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Our Rates of Concurrent or Differential Development of Urothelial Carcinoma in the Renal Pelvis, Ureter, and Bladder: A Single-center Experience

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Abstract

Objective: This study aimed to compare the age, gender, survival, and etiology of cases diagnosed with urothelial carcinoma (UC) in the genitourinary system simultaneously or later in a different localization (lower tract and/or upper tract).

Materials and Methods: Sixty-four patients diagnosed with concurrent or subsequent lower and/or upper tract UC in the Department of Pathology between 2010 and 2020 were evaluated for age, gender, survival, and etiology. Our study is a retrospective study.

Results: Fifty-eight patients were male and six were female. The ages of the patients ranged between 27 and 87 years. The patients were evaluated for noncoagulable and painless hematuria. While 52 of the patients were smokers, 12 of them were non-smokers. Ten of our patients were initially diagnosed with UC in the renal pelvis and/or ureter and three months to eight years later with UC in the bladder, whereas 14 patients were initially diagnosed with UC in the bladder and four months to 10 years later with UC in the renal pelvis and/or ureter. Of the remaining 40 patients, 14 were diagnosed with UC simultaneously in the bladder and ureter, nine in the renal pelvis and ureter, seven in the renal pelvis and bladder, and 10 in the renal pelvis, ureter, and bladder. The mean duration of symptoms before diagnosis was seven months (range; 7 days to 1.5 years).

Conclusion: Because UC can affect multifocal organs, close surveillance of patients diagnosed with upper or lower urinary tract disease UC and who are smokers is recommended at the time of diagnosis or especially during the first three years after diagnosis to prevent the formation of primary tumors in other regions.

Keywords: Urothelial carcinoma, renal pelvis, ureter, bladder

Introduction

The fourth most prevalent type of tumor is urothelial carcinoma (UC). It may be localized in either the lower (bladder or urethra) or upper (renal pelvis and ureter) urinary tract (1-7). UC is observed at a rate of 90-95% in the bladder and 5-10% in the renal pelvis (1,3).

Tumors developing in different histopathologies, organs, and intervals are referred to as multiple primary cancers. Multiple primary tumors are classified into two groups as synchronous or metachronous tumors (8). However, there is no consensus on the definition of synchronous and metachronous tumors. According to the Surveillance, Epidemiology, and End Results criteria, cancers newly diagnosed within two months of the first tumor diagnosis should be classified as synchronous, whereas cancers identified ≥2 months later should be classified as metachronous (8,9). On the other hand, Moertel (10) classifies it as a synchronous tumor if it occurs within the first six months after the initial tumor diagnosis and as a metachronous tumor if it occurs after six months.

Metachronous tumors are more likely to develop due to previous cancer treatments, whereas synchronous tumors are related to organ-specific carcinogens such as smoking and alcohol. Therefore, synchronous tumors tend to affect the head and neck, lungs, and urinary tract, usually associated with smoking (11). Three theories of the origin of multiple and recurrent urothelial tumors are worth mentioning (8,12,13).

- A piece of the urothelium (patch) is subjected to mutational stress and carcinogenic stimulation by waste accumulated in the urine in the field carcinogenesis model,

- In the intraluminal seeding hypothesis, cancer cells scattered from the primary tumor are reimplanted into the normal mucosa,

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The intraepithelial migration model assumes that tumor cells migrate to the normal mucosa.

Synchronous and metachronous tumors of the genitourinary system are common. In their study, Kilciksiz et al. (14) reported a rate of 30.9% when synchronous and metachronous tumors in the genitourinary system were evaluated together. A characteristic feature of the biological behavior of UCs is that they are multiple and therefore likely to appear synchronously or in a series along the entire urinary tract. The probability of UC in the bladder following UC in the upper urinary system is up to 50% (15). On the contrary, after bladder tumors, UC in the upper urinary tract has been reported at a rate of 2-8% (16,17).

This study aimed to compare the age, gender, survival, and etiology of cases diagnosed with UC in the genitourinary system simultaneously or later in a different localization (lower tract and/or upper tract).

Materials and Methods

Sixty-four patients diagnosed with concurrent or subsequent lower and/or upper tract UC in the Department of Pathology between 2010 and 2020 were evaluated for age, gender, survival and etiology. Our study is a retrospective study. A 10-year electronic diagnostic data search was performed in the hospital medical data management system using the keywords "renal pelvis UC or ureter UC" in the diagnosis line. In the first stage (since the incidence of UC in the renal pelvis and ureter is less), UC originating from the renal pelvis or ureter between the relevant dates were documented. Then, all pathology reports of these patients were retrospectively reviewed one by one. Only cases of UC in the renal pelvis or ureter were excluded from the study. Concomitant cases in the upper or lower tract region at the same time or later were included in the study.

The protocol followed in our hospital to investigate the presence of recurrence or a newly developed tumor in other regions of the cases or to follow-up is as follows:

- When tumors are detected in the renal pelvis and ureter, nephroureterectomy is performed.

Low-risk tumors: cystoscopy performed after three months. If no visible tumor was detected, subsequent cystoscopy was performed nine months later and then yearly for five years.

- High-risk tumors; cystoscopy, and urinary cytology performed after three months. If no visible tumor was detected, subsequent cystoscopy and cytology were performed every three months for a period of two years, and every six months thereafter until five years, and then yearly. The contralateral kidney and ureter were followed with ultrasonography.

- If UC is detected initially in the bladder, the upper tract (renal pelvis/ureter) is followed by computed tomography urography. If creatinine was high, magnetic resonance urography was performed.

This study was approved by the Başkent University Institutional Review Board (project no: KA 22/277, date: 14.06.2022) and supported by the Başkent University Research Fund.

Statistical Analysis

Descriptive statistics for the continuous variables are presented as the mean and standard deviation, while count and percentages for categorical variables.

The SPSS (version 21) statistical program was used for all statistical computations.

Results

A total of 64 patients were evaluated (58 male, 6 female). The mean age of the patients was 65.12 years. There were 15 (23.4%) patients younger than 60 years and 49 (76.6%) patients older than 60 years. Noncoagulable and painless hematuria was the most prevalent complaint, while flank pain was the second most common complaint. While 52 patients (81.25%) were smokers (20-80 packs-years), 12 patients (18.75%) were non-smokers. Furthermore, 13 (20.3%) patients had a history of nephrolithiasis.

Ten of our patients were initially diagnosed with UC in the renal pelvis and/or ureter and three months to eight years later with UC in the bladder (median: 22 months), whereas 14 patients were initially diagnosed with UC in the bladder and four months to 10 years (mean: 57 months) later with UC in the renal pelvis and/or ureter. Of the remaining 40 patients, 14 were diagnosed with UC simultaneously in the bladder and ureter, nine in the renal pelvis and ureter, seven in the renal pelvis and bladder, and 10 in the renal pelvis, ureter, and bladder (Table 1). Three of the cases had bilateral renal pelvic tumors. The mean duration of symptoms before diagnosis was seven months (range; 7 days to 1.5 years). Regarding Pt: Ten cases were pTa, 13 cases were pT1, 23 cases were pT2, 16 cases were pT3, and two was pT4. In eight of the cases, squamous differentiation areas were also present. Of the cases, 52 (81.25%) were alive and 12 (18.75%) were dead. Of our ex-cases, one patient with pTa died of heart failure, one of two cases with pT1 died of heart failure, and one case died of lung and breast carcinoma. Table 2 summarizes the clinical characteristics of our ex-patients.

In addition, three of our patients had gastric carcinoma, four had lung carcinoma (two small-cell, two non-small-cell), two had breast carcinoma, and one patient had lung and breast

Table 1. Clinical features of the cases

Feature	N
Male/female	58/6
Median age	65.2
Follow-up time	3 month - 10 year
Localization	
Diagnosed at different times	24
Renal pelvis and/or ureter + bladder	10
Bladder + renal pelvis and/or ureter	14
Diagnosed at the same time	40
Ureter + bladder	14
Renal pelvis + ureter	9
Renal pelvis + bladder	7
Renal pelvis + ureter + bladder	10

carcinoma, three had prostate carcinoma, one had renal cell carcinoma, and one had hepatocellular carcinoma. Lung metastasis was observed in two cases, bone metastasis was observed in one case, and prostate metastasis was observed in two cases.

Discussion

UC shares histology in the upper and lower tracts and contains similar risk factors. It is more common in men and is very rare in children under 50 years of age (3). In our series, the F/M ratio was 1/9, and 96.9% were more than 50 years old. Smoking, occupational exposure, heavy coffee consumption, high-dose analgesics, HPV, familial diseases (Balkan nephropathy, hereditary non-polyposis colorectal cancer syndrome), loss of chromosome 9, aromatic amines, chronic urinary tract infections, kidney stones, and arsenic exposure have been implicated in etiology (1,3,6,13,18,19). Although smoking is one of the major risk factors, it is associated with a rate of 60-80% (1,3,6). In etiology, stone and infection are observed at a rate of 20-30% (1). In our series, 52 patients (81.25%) were smokers. In 13 cases (20.3%), there was a history of nephrolithiasis, consistent with the literature.

Tumors of the upper urinary tract are rare, and the most common form is UC, with a rate of 90%. The renal pelvis accounts for 5% of all UC and the ureter 1 (1,3,13,19). UC is responsible for approximately 95% of bladder carcinomas (3,13). Hematuria is the most common symptom as well as anemia, flank pain, weight loss, fever, pyelonephritis, and a palpable mass (1). The most common complaint in our series was painless hematuria. Approximately 20-50% of patients with primarily upper tract UC are at risk of developing bladder cancer within two years (particularly between 5 and 15 months) after surgical treatment. The incidence of upper tract UC after primary bladder cancer is about 0.7-4%, and this occurs about 4-6 years after primary bladder cancer (19). Ten of our patients were first diagnosed with UC in the renal pelvis and/or ureter and three months to eight years later with UC in the bladder (median: 22 months), whereas 14 patients were first diagnosed with UC and four months to 10 years (median: 57 months) later with UC in the renal pelvis and/or ureter. Of the remaining 40 patients, 14 were diagnosed with UC simultaneously in the bladder and ureter, nine in the renal pelvis and ureter, seven in the renal pelvis and bladder, and 10 in the renal pelvis, ureter, and bladder. The mean duration of symptoms before diagnosis was seven months (range; 7 days to 1.5 years).

In multifocal UC, cancer cells from the primary lesion may be transplanted to other regions, or in patients with vesicoureteral reflux, reversible transplantation of cells, or smokers, waste products may be excreted by the same systemic route (3).

Radical cystectomy and concurrent nephroureterectomy are considered treatment options for invasive bladder tumors and synchronous UC upper urinary tract (20-22). In our series, cystectomy is performed for muscle invasion in bladder tumors; otherwise, intermittent resections and intravesical chemotherapy are used. Nephroureterectomy is the preferred treatment option for tumors located in the upper urinary tract.

Because the underlying bladder tumor was so close to the orifice, orifice resection was performed in eight of 14 patients in our cohort who initially acquired a bladder tumor and later an upper urinary tract tumor. At the time of diagnosis, three of the eight patients had hydroureteronephrosis on the affected side. Although it has been reported that orifice resection can cause vesicoureteral reflux, which can lead to tumor seeding in the upper urinary system it can be considered as a risk factor, studies reported that orifice resection is not a risk factor for tumor transplantation, and there is no statistical difference in the development of upper urinary system UC after bladder tumor in cases with or without orifice resection (23,24).

Diagnostic ureterorenoscopy for the differential diagnosis of upper urinary tract masses has been identified in the European Association of Urology guidelines as a risk factor for the development of metachronous bladder cancer (25). In our study, six patients who underwent ureterorenoscopy for the differential diagnosis of an upper urinary tract mass had a metachronous bladder tumor.

The prevalence of UC in the ureter, renal pelvis, and bladder in our study was similar to that observed in other studies. UC is mostly observed in men and the 6th decade of life, and smoking is the major risk factor.

Table 2. Clinical features of our expatients

Case	Gender	Localization	Stage	Metastasis	Additional tumor
1	M	Bilateral renal pelvis + ureter + bladder	Pt3	None	Renal cell carcinoma
2	F	The renal pelvis + bladder	Pt1	None	Lung small cell carcinoma + breast carcinoma
3	F	Bladder + ureter	Pt2	None	Breast carcinoma
4	M	The renal pelvis + ureter + bladder	Pt3	None	None
5	M	Renal pelvis + ureter + bladder	Pt2	Lung	None
6	M	The ureter + bladder	Pta	None	None
7	M	The renal pelvis + bladder	Pt3	None	None
8	M	The renal pelvis + bladder	Pt3	Bone	None
9	M	The bilateral renal pelvis + ureter + bladder	Pt2	None	None
10	M	The renal pelvis + ureter + bladder	Pt4	Prostate	None
11	M	Bladder + ureter	Pt1	None	None
12	M	The renal pelvis + ureter + bladder	Pt3	Lung	None

M: Male, F: Female

Study Limitation

The limitation of our study is that it is retrospective and the number of patients is relatively low. Our study should be supported by prospective studies.

Conclusion

As a result, UC can affect multifocal organs; therefore, close surveillance of patients diagnosed with upper or lower urinary tract disease UC and who are smokers is recommended at the time of diagnosis or especially during the first 3 years after diagnosis to prevent the formation of primary tumors in other regions.

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Ethics

Ethics Committee Approval: This study was approved by the Başkent University Institutional Review Board (project no: KA 22/277, date: 14.06.2022).

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Authorship Contributions

Surgical and Medical Practices: M.R.G., M.V.K., Concept: B.H., Design: B.H., M.R.G., Data Collection or Processing: B.H., M.R.G., M.V.K., Analysis or Interpretation: B.H., M.R.G., Literature Search: B.H., M.V.K., Writing: B.H.

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