SIMULTANEOUS BILATERAL UPPER URINARY TRACT UROTHELIAL CARCINOMA (UTUC) WITH LEFT NEPHROURETERECTOMY AND RIGHT ILEOURETERAL REPLACEMENT: A CASE REPORT OF CURATIVE APPROACH

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ABSTRACT

Objective: *The report aims to present a rare bilateral UTUC focusing on diagnostic and surgical treatment to improve the survival rate of patients with bilateral UTUC.****Case(s) Presentation:*** *We present a case report of a 59-year-old male who came in with gross hematuria accompanied with clots. Laboratory reveals a decreased renal function, while CT shows a bilateral mass in both ureters and left renal pelvis without bladder involvement. The patient then underwent left nephroureterectomy and right ureterectomy. In Intraoperative we preserve the right kidney by evaluating the tumor margin using ultrasound and ureteroscopy and deciding to substitute a full-length ureter with ileum as a precaution for a safety margin. Later on the pathological examination shown high-grade invasive urothelial cell carcinoma on both sides with staging pT2N0M0. Six months after surgery patient is in an excellent condition; weight and karnofsky score improvement. The Baseline Creatinin level was decreased, whereas CT showed no residual tumor in the right urinary tract system.****Discussion:*** *This article presents a rare case of bilateral UTUC with staging pT2N0M0 that was successfully treated with multidisciplinary care of radical and reconstructive surgery without chemotherapy.* ***Conclusion:*** *Bilateral UTUC is a scarce case, even among all urologic malignancies. Preserving kidney function in these cases is a priority to reduce further morbidity for the patient.*

Keywords: *Bilateral UTUC, nephroureterectomy, ileoureteral replacement.*

ABSTRAK

Tujuan: *Studi ini bertujuan untuk menyajikan kasus UTUC bilateral langka yang berfokus pada perawatan diagnostik dan bedah untuk meningkatkan tingkat kelangsungan hidup pasien dengan UTUC bilateral.* ***Presentasi kasus:****Kami menyajikan laporan kasus seorang pria berusia 59 tahun yang datang dengan gross hematuria disertai dengan bekuan darah. Laboratorium menunjukkan penurunan fungsi ginjal, sedangkan CT menunjukkan massa bilateral di kedua ureter dan pelvis ginjal kiri tanpa keterlibatan kandung kemih. Pasien kemudian menjalani nefroureterektomi kiri dan ureterektomi kanan.Pada intraoperative, kami melindungi ginjal kanan dengan mengevaluasi batas tumor menggunakan ultras onografi dan ureteroskopi dan memutuskan untuk mengganti ureter dengan ileum sebagai tindakan pencegahan untuk batas keamanan.Kemudian pada pemeriksaan patologis menunjukkan karsinoma sel urothelial invasif tingkat tinggi di kedua sisi dengan stadium pT2N0M0. Enam bulan setelah operasi, pasien dalam kondisi sangat baik; peningkatan berat badan dan skor karnofsky.Tingkat Kreatinin Dasar menurun, sedangkan CT menunjukkan tidak ada sisa tumor di sistem saluran kemih kanan.* ***Diskusi****:Artikel ini menyajikan kasus langka UTUC bilateral dengan staging pT2N0M0 yang berhasil diobati dengan perawatan multi disiplin bedah radikal dan rekonstruktif tanpa kemoterapi.****Simpulan:*** *UTUC bilateral adalah kasus yang langka, bahkan di antara semua keganasan urologi. Mempertahankan fungsi ginjal dalam kasus ini merupakan prioritas untuk mengurangi morbiditas lebih lanjut bagi pasien.*

Kata kunci: *UTUC bilateral, nefroureterektomi, penggantian ileoureteral.*

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INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a malignant lesion arising from the urothelial lining of the calyceal system to the distal ureter. It is an uncommon disease, accounting for only 5–7 % of all renal tumors and 5–10 % of all urothelial tumors, with an estimated annual incidence of 1–2 cases per 100,000 population.[1] While UTUC is uncommon, bilateral UTUC is an extremely rare disease that accounts for only 1.6% of all UTUC cases. It occurs 2-3 times more frequently in males than females.[2-4] The average age of occurrence is 65 to 79 years old.[2]

The risk factors for bilateral UTUC is similar to common urothelial carcinoma, which are age, sex, race, smoking, cyclophosphamide, aromatic amines exposure, history of infection and urinary lithiasis, hypertension, arteriosclerosis, Chronic Kidney Failure (CKD), phenacetin drug abuse.Two of the most common upper tract urothelial carcinoma symptoms are hematuria (70-80%) and flank pain (20-32%).[5] Systemic symptoms such as anorexia, weight loss, fever, night sweats, and fatigue are uncommon and usually associated with advanced or metastatic disease.[1]

Management of bilateral UTUC is still controversial; there is no consensus on the treatment of bilateral UTUC. Clinical trial data concerning the management of bilateral UTUC is still scarce due to the rarity of the case. Therefore, choosing a definitive therapy is challenging.[6-8] EAU Guidelines recommended that the surgical treatment for UTUC should be considered based on the risk stratification of the tumor. Nephroureterectomy is currently the gold standard treatment for UTUC without metastasis.[7] The report aims to present a rare bilateral UTUC focusing on diagnostic and surgical treatment to improve the survival rate of patients with bilateral UTUC.

CASE(S) PRESENTATION

A 59-year-old man presented to the urology clinic with gross intermittent hematuria with blood clot 1 year before admission. Today he also complained of swollen feet, anorexia, fatigue, malaise, progressive unexplained weight loss, hesitancy, oliguria, with hematuria still presenting with worm-like blood clots. He has been a heavy smoker, 1-2 packs per day for the last 45 years. He stopped smoking immediately after his complaint. His mother, younger sister, and 2 older brothers have been diagnosed with cancer. Previous medical history such as hypertension, diabetes, heart disease, lung disease, and allergies was denied. He works as a textile business owner.

The patient consulted with an internist. Laboratory examination showed an abnormal value of kidney function. Moreover, a contrast computed tomography (CT) scan examination in July 2021 showed left renal pelvis, mid ureter, and bilateral distal ureter tumor without bladder involvement (Figure 1). It also showed right grade III hydronephrosis with renal edema, left grade IV hydronephrosis, and bilateral hydroureter. However, there was still a doubt in the imaging whether there was a right renal involvement. He was diagnosed with acute kidney injury with a differential diagnosis of acute on chronic end-stage renal failure caused by bilateral tumor mass (Figure 2).

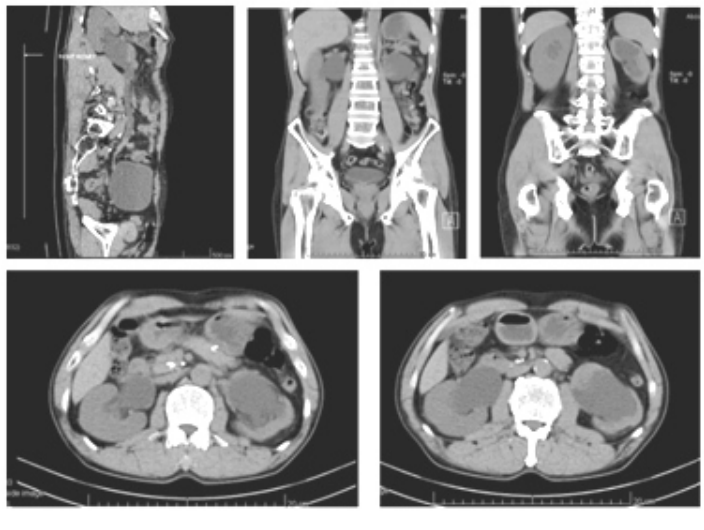

Figure 1. CT Scan on 21 July 2021 showed a bilateral tumor mass.

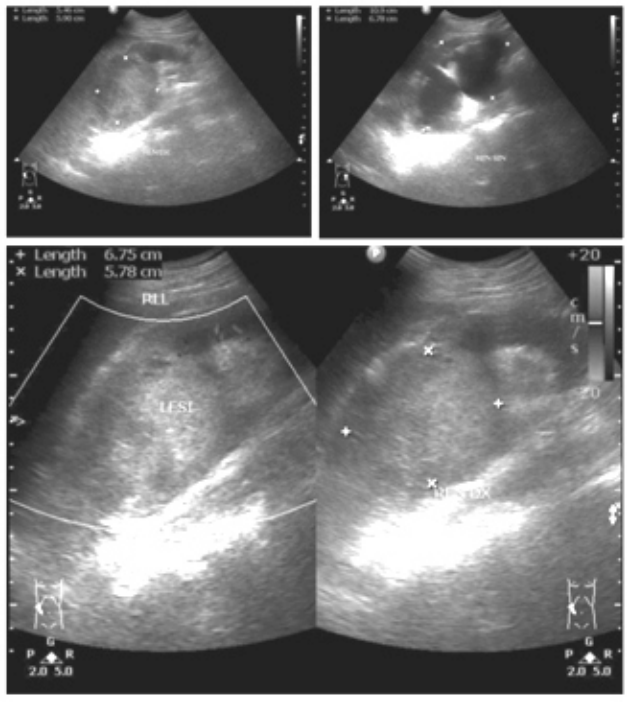

Figure 2. Ultrasonography in September 2021 showing left renal pelvis mass.

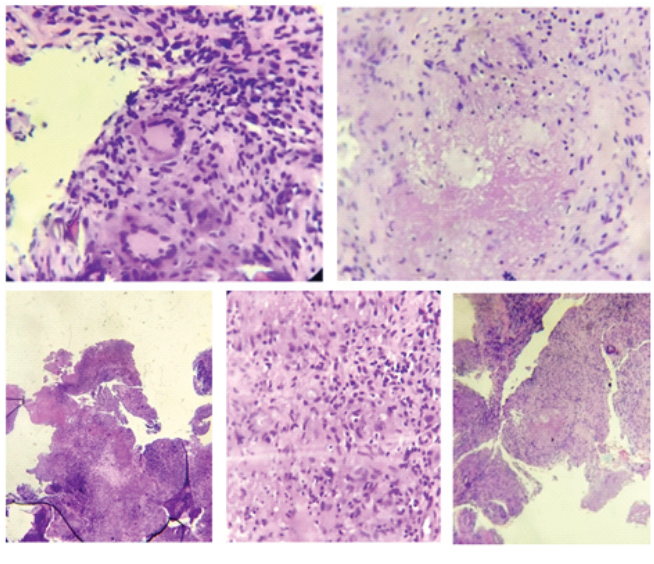

Figure. 3 Pathology results showed low-grade urothelial papillary carcinoma of the left and right ureters with an invasive focus on the right ureter and glandular cystitis.

The internist recommended the patient insertion of Double Lumen Catheter (DLC) to proceed with 3 hemodialysis (HD) sessions. The patient was then consulted by urology for urinary diversion by nephrostomy and definitive treatment for the bilateral tumor mass. A ureteral biopsy was performed, followed by a nephrostomy tube placement in the right kidney. Pathology results showed low-grade urothelial papillary carcinoma of the left and right ureters with an invasive focus on the right ureter and glandular cystitis (Figure 3). The patient was advised to proceed with surgery. The DLC was accidentally detached from the patient in September 2021 and was reinserted in December 2021 (Figure 4).

The patient then visited the urology clinic in December 2021; a contrast CT scan was performed for evaluation in December 2021 and showed an

increase in multifocal tumor mass in the left ureter (Figure 5). Cystoscopy and biopsy of the bilateral tumor mass were then performed for evaluation. The second cystoscopy and CT scan were performed to re-evaluate the patient's condition after 5 months of loss to follow up. The second CT scan confirmed the diagnosis of the left renal pelvis, mid ureter, and bilateral distal ureter tumor without right renal and bladder involvement. It also showed right grade III hydronephrosis with renal edema, left grade IV hydronephrosis, and bilateral hydroureter. The patient was diagnosed with bilateral UTUC pT2N0M0.

The patient developed sepsis and minimal bilateral pleural effusion during treatment due to a DLC tube infection; he was then admitted to ICU. He then recovered from his condition.

In January 2022, the patient underwent a left nephroureterectomy with a bladder cuff and a right partial ureterectomy with ileal-ureteral substitution (Figure 6). The most difficult challenge in this procedure was determining the tumor-free margin. As our hospital's frozen section is unavailable, we utilized intraoperative laparoscopic ultrasonography to determine the tumor-free margin. During preparation for nephroureterectomy, the patient's hemoglobin level was 8.6 g/dl. A blood transfusion was performed until his hemoglobin was elevated to 11 g/dl. His eGFR value was stable at 33 mL/min/1.73m^2. Liver function and albumin levels were within normal limits. Leukocyte was increased with increasing lactic acid and procalcitonin, suggesting sepsis. The patient still has a persisting symptom of red urine after surgery. Complaints of low back pain, sandy bladder, nor passing stone were denied. Furthermore, a routine CT scan or MRI was performed every three months.

Figure 4. Pleural effusion triggered by sepsis caused by DLC Infection.

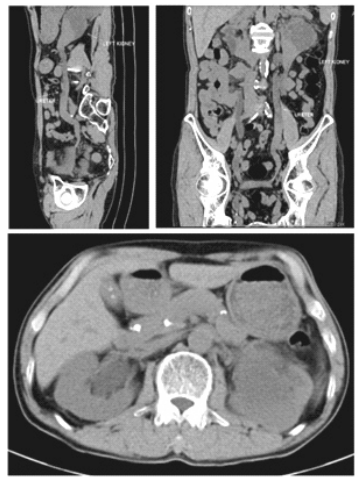

Figure 5. CT Scan in December 2021 showed an increase in multifocal tumor mass in the left ureter.

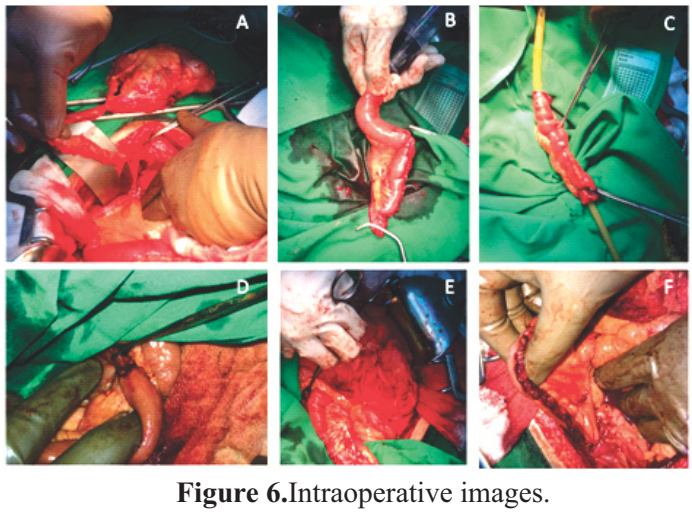

Figure 6. Intraoperative images.

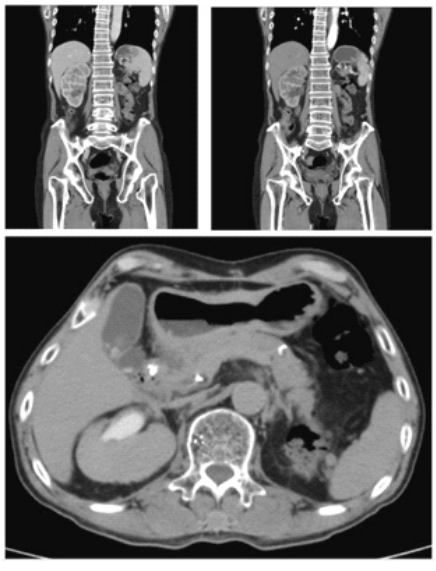

Figure 7. CT Scan in April 2022 showed no tumor mass present in the right pelvicalyceal system

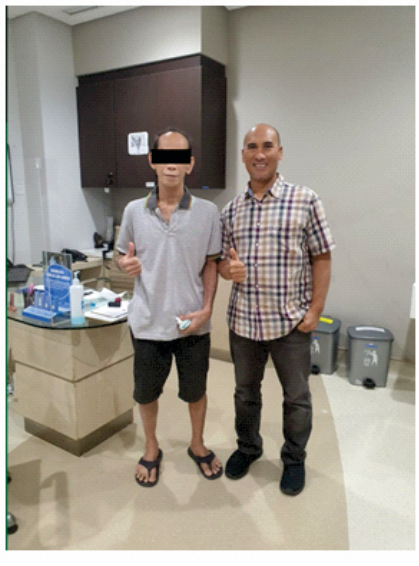

Figure 8. Seven Months Postoperative photograph of the patient with dr. Syamsu Hudaya, SpU(K).

In the first three months of follow-up, a contrast CT scan was performed in April (Figure 7). No tumor mass was present in the right pelvicalyceal system, showing successful surgery with right renal preservation. At six months follow-up following surgery, the patient is in excellent condition (Figure 8). There was no complaint. He denied having residual postoperative hematuria. The patient does not require hemodialysis following surgery.

DISCUSSION

Upper tract urothelial carcinoma (UTUC) is a malignancy that arises from the urothelial lining of the urinary tract from the calyceal system to the distal ureter. It is an uncommon entity, accounting for 5–7 % of all renal tumors and 5–10 % of all urothelial tumors, with an estimated annual incidence of 1–2 cases per 100,000 population.[1]This article presented a scarce case of bilateral UTUC, which accounts for 1-5% of UTUC. It occurs 2-3 times more frequently in males than female.[2-4]. A large Swedish study reported that only 1.6% of UTUCs were bilateral.[2] Holmäng et al. reported 15 patients with bilateral disease (1.6%) in their 936 UTUC patients.[9] They described 11 patients with pathologically bilateral urothelial cancer, among which 7 patients (63.6%) presented concordant low-grade and low-stage bilateral tumor and 4 patients (36.4%) presented discordant low-grade and low-stage tumor on one side and high grade or advanced stage tumor on the other. Fang et al. observed 39 (4.4%) patients with bilateral disease among 892 UTUC patients, with a concordant rate of 60.7% in histological grade between the two sides. [2]

In June 2020, the patient complained of intermittent gross hematuria with blood clot, a common symptom of UTUC. Pathology results showed low-grade urothelial papillary carcinoma of the left and right ureters with an invasive focus on the right ureter and glandular cystitis. CT Scan confirmed the patient had bilateral hydronephrosis. The patient also had acute kidney injury and routine HD. In January 2022, a left nephroureterectomy with bladder cuff and right partial ureterectomy with the ileal-ureteral substitution was performed. Diagnosis of bilateral UTUC was commonly based on the symptom complained by the patient.

Hematuria (70-80%) and flank pain (20-32%) were the two most common symptoms noticed by patients, which might not be highly specific to bilateral UTUC. However, the first complaint of our patient is gross hematuria. Notably, systemic symptoms, which are being unfit, lack of energy, and unexplained weight loss, could be associated with UTUC that should be evaluated promptly by supporting examination for metastatic detection.[2,5] This patient underwent an abdominal CT scan, cystoscopy, and repeat biopsy to support diagnosis and staging. These data also revealed risk stratification as recommended in the European Association of Urology (EAU) Guidelines on UTUC.[12] Thus, the patient was diagnosed with

bilateral UTUC of the ureter and chronic kidney disease due to bilateral hydronephrosis.

Few articles were reported showing the case of bilateral UTUC. Kanai et al. reported a case of simultaneous bilateral renal pelvic tumor in a patient male 64-year-old with the chief complaint of gross hematuria and left flank pain.[11] Uemura et al. reported a case of urothelial tumors that occurred simultaneously in the bilateral upper urinary tract and bladder, presenting with anuria.[12] The patient also had bilateral hydronephroses. Another report from Semko et al. also reported a case of bilateral urothelial cancer and hydronephrosis.[6] The patient also had acute post-renal kidney insufficiency and received routine HD. Matsuda et al. reported a bilateral low-grade upper-tract urothelial carcinoma patient who underwent a left nephroureterectomy and right total uterectomy with ileal ureteric replacement with a favorable prognosis.[13] The patient, a 66-year-old male with the chief complain of gross hematuria and bilateral hydronephrosis. Hydronephrosis in this patient resulted from bilateral UTUC, which can cause acute kidney injury in the patient.

Bilateral UTUC is associated with similar risk factors as common urothelial carcinoma.[5] Generally, cancer has some risk factors categorized into endogenous and exogenous. Some endogenous factors are non-modifiable such as biological aging and genetic susceptibility.[4] This patient had a family history of cancer in the patient's mother, younger sister, and two older brothers. The mother and younger sister had cervix cancer, the older brother had colon cancer, and the other older brother had rectal cancer. Lavi et al. reported a case of bilateral urothelial carcinoma in patients with hereditary nonpolyposis colorectal cancer syndrome. The underlying defect involves the mismatch repair (MMR) system, comprised of 4 genes producing the MMR proteins: ML1, MSH2, MSH6, and PMS2. MSH2 mutation seems to hold the highest risk factor for some cancer types, including bilateral UTUC. The most common manifestations are colon, endometrial, ovarian, rectal, and hepatobiliary. In this patient, we suspected that genetics contributed to bilateral UTUC.[14]

The exogenous factors are the most modifiable and are often modified to prevent cancer in the long term. These factors include radiation from radiologic examinations, chemical carcinogens from burnt food, and lifestyles including smoking, obesity, and lack of exercise.[4] A review study revealed tobacco smoking, occupational exposure to diesel fumes and aromatic amines (benzidine and β-naphthylamine for dyes, textiles, and chemicals industries), aristolochic acid in Chinese herbal remedy, and genetic susceptibility were the common risk factors in Western countries.[2] This case identified the patient's history of active smoking, the most common risk factor associated with UTUC. Tobacco smoking had 2.5 to 7 times increased relative risk of developing UTUC depending on the number of years (duration) of smoking, the number of cigarettes smoked daily, and the variability of individual genetic susceptibility.[5] Smoking seems to be a significant risk factor for an earlier diagnosis of UTUC, with anticipation of approximately five years for current smokers compared to non-smokers. Moreover, smoking has been associated with an increased risk of disease recurrence and cancer-specific mortality in patients treated with radical nephroureterectomy for UTUC.[2,4] The other risk factor that may play a role in bilateral UTUC is the exposed this patient to aromatic amine in textiles. The patient works as a textile business owner. This frequently exposed the patient to aromatic amines, which may be associated to the patient with UTUC.[2-4]

The pathophysiology of bilateral UTUC was still unclear. However, a study conducted two theories that could explain the underlying mechanism of bilateral UTUC existence.[5] The first theory was “Field Cancer” which showed that mutagens contained in urine are in contact with urothelium and induce the development of multiple tumor clones in some levels of the ureter. The second theory was “Intraluminal Seeding of Tumor Cells” which supported the development of multiple clones in multifocal cancer. Multiple localization and carcinogenic process recurrences might be associated with intraluminal migration and tumor cell grafting into the urinary tract wall or with the intraepithelial expansion of cells from the primary tumor.[5]

EAU Guidelines recommended the surgical treatment for UTUC should be considered based on the risk stratification of the tumor. In low-risk UTUC patients, kidney-sparing surgery was recommended to reduce the morbidity associated with radical surgery without worsening oncological outcomes. The survival was reported to be similar to radial nephroureterectomy (RNU). Otherwise, open RNU with bladder cuff excision is considered a standard treatment for high-risk UTUC.[12] This patient with bilateral UTUC underwent open surgery removing the left kidney and right ureter with ileal-ureteral

substitution, which is technically feasible in the selected case only. Our study was supported by other similar issues of low-grade bilateral UTUC treated with nephroureterectomy reported by Nason et al., Berrada et al.Matsuda et al.[3,5,14] Nason et al. reported a case of a 69-year-old smoker male with acute urinary retention and frank hematuria who performed a two-stage radical surgical approach, consisting of the initial stage of left radical nephroureterectomy and later stage (6 weeks apart) of right distal ureterectomy, cystoprostatectomy, and proper cutaneous ureterostomy formation.[14] The second report by Berrada et al. showed a 70-year-old male with left back pain and macroscopic hematuria, who also underwent two-stage radical approaches or left and right nephroureterectomy surgery with bladder cuff went off without any complication with 89 days interval.[5] Matsuda et al. as the third case reported a 66-year-old male who presented with bilateral hydronephrosis and underwent left nephroureterectomy and right total ureterectomy with ileal ureteric replacement with a good prognosis.[14]

The patient has no residual symptoms; moreover post-operative CT scan results show no residual tumor. In this case, we elected to do the nephron-preserving procedure, as the patient has bilateral UTUC, a contraindication to nephroureterectomy. According to the NCCN Guideline, depending on clinical and pathologic criteria and/or concomitant diseases that may contraindicate nephroureterectomy, nephron-sparing treatment is a treatment option for some individuals with UTUC.[15] The papillary, unifocal, low-grade tumor size of less than 1.5 cm, where cross-sectional imaging shows no indication of invasive disease, is a favorable clinical and pathologic criterion for nephron preservation.[15]

Despite the lack of randomized controlled trials, systematic evaluations of retrospective research have demonstrated that nephron-sparing methods for these patients produce comparable results to nephroureterectomy. Additionally, nephroureterectomy is contraindicated in individuals with bilateral disease, a single functional or anatomic kidney, chronic kidney disease, or renal insufficiency, and they should instead get nephron-sparing therapy.[15] Following nephron-sparing therapy, long-term surveillance (>5 years) is necessary, which includes urine cytology, cross-sectional urography, or endoscopic visualization.[15]

CONCLUSION

Bilateral UTUC is a scarce case even among all urologic malignancies. Preserving kidney function in these cases is a priority to reduce further morbidity for the patient. Careful assessment, thorough communication with the patient, and correct decision-making are essential to treating patients presenting with bilateral UTUC.

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