomalies was achieved before the analyses were performed. We collected data from a total of 133 consecutive patients treated for urethral carcinoma between 1993 and 2012. A total of 23 patients (17.3%) with evidence of distant metastatic disease at initial diagnosis were excluded from the final analysis. Furthermore, patients with a diagnosis of BC prior to the detection of urethral carcinoma or those with secondary urethral recurrence after radical cystectomy were excluded from this study.

Clinical and Histologic Assessment
We assessed the following clinical and pathologic parameters: age at primary treatment, gender, clinical and pathologic tumor stage, clinical and histopathologic lymph node (LN) involvement, histologic subtype, tumor grade, lymphovascular invasion, soft-tissue surgical margin (STSM) status, tumor location (proximal vs. distal), prior history of malignancy, modality of primary treatment, perioperative chemotherapy, preoperative serum creatinine level and the presence of synchronous BC at diagnosis of urethral carcinoma.

Clinical staging was based on preoperative bimanual examination, cystoscopy with biopsy and cross-sectional imaging. Histo-

logic assessment was performed at the center-specific pathology department and was based on the 1973 WHO grading system and 2002 TNM classification as approved by the AJCC [5]. The pathologic macro- and microscopic evaluation of specimens included cross-sectioning of the entire specimen with immunohistochemical staining to identify the presence of urothelial, squamous cell and adenocarcinoma or any other histological variant [6].

Treatment Approach
The overall majority of patients underwent surgery for primary treatment while only a small proportion of them were treated with radiotherapy and/or chemotherapy only (table 1). Regional LN dissection (LND) was performed at the discretion of the treating surgeon based on intraoperative findings and preoperative imaging. The level of LND was dependent on the location of the primary tumor, encompassing the inguinal LN, external and internal iliac, obturator and common iliac LN.

Follow-Up
Electronic hospital charts and physician records were reviewed to determine clinical outcomes. Due to the rarity of the disease, no standardized follow-up existed across all centers. Typically, follow-up consisted of physical examination with laboratory testing, intravenous pyelography, cystoscopy, urine cytology, urethral washings, cross-sectional imaging and bone scintigraphy, if indicated. Recurrence was defined as disease recurrence locally in the urethra and/or in LN and/or in distant organs.

Statistical Analysis
For univariate analyses, chi-square and Fisher's exact tests were used for nominal data and Student's t test for scaled data. Kaplan–Meier analysis with log-rank testing was employed to investigate the impact of the presence of synchronous BC on recurrence-free survival (RFS) and overall survival (OS). For determining RFS/OS, clinical outcomes were measured from the date of primary treatment to the date of first documented recurrence/death [7].

For multivariable analysis, Cox proportional hazards regression was carried out to evaluate predictors of recurrence. p values are two-sided and $p < 0.05$ was considered significant. Statistical analysis was performed using JMP® 11.0. Values are given as mean, median and interquartile range (IQR).

Results

The clinical and histopathologic tumor and patient characteristics are listed in table 1. The histological characteristics of BC are listed in table 2. Primary urethral cancers were of higher grade in patients with synchronous BC compared to patients with non-synchronous BC ($p = 0.020$). No further significant differences were found between the 3 groups. In the 51 patients who underwent LND in addition to primary tumor treatment, the median number of retrieved LN was 17 (IQR 13–21).

The location of recurrences in the 110 patients is outlined in table 1. With a median follow-up of 21 months

Table 1. Clinical and pathologic characteristics for cM0 urethral carcinoma in the 110 patients according to the timing of BC diagnosis

	No BC	Synchronous BC	Metachronous BC	p value
Number of patients, %	96 (87.2)	13 (11.8)	1 (0.9)	
Gender				0.56
Male	63 (65.6)	10 (76.9)	1	
Female	33 (34.4)	3 (23.1)	0	
Age, years				0.15
Median	66	72		
IQR	58–77	65–81	72	
cT stage				0.32
cTX	1 (1.0)	2 (15.4)	0	
cTa	12 (12.5)	2 (15.4)	1	
cTis	6 (6.3)	0 (0)	0	
cT1	32 (33.3)	5 (38.5)	0	
cT2	23 (24.0)	3 (23.1)	0	
cT3	18 (18.8)	0 (0)	0	
cT4	4 (4.2)	1 (7.7)	0	
pT stage				0.21
pT0	1 (1.1)	2 (15.4)	0	
pTa	12 (13.5)	1 (7.7)	0	
pTis	8 (9.0)	1 (7.7)	0	
pTis (pu)	3 (3.4)	2 (15.4)	0	
pTis (pd)	3 (3.4)	0 (0)	0	
pT1	13 (14.6)	1 (7.7)	1	
pT2	20 (22.5)	3 (25.0)	0	
pT3	16 (18.0)	1 (7.7)	0	
pT4	13 (14.6)	1 (7.7)	0	
cN stage				0.72
cNX	8 (8.3)	2 (15.4)	0	
cN0	76 (79.2)	11 (84.6)	1	
cN+	12 (12.5)	0 (0)	0	
pN stage				0.83
pNX	41 (47.1)	8 (61.5)	1	
pN0	38 (43.7)	0 (0)	0	
pN1	2 (2.3)	0 (0)	0	
pN2	6 (6.9)	5 (38.5)	0	
Tumor grade				0.020
G1	9 (9.4)	0	0	
G2	25 (26.0)	1 (7.7)	0	
G3	54 (56.3)	10 (76.9)	0	
GX	7 (7.3)	1 (7.7)	1	
Not available	1 (1.0)	1 (7.7)	0	
Histology				0.67
UC	41 (42.7)	8 (61.5)	1	
SCC	28 (29.2)	2 (15.4)	0	
AC	14 (14.6)	1 (7.7)	0	
Mixed (UC ± SCC ± AC)	7 (7.3)	1 (7.7)	0	
Leiomyosarcoma	1 (1.0)	0 (0)	0	
Melanoma	2 (2.1)	0 (0)	0	
Adenoid cystic carcinoma	1 (1.0)	0 (0)	0	
Sarcomatoid	0 (0)	0 (0)	0	
Undifferentiated	0 (0)	1 (7.7)	0	
Other	2 (2.1)	0 (0)	0	
Tumor location				0.18
Proximal	51 (53.1)	10 (76.9)	1	
Distal	45 (46.9)	3 (23.1)	0	
Prior history of malignancy				0.07
Present	19 (19.8)	5 (38.5)	1	
Absent	77 (80.2)	8 (61.5)	0	

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Table 1. (continued)

	No BC	Synchronous BC	Metachronous BC	p value
Per cancer entity				
Prostate	8 (8.3)	3 (23.1)	1	
Breast	3 (3.2)	0 (0)	0	
Lung	1 (1.0)	0 (0)	0	
Colorectal	3 (3.2)	0 (0)	0	
Kidney	1 (1.0)	1 (7.7)	0	
Testicular	1 (1.0)	0 (0)	0	
Vulvar	2 (2.1)	0 (0)	0	
Vaginal	1 (1.0)	0 (0)	0	
Uterus	1 (1.0)	0 (0)	0	
Oropharyngeal	1 (1.0)	0 (0)	0	
Lymphoma	0 (0)	1 (7.7)	0	
Pretreatment serum creatinine level, mg/dl				0.09
Median	1	1.3	0.7	
Mean	1.0	1.3		
IQR	0.8–1.2	1.0–1.6		
Modality of primary treatment				0.45
Transurethral resection	27 (28.1)	4 (30.8)	0	
Transurethral laser resection	1 (1.0)	0 (0)	0	
Partial urethrectomy	7 (7.3)	0 (0)	0	
Urethrectomy	25 (26.0)	1 (7.7)	1	
Prostatectomy	0 (0)	0 (0)	0	
Cyst(oprostat)ectomy plus urethrectomy	29 (30.2)	7 (53.8)	0	
Radiotherapy	2 (2.1)	0 (0)	0	
Chemotherapy	0 (0)	1 (7.7)	0	
Chemoradiotherapy	3 (3.2)	0 (0)	0	
Other	2 (2.1)	0 (0)	0	
Perioperative chemotherapy				0.61
Neoadjuvant	9 (9.4)	2 (15.4)	1	
Neoadjuvant plus adjuvant	4 (4.2)	0 (0)	0	
Adjuvant	14 (14.6)	3 (23.1)	0	
None	69 (71.8)	8 (61.5)	0	
Location of recurrence				0.55
LN	10 (10.4)	4 (30.8)	0	
Distant	2 (2.1)	1 (7.7)	0	
Urethral	16 (16.7)	3 (23.1)	0	
LN plus distant	6 (6.3)	0 (0)	1	
LN plus urethral	3 (3.1)	0 (0)	0	
Distant plus urethral	4 (4.2)	0 (0)	0	
LN plus distant plus urethral	6 (6.3)	0 (0)	0	
No recurrence	49 (51.0)	5 (38.5)	0	
STSM				0.43
pR0	56 (58.3)	6 (46.2)	1	
pR1	9 (9.4)	0 (0)	0	
pR2	4 (4.2)	1 (7.7)	0	
pRX	10 (10.4)	2 (15.4)	0	
Not available	17 (17.7)	4 (30.8)	0	
Lymphovascular invasion				0.43
LV0	22 (22.9)	5 (38.5)	0	
LVI	14 (14.6)	0 (0)	0	
LVX	38 (39.6)	6 (46.2)	1	
Not available	22 (22.9)	2 (15.4)	0	

AC = Adenocarcinoma; pu = prostatic urethra; pd = prostatic ducts; UC = urothelial carcinoma.

No significant differences obtained when patients with metachronous disease was added to the group of patients with BC.

Table 2. Clinical and pathologic BC characteristics in the 14 patients with urethral carcinoma

	Synchronous BC	Metachronous BC		Synchronous BC	Metachronous BC
Number of patients, %	13	1	Histology		
cT stage (BC)			UC	10 (77.0)	1
cTX	1 (7.7)	0	SCC	2 (15.4)	0
cTa	2 (15.4)	0	AC	0 (0)	0
cTis	0 (0)	0	Undifferentiated	1 (7.7)	0
cT1	2 (15.4)	1	Location of BC		
cT2	6 (46.2)	0	Lateral	5 (18.5)	0
cT3	1 (7.7)	0	Anterior	0 (0)	0
cT4	1 (7.7)	0	Posterior	1 (3.7)	0
pT-stage (BC)			Dome	0 (0)	0
pTX	1 (7.7)	0	Trigone	1 (3.7)	0
pT0	0 (0)	0	Floor	3 (11.1)	0
pTa	1 (7.7)	0	Left orifice	0 (0)	0
pTis	1 (7.7)	0	Right orifice	0 (0)	0
pT1	2 (15.4)	1	Neck	5 (18.5)	1
pT2a	5 (38.5)	0	Unifocal	8 (29.6)	1
pT2b	1 (7.7)	0	Multifocal	4 (14.8)	0
pT3a	1 (7.7)	0	STSM		
pT3b	0 (0)	0	pR0	9 (69.2)	1
pT4a	1 (7.7)	0	pR1	0 (0)	0
pT4b	0 (0)	0	pR2	0 (0)	0
pN stage (BC)			pRX	4 (30.8)	0
pNX	3 (23.1)	0	Lymphovascular invasion		
pN0	10 (76.9)	1	LV0	7 (53.8)	0
pN1	0 (0)	0	LVI	1 (7.7)	0
pN2	0 (0)	0	LVX	5 (38.5)	1
pN3	0 (0)	0			
Tumor grade					
G1	0 (0)	0			
G2	0 (0)	0			
G3	12 (92.3)	0			
GX	1 (7.7)	1			

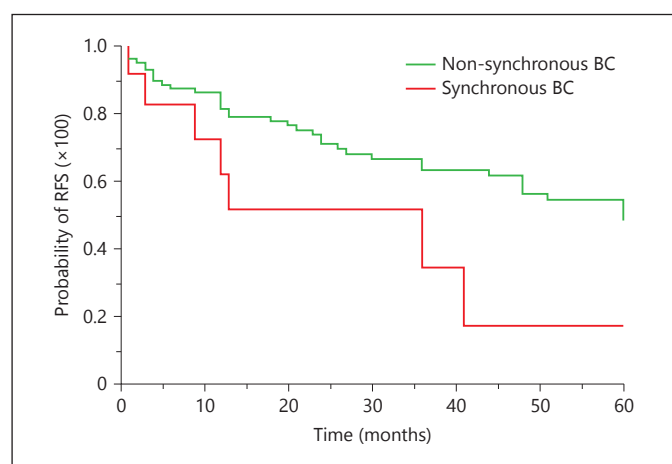AC = Adenocarcinoma; SCC = squamous cell carcinoma; UC = urothelial carcinoma.

Fig. 1. Kaplan–Meier analysis for RFS in the 110 patients staged cM0 according to the presence of synchronous vs. non-synchronous/no BC (p = 0.026).

(mean 32, IQR 4–48), recurrences occurred in 56 of the 110 patients (50.9%). The corresponding 3- and 5-year RFS rates were 60.5 and 45.3%, respectively. A total of 26 (23.6%) of the 110 patients died of other causes during the follow-up period, with a corresponding 3-year OS of 78.7%. Patients with synchronous BC exhibited significantly inferior 3-year RFS compared to patients with non-synchronous BC (63.2 vs. 34.4%; p = 0.026; fig. 1) with a trend toward inferior 3-year OS also approaching statistical significance (80.0 vs. 70.0%; p = 0.07). In patients with synchronous BC, receipt of perioperative chemotherapy (either given neoadjuvantly or adjuvantly) was not associated with a difference in 3-year OS (60%) compared to patients who did not receive chemotherapy (47.6%; p = 0.87).

In the univariate Cox regression analyses, recurrence was significantly associated with the presence of synchronous BC (p = 0.05), histopathologically advanced tumor

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Table 3. Univariate Cox regression analysis for RFS and OS in the 110 patients with cM0 primary urethral carcinoma according to clinical and pathologic tumor characteristics

Parameter	RFS		OS	
	RR (95% CI)	p value	RR (95% CI)	p value
Synchronous BC vs. no synchronous BC	2.29 (1.00–4.64)	0.05	2.63 (0.75–7.16)	0.11
Pathological tumor stage				
≥pT3 vs. ≤pT2	2.38 (1.32–4.19)	**0.004**	3.01 (1.21–7.31)	**0.019**
Pathologic nodal stage				
pN+ vs. pN0	3.22 (1.16–7.69)	**0.026**	2.82 (0.63–9.38)	0.15
pN+ vs. pNX	3.36 (1.21–8.13)	**0.022**	7.78 (1.49–36.80)	**0.017**
Clinical tumor stage				
≥cT3 vs. ≤cT2	1.66 (0.85–3.06)	0.13	1.74 (0.62–4.25)	0.26
Clinical nodal stage				
cN+ vs. cN0	4.09 (1.96–7.91)	**0.001**	3.47 (0.98–9.74)	0.053
cN+ vs. cNX	5.38 (1.44–34.82)	**0.010**	127.63 (4.98–3,279.10)	**0.008**
Tumor location				
Proximal vs. distal	2.89 (1.31–4.21)	**0.003**	2.44 (1.06–6.30)	**0.036**
Tumor grade				
G1/G2 vs. G3	1.36 (0.74–2.61)	0.33	3.14 (1.16–10.93)	**0.022**
Histology				
UC vs. non-UC	1.01 (0.59–1.75)	0.95	1.02 (0.44–2.43)	0.96
Gender				
Male vs. female	1.27 (0.72–2.33)	0.42	0.82 (0.37–1.90)	0.63
Age, years				
≥65 vs. <65	1.62 (0.86–3.11)	0.13	1.18 (0.51–2.82)	0.69
Serum creatinine level				
Continuously coded (total risk range)	1.28 (0.42–3.59)	0.65	0.70 (0.04–9.73)	0.80
Elevated vs. normal	0.79 (0.37–1.96)	0.58	0.74 (0.29–2.29)	0.57
Prior history of malignancy				
Present vs. absent	1.55 (0.75–3.04)	0.23	2.09 (0.81–5.17)	0.12
STSM				
pR0 vs. pR+ vs. pRX	18.47 (3.70–77.80)	**0.008**	29.84 (3.47–257.19)	**0.042**
Lymphovascular invasion				
LVI vs. LV0/X	1.69 (0.76–3.36)	0.18	2.73 (0.894–7.12)	0.07

RR = Relative risk; UC = urothelial carcinoma. Bold values indicate statistically significant difference.

stage (≥pT3; p = 0.004), clinically and histopathologically confirmed node-positive disease (p = 0.001 and p = 0.026), proximal tumor location (p = 0.003) and positive STSM (p = 0.008). No significant associations were found between recurrence and age, gender, clinical tumor stage, tumor grade, prior history of another malignant disease, pretreatment serum creatinine levels, lymphovascular invasion and histological subtype (table 2).

In the univariate analyses for OS, histopathologically advanced tumor stage (p = 0.019), clinically and histopathologically node-positive disease (cN+ vs. cNX, p = 0.014; pN+ vs. pNX, p = 0.017), proximal tumor location (p = 0.036), STSMs (p = 0.042) and tumor grade (p = 0.022) were all associated with an increased risk of death. No significant associations were found between overall mortality and lymphovascular invasion (p = 0.07), clini-

cal tumor stage, age, synchronous presence of BC, gender, prior history of malignant disease, pretreatment serum creatinine levels and histology (table 3).

In the multivariable Cox regression analysis, recurrence was significantly associated with clinically node-positive disease and proximal tumor location (both p < 0.001), as well as the presence of synchronous BC at the time of primary treatment (p = 0.020; table 4).

Discussion

Since urethral cancer is a rare tumor entity, the prognostic significance of clinical and pathologic risk factors prior to initiation of treatment is uncertain. As the incidence of BC is relatively much higher, the impact of

Table 4. Multivariate analysis for predicting recurrence in the 110 patients with cM0 bladder and urethral carcinoma

Variable	Full model			Final model		
	regression coefficient	HR (95% CI)	p value	regression coefficient	HR (95% CI)	p value
BC						
Synchronous vs. no BC/metachronous BC	0.795	4.91 (1.30–17.71)	0.020	0.383	2.14 (1.00–4.54)	0.05
Tumor location						
Proximal vs. distal	1.094	8.93 (3.07–33.70)	<0.001	0.486	2.64 (1.45–5.05)	0.001
Clinical nodal stage						
cN+ vs. cN0 vs. cNX	1.285	13.08 (3.40–50.61)	<0.001	0.926	6.37 (2.93–13.07)	<0.001
Tumor grade						
G3 vs. G1/G2	0.475	2.59 (0.93–7.58)	0.068			
Pathologic tumor stage						
≥pT3 vs. ≤pT2	0.348	2.00 (0.73–5.34)	0.17			
Lymphovascular invasion						
LVI vs. LV0 vs. LVX	0.685	1.98 (0.58–6.79)	0.27			
STSMs						
pR+ vs. pR0 vs. pRX	0.227	1.25 (0.27–6.29)	0.74			

HR = Hazards ratio.

concomitant BC in urethral carcinoma has not been evaluated, and no clinically meaningful prognostic analyses have been reported so far. We therefore set up a unique collaborative to determine important predictors of oncologic outcomes in patients with urethral carcinoma and accrued a total of 110 cases with cM0 disease.

In the present study, only one patient developed metachronous BC 41 months after primary treatment for urethral carcinoma. For this reason, we included patients with non-synchronous BC in a single prognostic stratum and compared this group to patients with synchronous BC. We found that most patients with synchronous BC had high-grade urethral carcinoma and exhibited inferior RFS compared to patients with non-synchronous BC. Additionally, the majority of patients with synchronous BC exhibited histopathologically confirmed muscle invasive disease. These findings indicate that the synchronous presence of both malignant diseases exerts a markedly adverse impact on outcomes. In addition, we found that approximately one-fourth of the patients in this cohort had a history of another malignancy, with prostate cancer being the most common. However, we did not observe an adverse impact of prior malignancy on RFS or OS. As this series is retrospective, we cannot accurately adjust for any causative association between the primary treatment for these malignancies and the carcinogenesis of urethral cancer.

As would be expected, recurrence was significantly associated with advanced clinical nodal stage, advanced histopathological tumor and nodal stage, proximal tumor location, STSMs and synchronous BC. These results are in accordance with prior studies [2, 8, 9]. For the multivariable analysis, we included all significant parameters from the univariate analyses that correlated with survival. Clinical nodal stage, tumor location and presence of synchronous BC were the only parameters found to be independently associated with RFS. Importantly, we recently reported that clinical nodal stage is a strong predictor for outcomes in primary urethral cancer [10]. As the number of events was low (n = 26 death events), we did not perform a multivariable analysis for OS.

This study has limitations inherent to its retrospective and multi-center design, which is requisite given the rarity of urethral carcinoma. Although we included patients treated at academic centers within the last 20 years, the number of included patients and follow-up period is limited due to the rarity and aggressiveness of the disease. Further potential biases include the absence of LND in approximately half of the patients and interobserver variabilities in the clinical staging and histopathologic assessment of specimens. In addition, adjustments for patient preferences, toxicities and side effects of primary treatment as well as comorbidities could not be taken into account.

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We recently reported that neoadjuvant chemo(radio) therapy also exerts a beneficial impact on outcomes in patients with clinically advanced primary urethral cancer (≥cT3 and or cN+) [11]. The number of patients with concomitant bladder and urethral carcinoma was rather small (n = 13) making it difficult to draw meaningful conclusions on the role of neoadjuvant chemotherapy. However, only 2 of the patients with concomitant bladder and urethral carcinoma received neoadjuvant chemotherapy even though both malignancies were staged as muscle invasive (≥pT2 BC: ≈62%; ≥pT2 urethral carcinoma ≈56%) in the majority of cases. Taking the results of the multivariable analysis into consideration, neoadjuvant chemotherapy is likely an important treatment strategy for patients with concomitant bladder and urethral carcinoma who have clinically node-positive disease and proximal urethral tumors.

As the incidence of BC is much higher compared to urethral cancer, one cannot exclude the possibility that primary BC developed first in the lower urinary tract which then metastasized to the urethra rather than occurring synchronously. Additionally, as this report includes different histological subtypes of urethral carcinoma, the tumor biology and treatment regimens may have impacted key outcomes. Therefore, combining all these cases into one group carries important limitations. However, population-based studies have shown that the histological subtype of urethral carcinoma does not appear to exert an impact on prognosis [1, 2, 8, 9]. Nonetheless, it has to be acknowledged that urethral cancer is a rare disease for which therapeutic strategies still need to be better defined [12]. Though secondary urethral cancer after RC for BC is more frequent than concomitant urethral and BC it is difficult to draw meaningful conclusions for clinical practice owing to distinct differences in tumor biologic characteristics [13]. Given this, to our opinion, our study gives important insights into the clinical course of patients with urethral carcinoma which may be further used for prognostication and clinical decision-making in daily practice.

Conclusions

This is the first series that has investigated the impact of synchronous BC on outcomes of patients with urethral cancer. The findings of this study highlight the impaired prognosis of these patients and should be an impetus to consider a multimodal approach for the subgroup of patients with concomitant bladder and urethral cancer.

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