Co-occurrence of clear cell renal cell carcinoma and bladder urothelial carcinoma: A case report and literature review

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Abstract. The co-occurrence of clear cell renal cell carcinoma (ccRCC) and bladder urothelial carcinoma (bUC) is rare, and owing to the lack of a unified treatment plan, the prognosis is poor. The present report describes the case of a 65-year-old male patient with a history of smoking and no history of malignant tumors who presented with hematuria at the Huanghe Sanmenxia Hospital Affiliated to Henan University of Science and Technology (Sanmenxia, China) in July 2021. Urinary system computed tomography urography revealed a right renal tumor, and cystoscopy revealed intravesical lesions. The patient underwent transurethral resection of a bladder tumor + laparoscopic partial nephrectomy + laparoscopic radical cystectomy and bilateral ureterostomy. Pathological examination revealed right-sided ccRCC (pT1aN0M0) and high-grade invasive bUC (pT2N0M0). After surgery, the patient underwent bilateral ureteral single J tube replacement in the outpatient clinic every 3 months. In September 2022, the patient presented with a mass on the right side of the neck. Further examination revealed a space-occupying lesion in the lower part of the left kidney and space-occupying lesions in the neck, axilla, mediastinal lymph nodes and liver. A neck lymph node puncture biopsy suggested UC, and the patient was diagnosed with metastatic UC (T4N0M1). The patient received tislelizumab (200 mg once every 3 weeks) + sunitinib (50 mg/day, administered for 4 weeks with a 2-week interval) for a total of 2 months and died of an advanced tumor in January 2023. In addition, the data of 36 patients with ccRCC and bUC from the literature were analyzed for the present report. The results showed that the median age at first onset was 56.5 years (range, 31-82 years) and the male-to-female ratio was 6:1. Smoking and male sex may be risk factors for this disease, which has a median survival time of 47.5 months. The survival analysis results showed that the pathological stage of bladder cancer may be associated with its prognosis. The present study reviews the potential risks, clinicopathological characteristics and treatment methods of co-occurrence of clear ccRCC and bUC. In conclusion, the high-risk factors for the co-occurrence of ccRCC and bUC were smoking and male sex, and the median survival time was 47.5 months. The pathological stage of bladder cancer may be related to the prognosis.

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Introduction

Renal carcinoma and bladder cancer are the most common cancer types among the urinary system tumors, and their incidence and mortality rates account for a considerable proportion of the global population with cancer. Statistics on 36 types of cancer in 185 countries and regions around the world in 2022 showed that bladder cancer and kidney cancer ranked 9 and 14th respectively, with incidence rates of 3.1 and 2.2%, respectively (1). The main subtypes of renal carcinoma include clear cell carcinoma, chromophobe cell carcinoma and papillary carcinoma, with clear cell renal cell carcinoma (ccRCC) accounting for 87.7% of cases in a multicenter study in Europe and the United States in 2005 (2). However, the latest 2024 National Comprehensive Cancer Network (NCCN) guidelines indicate that ccRCC accounts for 70% of renal tumors (3). In the 5th edition of the classification of urinary and male reproductive organ tumors released by the World Health Organization in 2022, the subclassification of type 1/2 papillary RCC was cancelled, and 'clear cell papillary RCC' was named 'clear cell renal cell tumor' (4).

Initially diagnosed bladder cancer can be roughly divided into three stages, of which non-muscle invasive bladder cancer (NMIBC) accounts for 70-75%, MIBC accounts for 20-25%, and locally advanced or metastatic bladder cancer accounts for 5% (5,6). In total, ~90% of patients with bladder cancer are pathologically diagnosed with urothelial carcinoma (UC), whereas the remaining 10% are diagnosed with sarcoma,

squamous cell carcinoma, adenocarcinoma, neuroendocrine carcinoma or small cell carcinoma (5,6). UC, also known as transitional cell carcinoma (TCC), is divided into upper tract UC (UTUC; originating from the renal pelvis and ureter), bladder UC (bUC; originating from the bladder and accounting for the largest proportion) and urethral UC (originating from the urethra) (7).

To the best of our knowledge, although both ccRCC and bUC are common diseases, their co-occurrence in the same patient is rare, and the current evidence on this disease is limited to case reports or small series. The total number of patients with ccRCC and bUC co-occurrence published in the worldwide literature is 380 [328 cases in the Surveillance, Epidemiology and End Results (SEER) database (8) + 17 cases in small series (9) + 35 cases in case reports]. The present report describes a rare case of concurrent ccRCC and bUC. The clinical features, treatments and outcomes of this rare disease have also been summarized based on previously published literature. To the best of our knowledge, the present study conducted the first literature review of the multiple primary malignancies associated with ccRCC and bUC.

Case report

In July 2021, a 65-year-old man was admitted to the Huanghe Sanmenxia Hospital Affiliated to Henan University of Science and Technology (Sanmenxia, China) with complaints of intermittent hematuria for 8 months, accompanied by frequent urination, urgency, dysuria, and incomplete and interrupted urination. The patient had no other abnormalities such as hypertension or heart disease. In 2004, the patient underwent a cholecystectomy for cholecystitis. The patient had type 2 diabetes for 6 years, and their blood sugar level was under satisfactory control using metformin [500 mg once a day (qd)] + glimepiride tablets (2.5 mg qd). The patient had smoked 10 cigarettes per day for 40 years. Color ultrasonography of the urinary system revealed thickening of the bladder wall (Fig. 1A) and hyperechoic right kidney (Fig. 1B). Blood flow signals were observed in a strongly echogenic area of the right kidney (Fig. 1C). The patient underwent further urinary system computed tomography urography (CTU) examination to assist in the assessment of their condition. A total of 1 h before the examination, the patient drank 500-1,000 ml of water and held their urine. During the examination, the patient was in a supine position with both arms raised. After routine scanning using a dual-source 64-row spiral CT machine (spiral mode; scanning layer thickness, 5 mm; rotation time, 0.8 sec; pitch, 1.375:1; tube voltage, 120 kV; Siemens Healthineers), iohexol (300 mg/ml; GE Healthcare) was injected at a flow rate of 3.0-3.5 ml/sec (injection volume of ~90 ml), and then arterial phase, venous phase and excretion phase scanning were performed (tube current 250-300 mA in the arterial phase and venous phase, and 80-150 mA in the excretion phase). Urinary system CTU showed an oval mass measuring ~20 mm in the upper pole of the right kidney (Fig. 1D and E). The renal mass was significantly enhanced in the arterial phase, showing a 'fast-in and fast-out' pattern ('fast-in' refers to the contrast agent entering the renal tumor, causing it to appear earlier than the renal cortex; 'fast-out' means that the contrast agent leaves the renal tumor earlier than it leaves the renal cortex) (Fig. 1D and E). Bladder CTU examination revealed no obvious abnormal tumors (Fig. 1F).

After 9 days, the patient underwent cystoscopy, which revealed multiple carpet-like tumor protrusions in the trigone area, posterior wall, and the left and right walls of the bladder. The largest mass was ~5x5 mm, located at the ureteral orifice on the left side of the bladder (data not shown). Pathological examination after transurethral resection of bladder tumor (TURBT) revealed high-grade invasive bUC. Firstly, the resected specimens were stained with hematoxylin and eosin (H&E). The resected specimens were fixed with 10% formalin, embedded in paraffin, and cut into 4-μm tissue sections. After the paraffin sections were dewaxed in xylene I and II for 5 min, they were incubated in 100, 100, 95 and 85% ethanol solutions for 1 min, 1 min, 30 and 20 sec, respectively, and then rinsed with distilled water for 30 sec. After staining with hematoxylin (Shandong Chiwell Biotechnology Co., Ltd.) for 6-10 min, the sections were rinsed with running water for ~15 min to obtain blue color. Subsequently, the sections were placed in a 1% hydrochloric acid-ethanol solution for ~5 sec, and were rinsed with running water for 30 sec, incubated in 95% ethanol for 1 min for dehydration, counterstained with eosin stain (Shandong Chiwell Biotechnology Co., Ltd.) for 1.0-1.5 min, and then incubated in 85, 95, 100 and 100% ethanol solutions for 10, 20, 30 sec and 1 min, respectively, for dehydration. After excess alcohol was removed, the sections were soaked in xylene I (20 sec) and II (40 sec) until they became transparent, and sealed with neutral gum. H&E staining was performed at room temperature (~25˚C). Secondly, immunohistochemistry was performed on the resected specimens. The resected specimens were fixed with 10% formaldehyde, embedded in paraffin, sliced (~4 μm thick), dewaxed and rehydrated as aforementioned. The sections were rinsed with purified water three times (5 min each) to remove the ethanol, placed in preheated 0.50 M EDTA buffer (pH 8.0) in a boiling water bath for 20 min, and naturally cooled down to room temperature. The slides were rinsed with purified water three times (5 min each) to remove the EDTA buffer, and subsequently placed in 3% hydrogen peroxide at room temperature (5 min) to block the endogenous peroxidases. After washing three times with PBS (pH 7.2-7.4; 5 min each), primary antibodies from Shanghai Jiehao Biotechnology Co., Ltd., were added to the sections (diluted in PBS) and incubated at 37˚C for 60 min. The detailed information of the primary antibodies used in the present study is as follows: Cytokeratin (CK)20 (1:100; cat. no. CRM-0632); CK5/6 (1:100; cat. no. CM-0531); CK7 (1:100; cat. no. CM-0541); GATA-3 (1:100; cat. no. GM-0091); p40 (1:100; cat. no. PRM-0271); p53 (1:100; cat. no. PM-0051); Ki-67 (1:100; cat. no. KM-0021); α-smooth muscle actin (α-SMA; 1:100; cat. no. AM-0051); CD117 (1:100; cat. no. CRM-0421); transcription factor E3 (TFE-3; 1:100; cat. no. TRM-0141); CK(Pan) (1:100; cat. no. CM-0641); CD34 (1:100; cat. no. CM-0271); PAX-8 (1:100; cat. no. PRM-0291); vimentin (1:100; cat. no. VM-0031); epithelial membrane antigen (EMA; 1:100; cat. no. EM-0041); and carbonic anhydrase 9 (CA-9; 1:100; cat. no. CR-0811). After washing three times with PBS (pH 7.2-7.4; 5 min each), the secondary antibody (anti-mouse/rabbit IgG peroxidase polymer; 1:20, cat. no. KY-202; Shanghai Jiehao Biotechnology Co., Ltd.) was added and incubated at room temperature for 30 min.

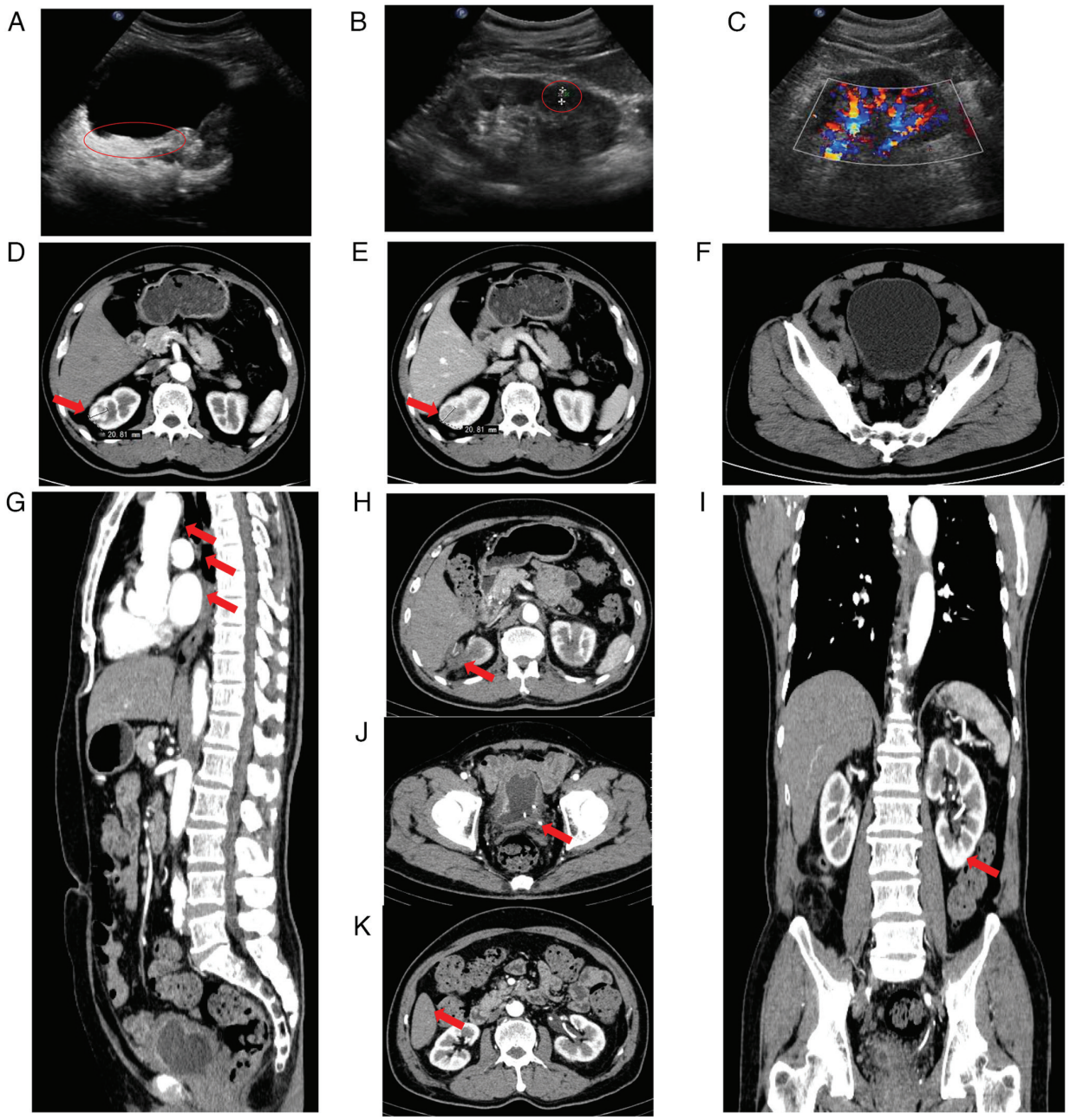

Figure 1. (A) Urinary system color Doppler ultrasound showing bladder wall thickening (circular shape, thickening of the bladder wall). (B) Urinary system color Doppler ultrasound showing increased echogenicity of the right kidney (circular shape, this area of the kidney was more echogenic). (C) Urinary system color Doppler ultrasound showing blood flow signals in the strong echo area of the right kidney (rectangular shape, there were blood flow signals in the normal area and the strong echo area of the right kidney). (D and E) CTU of the urinary system revealing a mass ~2 cm in size at the upper pole of the right kidney, showing a 'fast-in and fast-out' pattern (arrow points to the lesion in the upper pole of the right kidney). (F) CTU of the bladder showing no abnormalities. SPECT showing (G) no mediastinal lymph node metastasis (arrows point to lymph node level), (H) loss of the upper pole of the right kidney and a small amount of exudate after laparoscopic partial nephrectomy (arrow points to the right partial nephrectomy area), (I) no left renal metastasis (arrow points to the lower pole of the left kidney) and (J) the postoperative bladder showing diffuse bladder wall thickening. The high-density shadow in the bladder indicates a left ureteral stent (placed after transurethral resection of bladder tumors to prevent left ureteral stenosis) (arrow points to the high-density shadow). (K) SPECT showing no liver metastasis (arrow points to the liver). CTU, computed tomography urography; SPECT, single-photon emission computed tomography.

3,3'-Diaminobenzidine was used for color development and hematoxylin was used for counterstaining for 8 min at room temperature. After ethanol dehydration, the slides were sealed with resin. The pathological sections were observed using a light microscope (DM1000; Leica Microsystems, Inc.). The immunohistochemistry results were as follows: CK20(+) (Fig. 2B), CK5/6(-) (Fig. 2C), CK7(+) (Fig. 2D), GATA-3(+) (Fig. 2E), p40(-) (Fig. 2F), p53(+, mutant) (Fig. 2G), Ki-67(+, 30%) (Fig. 2H) and α-SMA(+) (Fig. 2I). H&E results showed high-grade cancer with cells exhibiting disordered polarity (the long axis of the nucleus is not perpendicular to the fibrovascular axis; a), enlarged nuclei (>3 times larger than the normal size; b), chromatin condensation (c), nipple fusion (d) and low intercellular connectivity (e) (Fig. 2A). SMA is part of the microfilament system of cytoskeletal proteins and is present in the smooth muscle, muscularis and muscularis

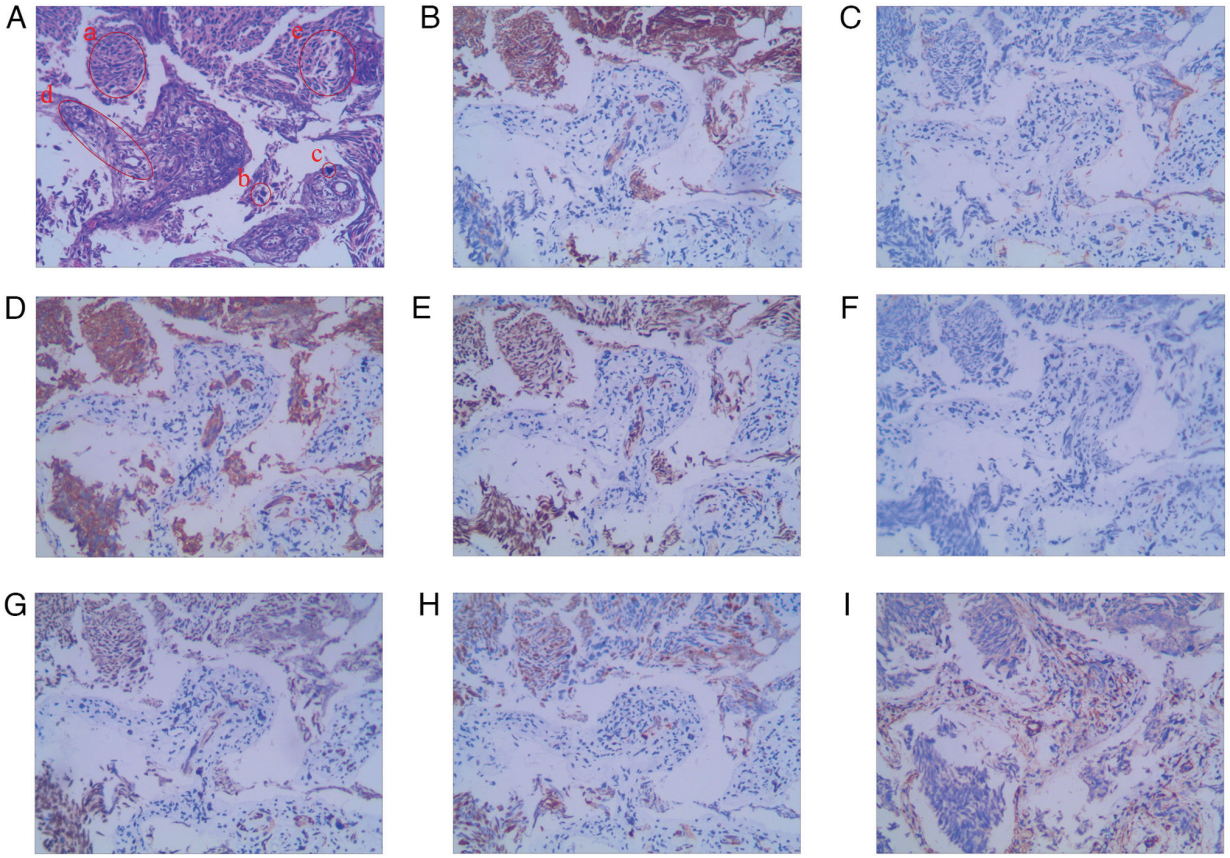

Figure 2. (A) Hematoxylin and eosin staining indicating that the tumor is bladder urothelial carcinoma. Tumor cells are (B) CK20(+), (C) CK5/6(-), (D) CK7(+), (E) GATA-3(+), (F) p40(-), (G) p53(+, mutant), (H) Ki-67(+, 30%) and (I) α-smooth muscle actin (+). Magnification, x100. CK, cytokeratin.

propria of the vascular wall (10). The present immunohistochemical results showed a α-SMA(+) phenotype (Fig. 2I); therefore, this was considered to be a muscle-invasive carcinoma. CK20, CK7 and GATA-3 are markers for the joint diagnosis of UC. The pathological results were all positive (Fig. 2B, D and E); therefore, a diagnosis of UC was made. TP53 is a tumor suppressor gene that is mutated in half of all human cancers (11). p53 expression is upregulated in urothelial carcinoma tissue compared with normal urothelial tissue, and high p53 expression predicts shorter survival in patients with non-muscle-invasive bladder cancer, but is not associated with prognosis in the muscle-invasive group (12). The present result was p53(+, mutant), which further confirmed the diagnosis of UC. Since the specimen was bladder tissue, a diagnosis of bUC was considered. Other possible diagnoses were excluded as follows: i) Squamous cell carcinoma was excluded, as there was no urothelial component, predominantly basal cell or clear cell features (if a urothelial component is present, UC with squamous differentiation can be considered); and ii) adenocarcinoma was excluded, as there was no urothelial differentiation with true glandular elements (mucus-secreting ductules or intestinal glands) in the tumor (if adenocarcinoma is mixed with UC, UC with glandular differentiation is considered) (13). If there was no metastasis, combined with the patient's good condition at the time and the presence of a right kidney tumor, radical cystectomy and partial right nephrectomy could be performed simultaneously. The patient was recommended to undergo a whole-body single-photon emission computed tomography (SPECT) examination to determine whether there was metastasis. However, the patient refused to undergo a total cystectomy and therefore requested a partial right nephrectomy only.

A total of 9 days later, a laparoscopic right partial nephrectomy was performed to remove the right renal mass completely. Pathological examination of the specimen revealed a ccRCC in the right kidney with clean resection margins. The immunohistochemistry results were as follows: CK20(-) (Fig. 3B), CK7(-) (Fig. 3C), GATA-3(-) (Fig. 3D), CD117(-) (Fig. 3E), TFE-3(-) (Fig. 3F), CK(+) (Fig. 3G), CD34(+) (Fig. 3H), PAX-8(+) (Fig. 3I), vimentin(+) (Fig. 3J), EMA(focal +) (Fig. 3K) and Ki-67(+, <1%) (Fig. 3L). H&E results revealed ccRCC with tumor cells arranged in nests and alveoli (a; Fig. 3A). The tumor cells were round (b) or polygonal (c) and relatively large, with transparent cytoplasm (d). The nuclei were centrally located (e), round and uniform in size, and the interstitium contained a network of small, thin-walled sinusoidal vessels (f; Fig. 3A). CD34 immunohistochemical images showed typical 'chicken cage-like' changes (grid-like changes in blood vessels; Fig. 3H). The immunohistochemical results of CK20 and GATA-3 were negative thus excluding UC (14), the results for CD117 and CK7 were negative thus excluding chromophobe cell carcinoma (15), and the PAX-8 result was positive, as found in both renal tumors (16) and UC (17). EMA is expressed in several tumors, therefore its diagnostic value is not high and it needs to be used in combination with specific epithelial differentiation markers (18); however, the

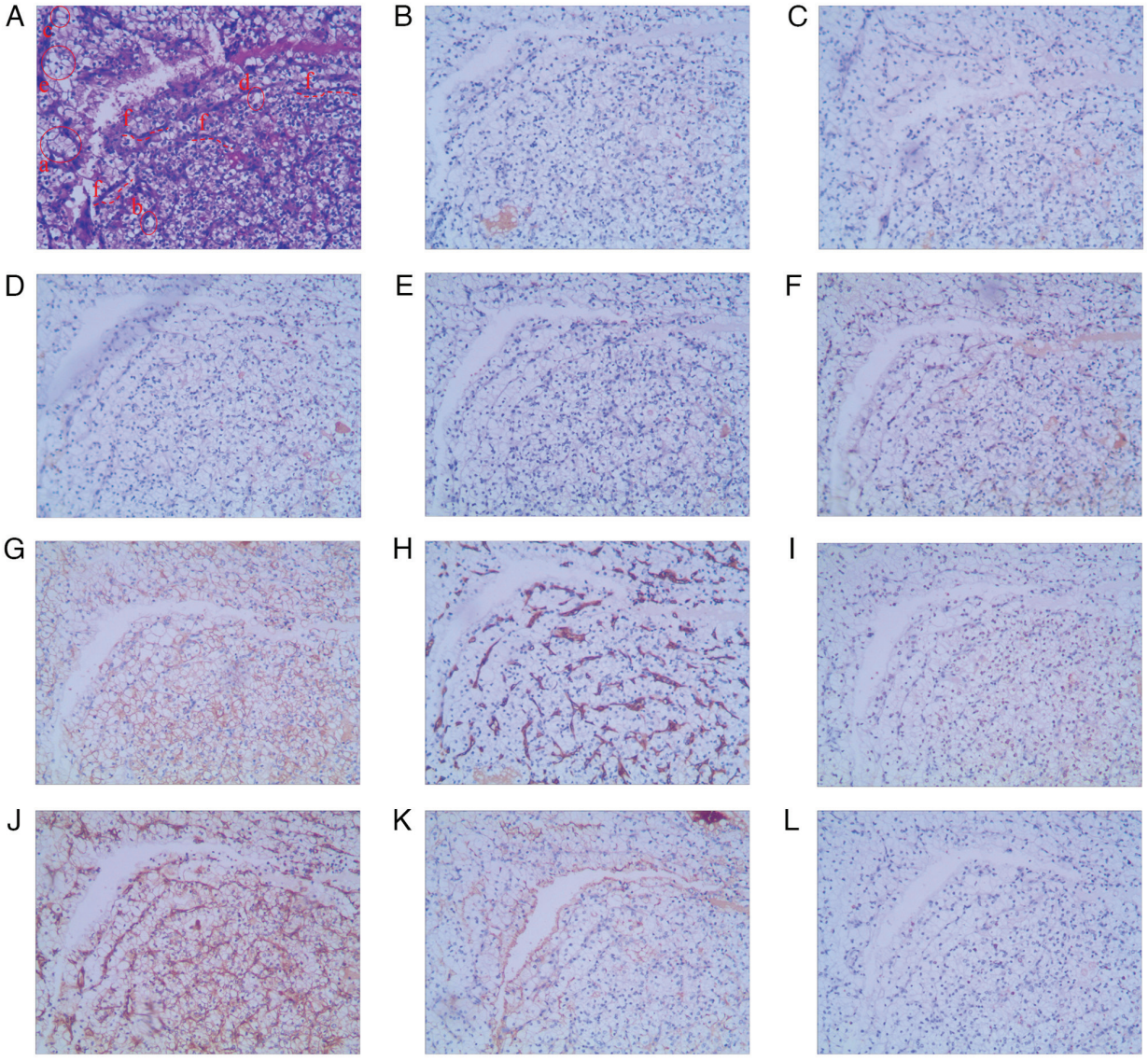

Figure 3. (A) Hematoxylin and eosin staining indicating that the tumor is renal cell carcinoma. Tumor cells are (B) CK20(-), (C) CK7(-), (D) GATA-3(-), (E) CD117(-), (F) transcription factor E3(-), (G) CK(+), (H) CD34(+), (I) PAX-8(+), (J) vimentin(+), (K) epithelial membrane antigen (focal +) and (L) Ki-67(+, <1%). Magnification, x100. CK, cytokeratin.

aforementioned immunohistochemical results showed that CK and vimentin were strongly expressed in renal tubular epithelial cells, suggesting renal carcinoma. No tumor cells were found on the pathological section resection margins; therefore, the resection margins were considered clean. Other possible diagnoses were excluded as follows: i) In chromophobe RCC, the tumor cell membrane is thick and clear, the cytoplasm is rich, the nuclei are shrunken, the interstitial blood vessels are mostly thick-walled, and CD117 and CK7 are diffusely positive (15); and ii) in clear cell papillary RCC, the tumor cell cytoplasm is clear, the cell nuclei are arranged linearly away from the basement membrane, there are various growth patterns, such as cystic, tubular, papillary and solid, and CK7 is diffusely positive (19). According to the TNM system of the American Joint Committee on Cancer (AJCC) (20) and the clinical staging of renal cancer (21), the pathological stage was T1a. However, confirmation of the presence or absence of lymph node metastasis and distant metastasis requires further whole-body SPECT examination. The patient refused SPECT and requested to discuss with their family whether to undergo radical cystectomy.

After surgery (laparoscopic right partial nephrectomy), the patient received regular intravesical instillations of epirubicin (50 mg per week for 2 months). At 2 months after the surgery, the patient developed an intermittent fever (maximum temperature, 39.1˚C) and urinary tract infections caused by *Klebsiella pneumoniae* and *Pantoea agglomerans* (bacterial detection was performed using the MA-120 microbial identification and drug sensitivity analysis system; Zhuhai Meihua Medical Technology Co., Ltd.). The patient was then treated with sulbactam [0.5 g; every 12 h (q12 h)], cefoperazone (1 g; q12 h) and nitrofurantoin (50 mg; three times a day) for 5 days. The patient finally agreed to undergo a radical cystectomy. A SPECT scan was performed on the patient in September 2021. The patient was intravenously injected with 25 mCi of technetium (99mTc) methylenediphosphonate injection contrast agent 2-4 h before the examination. After emptying their bladder, the patient laid flat on the SPECT scanning bed

(Symbia T16 SPECT/CT; Siemens Healthineers) and underwent whole-body bone imaging, cervical and pelvic SPECT, and CT enhanced scanning. The following SPECT parameters were used: Acquisition angle, 6˚/frame; acquisition time, 15 sec/frame; matrix, 128x128; and rotation, 360˚. The CT scanning parameters were as follows: Tube voltage, 110 kV; tube current, 160 mA; and slice thickness, 1.5 mm. Image fusion was performed using the dedicated software Syngo MI VA70A (Syngo MI Applications VA70A; Siemens AG) for the image post-processing workstation. SPECT showed postoperative changes without distant or lymph node metastasis (Fig. 1G-K). According to the AJCC TNM system and clinical staging (21), the pathological stage of ccRCC was pT1aN0M0 and the clinical stage was I, with the right renal tumor being ~2 cm in size.

Combined with the results of the SPECT examination and previous bladder pathological examination, according to the TNM system of the AJCC and the clinical staging of bladder cancer (22), the pathological stage of bladder cancer was T2 and the clinical stage was II. However, the specific pathological staging needs to be determined by pathological examination after radical cystectomy. According to the guidelines for the diagnosis and treatment of bladder cancer (22), radical cystectomy is recommended for T2 MIBC without lymph node metastasis.

In October 2021, a laparoscopic radical resection of the bladder, prostate, seminal vesicle and distal ureter, a pelvic lymph node dissection and bilateral cutaneous ureterostomies were performed. The pathological results of H&E staining performed according to the aforementioned method revealed high-grade invasive bUC that had infiltrated the entire bladder (Fig. S1A). The bilateral seminal vesicles (Fig. S1B and C), upper bladder resection margin (Fig. S1D), lymph nodes (Fig. S1E and F), junction of the prostate and bladder (Fig. S1G), vas deferens (Fig. S1H and I), prostate (Fig. S1J) and ureters (Fig. S1K and L) were not invaded. Bladder cancer was evaluated according to the AJCC TNM and aforementioned clinical staging (22), and it was confirmed that the pathological stage of bladder cancer was pT2N0M0 and the clinical stage was II. The pathological results of this case showed that the tumor invaded the entire bladder layer (Fig. S1A), but did not invade the perivesical fat tissue (Fig. S1D), and no distant metastasis was found.

After the diagnosis of dual cancer, it was recommended that the patient and their family undergo genetic testing to exclude, or prevent in advance, any gene-related diseases. However, the patient and their family refused for financial reasons, and as some patients do not believe in the concept of preventing diseases before their occurrence.

Postoperative chemotherapy and regular follow-up were recommended according to the postoperative pathology findings suggestive of MIBC. However, the patient refused chemotherapy and regular review, and only underwent bilateral ureteral single J tube replacement in the outpatient clinic every 3 months. Abdominal X-ray showed bilateral ureteral single J tubes exiting from the right abdominal wall (Fig. 4A). In September 2022, the patient visited the Outpatient Department of the Huanghe Sanmenxia Hospital Affiliated to Henan University of Science and Technology for the treatment of hoarseness, cough while drinking water and dyspnea. Physical examination revealed multiple swollen lymph nodes in the neck and armpits on both sides, the largest of which was ~20 mm and was located at level IV of the right side of the neck. SPECT examination results in September 2022 showed no tumor recurrence in the right kidney and pelvis, and a 19x24x23-mm mass was observed in the lower pole of the left kidney (Fig. 4B and E); multiple swollen lymph nodes were observed in the bilateral neck (Fig. 4F), mediastinum (Fig. 4C), axilla and portal vein (data not shown), considering the possibility of metastasis; and nodules with a diameter of ~5 mm were observed in the S6 segment of the liver (Fig. 4D), indicating a potential metastasis.

A right neck lymph node biopsy was performed in October 2022. Lymph node pathology results suggested metastatic UC. The immunohistochemistry results were as follows: CK5/6(+) (Fig. 5B), CK7(+) (Fig. 5C), GATA-3(+) (Fig. 5D), PAX-8(+) (Fig. 5E), Ki-67(+, 80%) (Fig. 5F), p40(focal +) (Fig. 5G), CA-9(-) (Fig. 5H) and CK20(-) (Fig. 5I). H&E staining images showed tumor cell infiltration (Fig. 5A). Positive expression of PAX-8 indicates that the tumor originates from the kidney or urothelial tissue (Fig. 5E). CA-9 is a specific tumor marker for metastatic renal cancer, and negative expression excludes renal cancer metastasis (Fig. 5H) (23). p40 positivity indicates squamous cell cancer, but in this case the expression was focal and had no practical significance (Fig. 5G) (24). CK5/6, CK7, GATA-3 and CK20 are all epithelial tissue tumor markers, which are used together for the diagnosis of UC, among which the relative specificity of GATA-3 is 86% (14,25). In this case, the pathological results showed that CK5/6 (Fig. 5B), CK7 (Fig. 5C) and GATA-3 (Fig. 5D) were all positive, and CK20 (Fig. 5I) was negative; therefore, the lymph node tissue was invaded with metastatic bUC. Bladder cancer was evaluated based on the AJCC TNM and clinical staging. The patient had distant lymph node metastasis, the pathological stage was M1, and the clinical stage was IV.

It was recommended that the patient undergo a liver and left kidney biopsy to clarify the pathological type and assist in further diagnosis and treatment. The patient rejected these suggestions as they already had multiple tumors and had been confirmed with UC with lymph node metastasis. Regardless of the results of the pathological examination of the liver and left kidney, the patient was already in the late stage of cancer; therefore, they did not wish to experience further pain from biopsy punctures, surgery, radiotherapy and chemotherapy. The only treatment they would accept was oral medication to relieve the current pain.

Combined with the patient's clinical data, empirical analysis suggested that the left renal mass may be a recurrence of ccRCC. Firstly, Fig. 4G shows bilateral renal SPECT scans. SPECT examination results showed that the tumor was unevenly enhanced during the cortical phase (Fig. 4H); the tumor disappeared rapidly during the excretory phase, with a density lower than that of normal renal parenchyma, and the tumor was observed to compress the renal pelvis (Fig. 4I). Secondly, the 'Guidelines for the Diagnosis and Treatment of Urological and Men's Diseases in China (2022 Edition)' (26) mentioned that metastatic renal cancer caused by other cancers is relatively rare, and its clinical characteristics are bilateral renal metastasis and multiple metastatic lesions. The patient only had a single tumor in the lower pole of the left

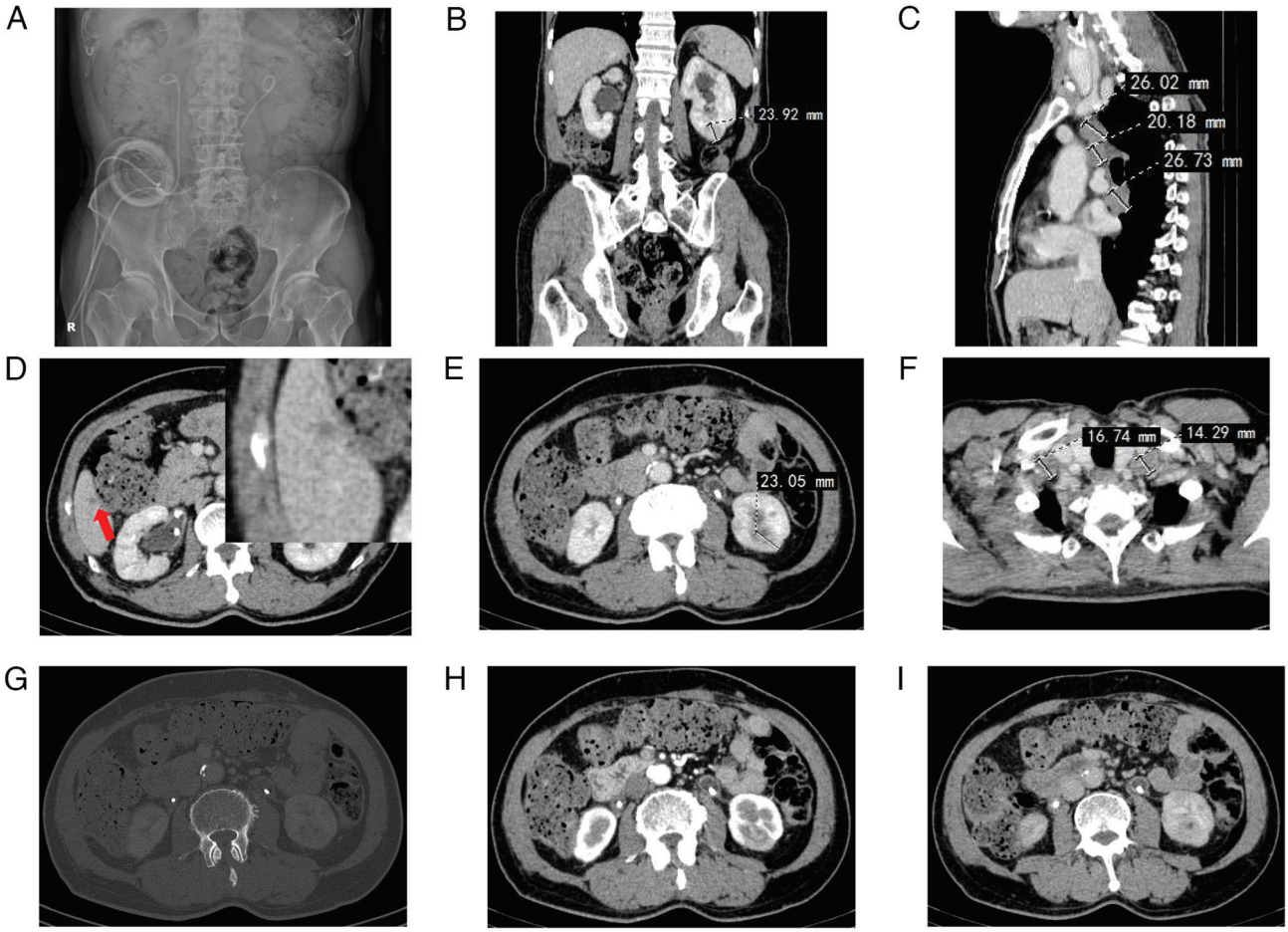

Figure 4. (A) Abdominal X-ray after radical cystectomy and bilateral ureterostomy. (B) Coronal plane and (E) transverse plane SPECT showing a new tumor 19x24x23 mm in size in the left kidney (the measurements shown refer to the size of the left kidney tumor). SPECT showing (C) multiple lymph node metastases in the mediastinum (the measurements shown refer to the size of the mediastinal lymph nodes), (D) a nodule measuring ~5 mm in diameter in the S6 segment of the liver (the red arrow points to the lesion) and (F) bilateral cervical lymph node metastasis (the measurements shown refer to the size of the bilateral cervical lymph nodes). (G) Bilateral renal SPECT scan. SPECT scan showing (H) bilateral renal cortical stage and (I) bilateral renal excretion period. SPECT, single-photon emission computed tomography.

kidney, which did not meet the clinical characteristics of renal metastatic carcinoma, and they had a history of right-sided ccRCC; therefore, it was more likely that the left kidney may be a recurrence of ccRCC.

For liver tumors, since both bUC and ccRCC can metastasize to the liver, it is impossible to clearly determine their pathological type. According to the AJCC bladder cancer staging (22), the following assumptions can be made: If the liver metastasis comes from UC, the pathological stage is M1b and the clinical stage is IVB; if the metastasis comes from ccRCC, the pathological stage is M1a and the clinical stage is IVA. Therefore, the patient was diagnosed with metastatic UC, with pathological stage M1 and clinical stage IV. The patient and their family refused further radiotherapy and chemotherapy, as they believed that the side effects of chemotherapy and radiotherapy would outweigh the therapeutic effects to the disease itself.

Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor (TKI) that inhibits tumor cell proliferation and antitumor angiogenesis by acting on targets such as vascular endothelial growth factor receptors 1-3 (VEGFR1-3), c-KIT, platelet-derived growth factor receptor-α and -β and FMS-like tyrosine kinase 3 (27). Both the United States Food and Drug Administration (FDA) (21) and the Chinese FDA (28) have approved sunitinib for the treatment of metastatic RCC. Tislelizumab, a programmed cell death protein 1 (PD-1) inhibitor originally developed in China, is specifically designed to minimize Fcγ receptor binding of anti-PD-1 antibodies, thereby limiting antibody-dependent phagocytosis. Tislelizumab has higher affinity than pembrolizumab or nivolizumab, all of which provide a potential mechanism of resistance to anti-PD-1 therapies (29). Tislelizumab was approved by the China National Medical Products Administration for the treatment of locally advanced or metastatic UC (30). The antitumor mechanisms of pembrolizumab, nivolizumab and tislelizumab are similar. The present patient had both ccRCC and bUC, and there is currently no unified guideline for this type of patient. The use of tislelizumab + sunitinib is empirically recommended to treat patients, aiming to maximize the benefits to patients through dual antitumor mechanisms. The reason for choosing tislelizumab instead of pembrolizumab or nivolizumab is that the target affinity of tislelizumab is 35-60 times higher than that of pembrolizumab or nivolizumab (31).

After communicating with the patient and their family, a regimen of tislelizumab (200 mg once every 3 weeks; BeiGene, Ltd.) + sunitinib (50 mg/day; administered for

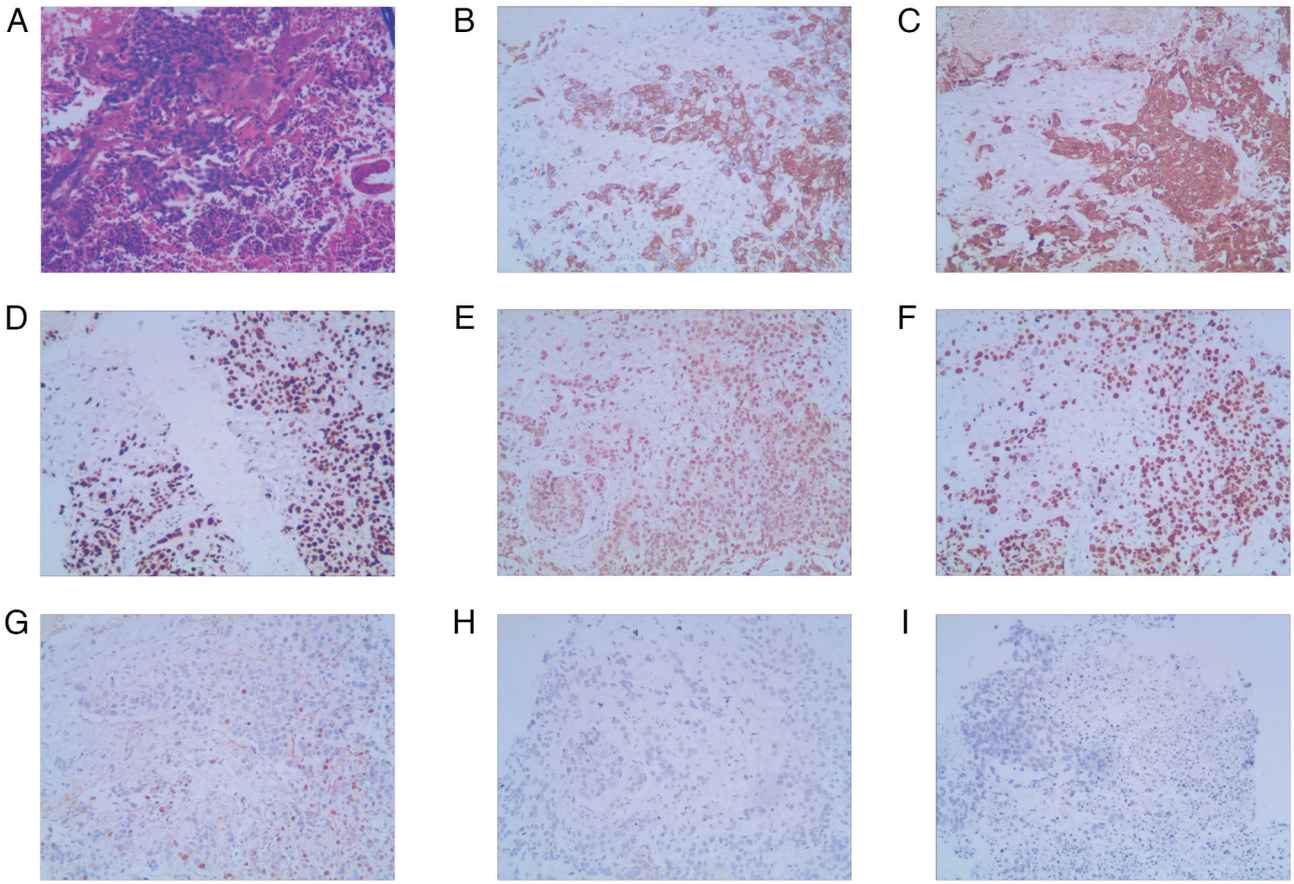

Figure 5. (A) Hematoxylin and eosin staining showing metastatic urothelial carcinoma in the lymph nodes. Tumor cells are (B) CK5/6(+), (C) CK7(+), (D) GATA-3(+), (E) PAX-8(+), (F) Ki-67(+, 80%), (G) p40(focal +), (H) carbonic anhydrase 9(-) and (I) CK20(-). Magnification, x100. CK, cytokeratin.

4 weeks with a 2-week interval) was adopted to control disease progression for 2 months. In January 2023, the patient died of tumor metastasis, and no autopsy was performed.

Discussion

From the establishment of the databases to May 19, 2024, a comprehensive literature search was conducted in the China National Knowledge Infrastructure database (https://www.cnki.net/) and Wanfang Data (https://wanfangdata.com.cn/) using 'clear cell renal cell carcinoma' and 'bladder urothelial carcinoma' as Chinese search terms. In addition, relevant English studies were searched in Web of Science (webofscience.com) and PubMed (https://pubmed.ncbi.nlm.nih.gov) using the search terms 'clear cell renal cell carcinoma' and 'bladder urothelial carcinoma' from the inception of the databases to May 19, 2024. The initial search identified 3,656 studies. The inclusion criteria were as follows: i) Case reports or case series of ccRCC combined with bUC or TCC; ii) all included cases had clear pathological types; iii) the included studies had available full texts; and iv) the included studies presented patient information, such as sex, age, smoking, previous history, diagnosis time of renal cancer and bUC, and follow-up status. The exclusion criteria were as follows: i) Irrelevant studies; ii) unable to download full text; and iii) incomplete patient information. Two researchers independently screened the studies according to the inclusion criteria and a third researcher was involved in the decision-making process for study inclusion. When reading the references of the 31 included studies, three further studies met the inclusion criteria, and ultimately 34 studies were included in the literature review. There were 7 articles in Chinese (to ensure high quality of evidence, only core journals were included, because core journals usually have stricter review processes, more authentic information and greater academic influence), 11 articles in Japanese (indexed by PubMed or Web of Science) and 16 articles in English. Japanese articles could be read using Google Translate (https://translate.google.com). The literature screening process is illustrated in Fig. 6.

The relevant survival analyses were performed using the data extracted in Table SI. For patients with multiple primary cancers associated with ccRCC and bUC, the Kaplan-Meier method in GraphPad Prism 5 software (Dotmatics) was used to evaluate the effects of the tumor onset time interval and ccRCC and bUC pathological stage on survival, and the log-rank test was used to test the differences between the survival curves. $P<0.05$ was considered to indicate a statistically significant difference.

A total of 35 patients were included in 34 articles, and together with the present case, a cohort of 36 patients diagnosed with ccRCC complicated by bUC was included in the literature review. The clinical characteristics of all the cases reviewed in the literature are presented in Tables SI and SII. The median age at first cancer diagnosis was 56.5 years (range, 31-82 years).

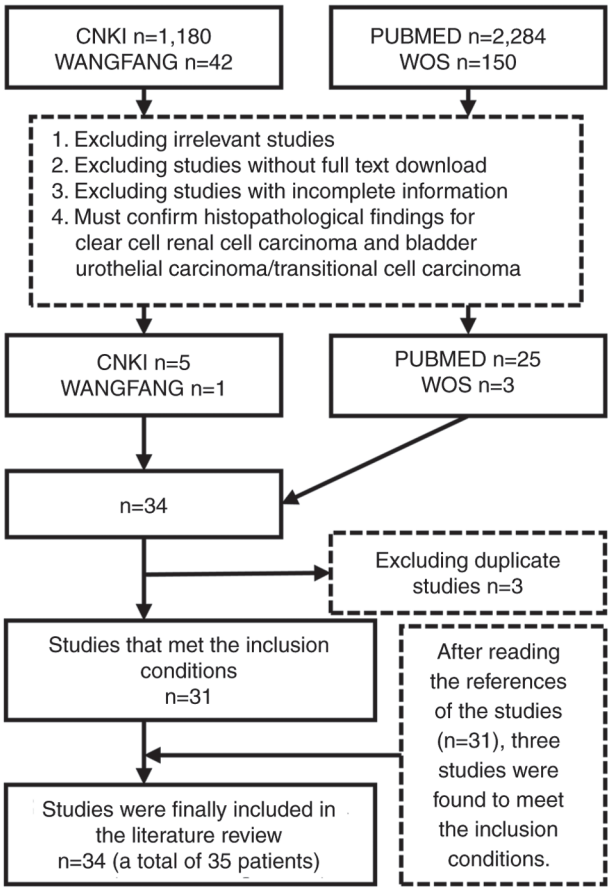

Figure 6. Steps in the literature search. From the establishment of the database to May 19, 2024, relevant studies were searched in CNKI, WANFANG, WOS and PubMed databases using 'clear cell renal cell carcinoma' and 'bladder urothelial carcinoma' as search terms, and 3,656 studies were initially retrieved (CNKI, 1,180; WANFANG, 42; PubMed, 2,284; WOS, 150). After screening the inclusion criteria, 34 studies were obtained, and after excluding three duplicate studies, 31 studies were obtained. When reading the 31 studies, three studies that met the inclusion criteria were found in the references. Finally, 34 studies were included for review, of which one study contained 2 patients, and a total of 35 patients were included. CNKI, China National Knowledge Infrastructure; WOS, Web of Science.

Most cases occurred in males, with a male-to-female ratio of 6:1. A total of 16 (44.4%) patients had a history of smoking. However, only 11.1% (4 cases) of the patients had a family history of cancer. Regardless of whether renal or bladder cancer is the first type of cancer, the first symptom in most patients is hematuria, which may be intermittent, continuous, macroscopic or microscopic. A small number of patients (11.1%) have symptoms of prostatitis, such as difficulty in urination, frequent urination, urgency and incomplete urination. Few patients with renal cancer (5.6%) as the primary cancer experience lower back or hip pain. A total of 9 patients had dual primary cancers of the urinary system (including ccRCC and bUC) (32-39). A total of 11 patients were diagnosed with triple primary cancers of the urinary tract, including prostate cancer, ccRCC and bUC (40-50). The remaining 16 patients also had other types of cancer, such as von Hippel-Lindau disease (51), uterine cancer (52), renal UC (53), renal pelvic cancer (54), ureteral UC (55), renal pelvic and ureteral TCC (32,56,57), hepatic carcinoma (58), metastatic clear cell carcinoma (59), tubular cystic RCC (60), ureteral inverted papilloma cancer (61), esophageal cancer (62), ureteral fibroepithelial polyps (63), neuroendocrine tumor (64), rectal adenocarcinoma (65), and metastatic UC (present case).

In published reports on multiple primary urinary tract cancers, ccRCC was mainly in stages T1 (32,34-38,40,45-49, 54,56,60,62) (present case) and T2 (33,39,41,44,51-55,57, 64,65), accounting for 47.2 and 33.3% of the cases, respectively. A total of 20 patients (55.6%) underwent total (33,36,37, 39,40,43,45,51,53,58,59) or partial (44,48,49,52,54,60,62,63) (present case) nephrectomy as the primary treatment, and 8 patients underwent nephroureterectomy (41,54,57) or nephroureter and partial cystectomy (32,34,47,56,61) according to their clinical stage and condition. A total of 3 patients with concurrent bladder cancer underwent nephroureterectomy and cystectomy simultaneously (43,46,53). To prevent recurrence or progression of renal cancer after surgery, certain patients receive chemotherapy with fluorouracil (54), and others use immunosuppressants, such as interferon (41,42,44), interleukin-2 (44), nivolumab (49), ipilimumab (49), tislelizumab and sunitinib (present case). A patient who had previously been receiving hemodialysis for renal failure was found to have bladder, kidney and ureteral tumors and continued to receive hemodialysis treatment after surgery (57).

Among the multiple primary urinary tract cancers in the present review, the pathological stages of bUC were mainly T1 (32-35,38-42,44-46,48,49,51,53,54,57,59,63, 64) and T2 (37,38,43,47,60,65) (present case), accounting for 58.3 and 19.4% of cases, respectively, including 1 case (52) in the T3 stage and 1 case (55) in the T4 stage. The main surgical methods for bUC were TURBT (63.9%) (32-35,38-44,48-51,54,56-59,61,62) and radical cystectomy (30.6%) (36,45,46,52,53,60), among which 13.9% of the patients underwent radical cystectomy after being diagnosed with bladder cancer by TURBT (37,47,64,65) (present case). Intravesical chemotherapy (35,37,38,41,50,55,61,62,65) and Bacillus Calmette-Guérin (39) therapy were the main treatments after TURBT.

Based on the different onset times of ccRCC and bUC-related multiple cancers, they can be divided into synchronous multiple primary malignant neoplasms (SMPMN; ≤6 months) and metachronous MPMN (MMPMN; >6 months). In the present review, 20 patients had SMPMN (34,35,37-39,42,43, 45-47,49-51,53,54,57,59,60,64) (present case) and 16 patients had MMPMN (32,33,36,38,40,41,44,48,52,55,56,58,61-63,65). The median survival or follow-up time since the last cancer diagnosis was 20 and 48 months in the SMPMN and MMPMN groups, respectively.

For patients with multiple primary cancers associated with ccRCC and bUC, the tumor onset time interval (P=0.533; Fig. 7A) and ccRCC pathological stage (P=0.455; Fig. 7B) had no significant effect on the survival rate; however, the bUC pathological stage had a significant effect on the survival rate (P=0.021; Fig. 7C).

Bladder cancer is currently the 9th most common malignant tumor worldwide (1). According to statistics in 2022, there were ~614,000 new cases of bladder cancer and 220,000 deaths worldwide (1). The incidence and mortality rates in men were higher than those in women (1). Bladder cancer is the sixth most common cancer in men and the ninth leading cause of cancer death (1). bUC accounts for >90% of all bladder cancer

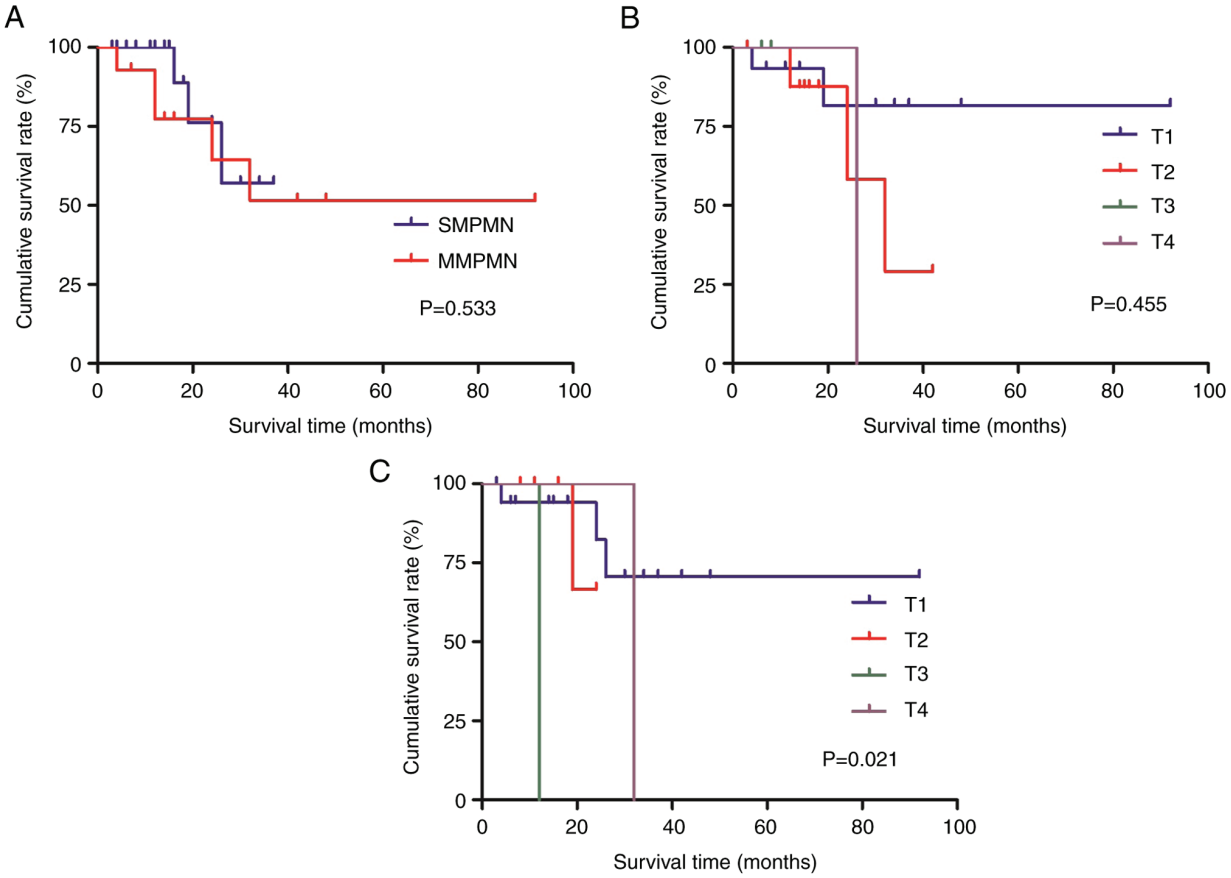

Figure 7. (A) Cumulative survival rates of synchronous and metachronous ccRCC- and bUC-related multiple primary cancers. (B) Cumulative survival rates of patients with different staging of ccRCC-related multiple primary cancers. (C) Cumulative survival rates of patients with different staging of bUC-related multiple primary cancers. ccRCC, clear cell renal cell carcinoma; bUC, bladder urothelial carcinoma; SMPMN, synchronous multiple primary malignant neoplasms; MMPMN, metachronous multiple primary malignant neoplasms.

cases (5). Smoking is the most common risk factor, while other risk factors include occupational factors, such as exposure to paint, rubber, petroleum, dyes and coal, and iatrogenic factors, such as pelvic radiotherapy, chemotherapy, long-term indwelling catheterization, chronic inflammatory stimulation and schistosomiasis infection, associated with geographical or socioeconomic reasons (6,66). The main clinical manifestation in most patients is painless gross hematuria; however, if lower urinary tract symptoms are present, such as frequency, urgency and difficulty in urination, bladder cancer should be suspected (6,22,67).

Since the advent of cystoscopy, TURBT has been the main method for the initial diagnosis and staging of bladder cancer, and is also the main method for the treatment of NMIBC (6,22).

The current standard surgical approach for MIBC is radical cystectomy combined with urinary diversion (68). With advancements in technology, the surgical methods of radical cystectomy have evolved from traditional open surgery to laparoscopic or robotic surgery. Khan *et al* (69) compared the prognosis of patients with bladder cancer who underwent three surgical procedures (open radical cystectomy, laparoscopic radical cystectomy and robotic-assisted radical cystectomy) and found no difference in 90-day complication rates among the three surgeries according to the Clavien-Dindo complication classification system (70).

Griffiths *et al* (71) confirmed that neoadjuvant chemotherapy with cisplatin, methotrexate and vinblastine is beneficial for the treatment of MIBC. This view is also supported by the results of a systematic review and meta-analysis of neoadjuvant chemotherapy for invasive bladder cancer (72). Currently, the main treatments for metastatic UC include chemotherapy, such as gemcitabine combined with cisplatin (73,74), immune checkpoint inhibitors, such as avelumab (75) and pembrolizumab (76), and radiotherapy; however, radiotherapy alone has no obvious benefit on overall survival (22).

For patients who are unable or unwilling to undergo radical cystectomy and who clearly understand the risks and need for careful follow-up, the American Urological Association guidelines recommend 'trimodal therapy', which is maximal TURBT combined with chemoradiotherapy (77).

New guidelines from the FDA and the European Society for Medical Oncology recommend enfortumab vedotin plus pembrolizumab as the first-line standard treatment for advanced UC, with an advantage shown in terms of patient survival compared with chemotherapy (78,79). Nivolumab plus gemcitabine-cisplatin or platinum plus avelumab are alternative treatments (78).

The prognosis and treatment of bUC mainly depends on histopathology and TNM staging. The degree of muscle layer invasion determines whether a patient is staged as pT1 (NMIBC) or pT2 (MIBC). The 5-year overall survival

rates of pT1, pT2 and pT3 bUC are 75, 50 and 20%, respectively (22,67).

According to the recommendations of domestic (26) and international (22) guidelines, the patient in the present report was first diagnosed with bladder cancer through TURBT, and then underwent radical cystectomy combined with urinary diversion. Regular follow-up and treatment were not performed after the operation, which eventually led to the occurrence of metastatic UC. Tislelizumab was administered to treat metastatic bladder cancer, but the patient ultimately had a poor prognosis.

Renal cancer is a growing disease with an estimated 400,000 new cases per year worldwide and an annual mortality rate of nearly 175,000 individuals (80); it accounts for ~3% of adult malignancies (81). ccRCC is the predominant and aggressive histological subtype of adult renal cancer. The NCCN guidelines state that ~85% of renal tumors are RCC, of which ~70% are ccRCC (3). However, Wilms' tumors account for 90% of childhood renal cancer cases (80).

High blood pressure (80,82), smoking (80,83,84), high body mass index, obesity (80), alcohol consumption, lack of exercise and multiple births in women (84) are risk factors for renal cancer.

Most cases of renal cancer are discovered incidentally during abdominal ultrasonography or CT scans. Only a minority (<10%) of patients present with the classic triad of kidney cancer, which includes hematuria, flank pain and a palpable abdominal mass (85). The main treatments for localized renal cancer include partial nephrectomy, total nephrectomy and tumor ablation (85,86). Patients with metastatic renal cancer, which is usually not treatable with surgery, may benefit from immune checkpoint and targeted protease inhibitors (85). Since 2005, protein kinase inhibitors have been used to treat metastatic RCC by targeting growth factor receptors, such as fibroblast growth factor receptor, MET oncogene and VEGFR. Since 2015, PD-1 inhibitors (nivolumab and ipilimumab) have been used to inhibit renal cancer cells. Currently, the standard treatment for most patients with metastatic renal cancer is a combination of immune checkpoint inhibitors and protein TKIs. For patients who cannot tolerate immunosuppressants, single-drug therapy can be used (85,86).

A total of three studies (41,42,44) included in the present review reported the use of interferon and IL-2 alone or in combination for postoperative adjuvant therapy of RCC, all of which were published before 2010. However, it was subsequently confirmed that there was no clinical benefit in the use of interferon-α and/or IL-2 for RCC above stage T2 (87).

Routine preoperative renal mass biopsy of small renal masses is not recommended by the current guidelines (26). The main reasons include inaccurate biopsy results, complications of renal mass biopsies and needle tract implantation (88), which ultimately lead to a high rate of unnecessary nephrectomy/partial nephrectomy for benign renal tumors (18-26%) (89). Gao *et al* (88) reported that a preoperative renal mass biopsy could reduce the rate of unnecessary partial/radical nephrectomy to 3%.

A partial nephrectomy was performed on the right renal tumor of the present patient in accordance with the guidelines (26). During follow-up, the right renal tumor did not recur, but a mass appeared in the left kidney. After evaluation, it was suspected that the mass in the left kidney could be a recurrence of renal cancer. Sunitinib was administered for treatment, but the patient eventually died of multiple advanced tumors.

The presence of two or more histologically different malignancies in the same individual is known as MPMN. In 1932, Warren (90) proposed diagnostic criteria for MPMN, namely that each tumor must occur in a different site or organ, have its own pathological morphology and be histologically malignant, and that metastasis or recurrence is excluded. According to the literature, the incidence of multiple primary neoplasms in patients with cancer is 2.4-8.0% and can be as high as 17.0% at 20 years of follow-up. The main factors causing their occurrence include the host (genetics, hormones and previous cancer history) and the environment (tobacco and alcohol consumption, geography, pathogens and occupation) (91).

Gul *et al* (92) showed that the incidence of RCC and bladder cancer is higher in men compared with that in women, and that the higher smoking rate in men is partly responsible for the difference in incidence between men and women; however, hormones, genetics and differences in gene mutation patterns between men and women also play a role. Based on the SEER database, Wu *et al* (8) studied the clinical and pathological characteristics of 704 patients with RCC and UC, 566 of whom had bUC, with a male-to-female ratio of 4.66:1. The results showed that the risk of co-occurrence of RCC and UC increased in older (>65 years old), male and Caucasian populations. The results of the present review showed that the median age at onset of ccRCC- and bUC-related multiple primary cancers was 56.5 years, the incidence rate in males was six times (30:5) higher than that in females, the incidence rate in smoker was 2.67 times (16:6) higher than that in non-smokers and only 1 female patient was diagnosed with this disease among all smokers. Therefore, we hypothesized that male sex and smoking may be risk factors for the co-occurrence of ccRCC and bUC. This is consistent with previously published results (92). However, only 11.1% of the patients with cancer had a family history of cancer. Therefore, whether a family history of cancer is a risk factor remains to be verified. The patient in the present report was male with a history of smoking and was diagnosed with two types of cancer, which is consistent with previous reports (32,37-39). The patient had no family history of cancer; therefore, whether the patient had a genetic mutation needs to be considered. However, the patient and their family refused genetic testing.

The clinical manifestations of ccRCC- and bUC-related multiple malignancies are similar to those of single ccRCC and bUC. Most patients present with hematuria, which may be accompanied by lower urinary tract irritation or lower back pain. The main clinical manifestation of the current case was hematuria, accompanied by urinary tract irritation symptoms, and no lower back pain.

Wu *et al* (8) showed that the proportions of pathological stage I/II for RCC and UC were 81.1 and 93.3%, respectively. Most patients with RCC underwent a total or partial nephrectomy, whereas 87.1% of patients with bUC underwent a partial resection and only 1.4% underwent a local tumor resection. In the present review, 80.5% of patients with ccRCC and 77.7% of patients with bUC were in stages T1 and T2; therefore, the current results show that the proportion of renal cancer

in the T1/2 stage was consistent with the results reported by Wu *et al* (8), while the proportion of bladder cancer in the T1/2 stage was different. However, this result may have a certain publication bias, as most patients in the early stage can undergo surgery to obtain clear pathological data, whereas most patients in the late stage do not have the opportunity for surgery (since patients with advanced cancer often have metastasis to distant or surrounding tissues, which usually indicates a poor prognosis) and cannot obtain clear pathological data; therefore, patients in the late stage may be omitted from publications. In the present review, 27.8% of patients underwent nephrectomy, 27.8% underwent partial nephrectomy, 27.8% underwent nephrectomy and/or ureterectomy and/or cystectomy, and only 1 patient underwent renal biopsy for RCC, there was no difference in the proportion of surgical approach for RCC, but for bUC, 63.9% of patients underwent TURBT, 16.7% underwent radical cystectomy and 13.9% underwent radical cystectomy after TURBT. The SEER database only includes cancer data from the United States. The data collected in the present review were from studies performed in China, the United States, Japan, France and other countries, which were mainly case reports or small studies. Differences in the economic, regional and medical levels may explain the differences in the surgical methods used. The patient in the present report underwent partial nephrectomy and radical cystectomy in stages. Initially, the patient was recommended to undergo a whole-body SPECT examination to evaluate their systemic condition. If there was no metastasis to other organs or lymph nodes, a partial nephrectomy and a radical cystectomy would be performed at the same time. However, partial nephrectomy combined with radical cystectomy is more difficult. Because it involves multiple organs of the human body (kidneys, ureters, bladder and prostate) at the same time, it requires superb surgical skills. The surgery time involving multiple organs at the same time is longer than the surgery time for a single organ, and it is also a great challenge for the postoperative recovery of the patient.

Qi *et al* (9) followed up 27 patients with combined RCC and UC, 17 of whom had both renal cancer and bladder tumors. The study showed no difference in survival between patients who underwent partial nephrectomy and total nephrectomy (9). However, detailed information on the patients of the study by Qi *et al* (9) could not be obtained; therefore, these patients were not included in the present review. Wu *et al* (8) demonstrated that the co-occurrence of bladder cancer and RCC was not a risk factor for survival outcomes in RCC. Previous studies have suggested that individuals with papillary RCC have an increased risk of subsequently developing bladder (93,94) or prostate (94) cancer, while another study did not confirm this association (95). The present review demonstrated that the survival rate of ccRCC- and bUC-related multiple primary tumors was not associated with the tumor onset time interval (P=0.533) or the pathological stage of ccRCC (P=0.455), but may be related to the pathological stage of bUC (P=0.021), which is inconsistent with the conclusion by Wu *et al* (8). The present literature review results showed that the median survival time for ccRCC- and bUC-related multiple primary tumors was 47.5 months, with a median survival of 20 months for SMPMN and 48 months for MMPMN. The follow-up of the present case lasted only 19 months from onset to death, which is consistent with the median survival time of 20 months drawn from the literature review. Due to the low incidence of the disease, more studies are needed in the future to clarify whether the occurrence of bladder cancer or RCC affects the prognosis of patients with ccRCC- and bUC-related multiple primary tumors.

Some cases of multiple primary malignancies associated with gene deletions or mutations are called gene-related syndromes, such as Lynch syndrome. Lynch syndrome, also known as hereditary non-polyposis colorectal cancer, is an autosomal dominant disorder caused by germline mutations in one of the four mismatch repair genes or the EpCAM gene. The clinical manifestations of the syndrome include UTUC (2-20%), colorectal cancer (30-73%), endometrial cancer (30-51%) and other extraintestinal tumors (96). According to Lynch syndrome diagnosis and treatment guidelines, renal and bladder cancers do not belong to Lynch syndrome (97). Results of a systematic review and meta-analysis showed that Lynch syndrome was associated with a significantly increased relative risk of renal and bladder cancer, although the quality of the evidence was assessed as 'low' (98). Among the reports included in the present literature review, six involved UTUC or rectal adenocarcinoma in addition to bUC and ccRCC (53-57,65). Therefore, it is important to perform genetic testing in patients with both bUC- and ccRCC-related primary multiple cancers to determine whether they have Lynch syndrome. Although the patient in the present report rejected genetic testing, it is believed that genetic testing is important for further studying this disease.

Currently, there are no uniform clinical guidelines or pieces of prospective experimental evidence for the treatment of patients with multiple primary neoplasms, and most cases are managed based on previous case reports (91). The treatment of ccRCC- and bUC-related multiple primary malignant tumors requires the formulation of a surgical plan that maximizes the patient's own interests based on the actual condition of the patient and the determination of further diagnostic and treatment measures, such as radiotherapy, chemotherapy, targeted therapy or combined therapy, according to changes in the patient's condition.

The present study has certain limitations. First, due to insufficient information from the included literature, it was not possible to analyze whether alcohol consumption, hypertension, diabetes and aristolochic acid exposure history were risk factors for the comorbidity of ccRCC and bUC. Second, certain patients included in the literature review had other cancers besides ccRCC and bUC, such as prostate cancer, UTUC, esophageal cancer and rectal cancer, which may be factors leading to the occurrence of other primary cancers. Third, the present study focused on ccRCC and bUC, and did not include UTUC. According to the study by Wu *et al* (99), the most common secondary tumors of UTUC in Taiwan are RCC and hepatocellular carcinoma. Patients with UTUC and a history of cancer have a higher risk of developing other primary malignancies (99). Fourth, due to the low incidence of the co-occurrence of bUC and ccRCC, only 36 patients were included for analysis. In the future, a multicenter joint study on this type of patients with multiple primary cancers needs to be conducted to gain a deeper understanding of the disease. Fifth, dual and

multiple cancers may be related to gene mutations. Although none of the included cases underwent genetic testing, the importance of genetic testing in identifying multiple cancers cannot be excluded. Last, coexistence of RCC and bUC may be related to Lynch syndrome, but genetic testing has not been performed to verify this, and more cases are needed in the future to supplement the present study.

In summary, ccRCC and bUC comorbidity is a rare phenomenon, and there are no clear epidemiological, therapeutic and prognostic characteristics. Previous studies have reported the comorbidity of ccRCC and bUC; however, these studies were limited by the lack of detailed case data or small sample sizes. The present study comprehensively summarized the typical characteristics of ccRCC- and bUC-related multiple primary malignancies. In conclusion, the risk factors for ccRCC- and bUC-related multiple primary malignancies are male sex and smoking, and whether a family history of tumors is a risk factor remains to be confirmed. The median age at the onset of ccRCC- and bUC-related multiple primary malignancies was 56 years, and the median survival was 47.5 months (SMPMN, 20 months; MMPMN, 48 months). The cumulative survival rate is not related to the interval between tumor onset and the pathological stage of ccRCC, but may be related to the pathological stage of bUC. In the present case, the patient had both ccRCC and bUC, namely SMPMN. After surgery, the patient recovered well but eventually developed cervical lymph node metastasis with a UC origin, suggesting that the pathological stage of bladder cancer is crucial for prognosis. The overall survival rate from disease onset to death was 19 months.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

SW, YZ and KW conceived and designed the present study, and collected the data for the case report. SW, XW and XY analyzed and interpreted the data. MY obtained pathological data. SW wrote the manuscript, and all authors discussed the results and commented on the manuscript. CW made substantial contributions to the conception and design of the study. SW and CW confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Huanghe Sanmenxia Hospital Affiliated to Henan University of Science and Technology (Sanmenxia, China; approval no. 202402190018). The patient's wife provided initial written informed consent to participate in the treatment.

Patient consent for publication

Written informed consent for publication of the clinical details and images was obtained from the patient's wife.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Patard JJ, Leray E, Rioux-Leclercq N, Cindolo L, Ficarra V, Zisman A, De La Taille A, Tostain J, Artibani W, Abbou CC, *et al*: Prognostic value of histologic subtypes in renal cell carcinoma: A multicenter experience. J Clin Oncol 23: 2763-2771, 2005.
3. Motzer RJ, Jonasch E, Agarwal N, Alva A, Bagshaw H, Baine M, Beckermann K, Carlo MI, Choueiri TK, Costello BA, *et al*: NCCN guidelines® insights: Kidney cancer, version 2.2024. J Natl Compr Canc Netw 22: 4-16, 2024.
4. Mohanty SK, Lobo A and Cheng L: The 2022 revision of the World Health Organization classification of tumors of the urinary system and male genital organs: Advances and challenges. Hum Pathol 136: 123-143, 2023.
5. Jones RJ, Crabb SJ, Linch M, Birtle AJ, Mcgrane J, Enting D, Stevenson R, Liu K, Kularatne B and Hussain SA: Systemic anticancer therapy for urothelial carcinoma: UK oncologists' perspective. Br J Cancer 130: 897-907, 2024.
6. Lopez-Beltran A, Cookson MS, Guercio BJ and Cheng L: Advances in diagnosis and treatment of bladder cancer. BMJ 384: e076743, 2024.
7. Rouprêt M, Seisen T, Birtle AJ, Capoun O, Compérat EM, Dominguez-Escrig JL, Andersson IG, Liedberg F, Mariappan P, Mostafid AH, *et al*: European association of urology guidelines on upper urinary tract urothelial carcinoma: 2023 Update. Eur Urol 84: 49-64, 2023.
8. Wu K, Liu X, Wang Y, Wang X and Li X: Clinicopathological characteristics and outcomes of synchronous renal cell carcinoma and urothelial carcinoma: A population-based analysis. Front Public Health 10: 994351, 2022.
9. Qi N, Chen Y, Gong K and Li H: Concurrent renal cell carcinoma and urothelial carcinoma: Long-term follow-up study of 27 cases. World J Surg Oncol 16: 16, 2018.
10. Council L and Hameed O: Differential expression of immunohistochemical markers in bladder smooth muscle and myofibroblasts, and the potential utility of desmin, smoothelin, and vimentin in staging of bladder carcinoma. Mod Pathol 22: 639-650, 2009.
11. Olivier M, Hollstein M and Hainaut P: TP53 mutations in human cancers: Origins, consequences, and clinical use. Cold Spring Harb Perspect Biol 2: a001008, 2010.
12. Borowczak J, Szczerbowski K, Maniewski M, Zdrenka M, Słupski P, Andrusewicz H, Bysik-Miśkurka J, Rutkiewicz P, Bodnar M and Szylberg A: The prognostic role of p53 and its correlation with CDK9 in urothelial carcinoma. Clin Transl Oncol 25: 830-840, 2023.
13. Vlachou E, Johnson BR, Baraban E, Nadal R and Hoffman-Censits J: Current advances in the management of nonurothelial subtypes of bladder cancer. Am Soc Clin Oncol Educ Book 44: e438640, 2024.
14. Naik M, Rao BV, Challa S, Fonseca D, Sudha SM, Giridhar A, Sharma R, Raju KVVN and Rao TS: Utility of GATA-3 and associated immunohistochemical markers in the differential diagnosis of poorly differentiated urothelial carcinoma. J Cancer Res Ther 19 (Suppl): S0, 2023.
15. Zhou J, Yang X, Zhou L, Zhang P and Wang C: Combined immunohistochemistry for the 'three 7' markers (CK7, CD117, and claudin-7) is useful in the diagnosis of chromophobe renal cell carcinoma and for the exclusion of mimics: Diagnostic experience from a single institution. Dis Markers 2019: 4708154, 2019.

16. Barr ML, Jilaveanu LB, Camp RL, Adeniran AJ, Kluger HM and Shuch B: PAX-8 expression in renal tumours and distant sites: A useful marker of primary and metastatic renal cell carcinoma? J Clin Pathol 68: 12-17, 2014.
17. Gorbokon N, Baltruschat S, Lennartz M, Luebke AM, Höflmayer D, Kluth M, Hube-Magg C, Hinsch A, Fraune C, Lebok P, *et al*: PAX8 expression in cancerous and non-neoplastic tissue: A tissue microarray study on more than 17,000 tumors from 149 different tumor entities. Virchows Arch 485: 491-507, 2024.
18. Leroy X, Copin MC, Devisme L, Buisine MP, Aubert JP, Gosselin B and Porchet N: Expression of human mucin genes in normal kidney and renal cell carcinoma. Histopathology 40: 450-457, 2002.
19. Yan WX, Cao WR, Zhao J, Zhang W, Wang XL, Yuan Q and Dang SQ: Clear cell papillary renal cell carcinoma: A clinicopathologic analysis of 6 cases. Int J Clin Exp Pathol 8: 4595-4599, 2015.
20. Amin MB, Edge SB, Greene FL and Brierley JD: AJCC cancer staging manual. 8th edition. New York, Springer, 2017.
21. Pandey J and Syed W: Renal cancer. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2024.
22. Kaseb H, Leslie SW, Soon-Sutton TL and Aeddula NR: Bladder cancer. In: StatPearls. Treasure Island: StatPearls Publishing, 2023.
23. Kim HL, Seligson D, Liu X, Janzen N, Bui MHT, Yu H, Shi T, Belldegrun AS, Horvath S and Figlin RA: Using tumor markers to predict the survival of patients with metastatic renal cell carcinoma. J Urol 173: 1496-1501, 2005.
24. Gailey MP and Bellizzi AM: Immunohistochemistry for the novel markers glypican 3, PAX8, and p40 (ΔNp63) in squamous cell and urothelial carcinoma. Am J Clin Pathol 140: 872-880, 2013.
25. Queipo FJ, Unamunzaga GM, Negro BF, Fuertes SG, Cortés MÁ, Tejedor EC, Mañas CMB, Ariño AB, Sjödahl G and Beorlegui C: Immunohistochemistry subtyping of urothelial carcinoma is feasible in the daily practice. Virchows Arch 481: 191-200, 2022.
26. Huang J and Zhang X: Chinese guidelines for diagnosis and treatment of urology and andrology diseases (2022 edition), 2022.
27. Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, Ginsberg MS, Kim ST, Baum CM, DePrimo SE, *et al*: Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 24: 16-24, 2006.
28. Guo J, Ma J, Sun Y, Qin S, Ye D, Zhou F, He Z, Sheng X, Bi F, Cao D, *et al*: Chinese guidelines on the management of renal cell carcinoma (2015 edition). Chin Clin Oncol 5: 12, 2016.
29. Ye D, Liu J, Zhou A, Zou Q, Li H, Fu C, Hu H, Huang J, Zhu S, Jin J, *et al*: Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma. Cancer Sci 112: 305-313, 2021.
30. Liu Y, Liu Q, Huang L, Ren X, Huang J and Feng YF: A programmed death receptor-1 inhibitor-Tislelizumab. Clin Med J 20: 37-42, 2022 (In Chinese).
31. Hong Y, Feng Y, Sun H, Zhang B, Wu H, Zhu Q, Li Y, Zhang T, Zhang Y, Cui X, *et al*: Tislelizumab uniquely binds to the CC' loop of PD-1 with slow-dissociated rate and complete PD-L1 blockage. FEBS Open Bio 11: 782-792, 2021.
32. Yokoyama I, Berman E, Rickert RR and Bastidas J: Simultaneous occurrence of renal cell adenocarcinoma and urothelial carcinoma of the renal pelvis in the same kidney diagnosed by preoperative angiography. Cancer 48: 2762-2766, 1981.
33. Oka H, Kobayashi S, Kobayashi T, Shugino Y, Matsui Y, Fujikawa K, Iwamura H, Hukuzawa S, Soeda A and Takeuchi H: Multiple primary cancers limited to the urological field. Hinyokika Kiyo 47: 405-409, 2001 (In Japanese).
34. Srinath N, Dinesh US and Sharma GP: A case of synchronous renal cell carcinoma (Rt) and transitional cell carcinoma urinary bladder. Med J Armed Forces India 62: 190-191, 2011.
35. Zhang H, Ye D, Yao X, Zhang S, Dai B, Shen Y, Zhu Y, Zhu Y, Shi G, *et al*: Clinical analysis of multiple primary malignant tumors and concurrent renal cell carcinoma. J Army Med Univ 31: 1261-1263, 2009 (In Chinese).
36. Rotellini M, Fondi C, Paglierani M, Stomaci N and Raspollini MR: Clear cell carcinoma of the bladder in a patient with a earlier clear cell renal cell carcinoma: A case report with morphologic, immunohistochemical, and cytogenetical analysis. Appl Immunohistochem Mol Morphol 18: 396-399, 2010.
37. Smith MT, Taylor FD, Gianakopoulus WP and Brown RR: Two separate synchronous primary genitourinary tumors. Rev Urol 14: 104-107, 2012.
38. Zhu Q, Gu J, Zhang Y, Shi J, Sun F, Shen J, Yang Y and Wang N: Clinical analysis of 21 cases of multiple primary cancers associated with bladder cancer in elderly patients. Chin J Clin Oncol 39: 993-996, 2012 (In Chinese).
39. Djafari AA, Moradi A, Rahnama H and Rahavian A: The first case report of synchronous primary papillary type 2 renal cell carcinoma of kidney and transitional cell carcinoma of bladder. Urol Case Rep 37: 101601, 2021.
40. Dieckmann KP and Nekarda H: Triple malignancy of the genitourinary tract. Int Urol Nephrol 20: 485-488, 1988.
41. Harima M, Narita K, Kobayakawa H, Tsujino T, Yamamoto S, Fukushima S and Kishimoto T: A case of synchronous triple primary cancers of prostate, kidney and bladder. Hinyokika Kiyo 44: 675-678, 1998 (In Japanese).
42. Takada T, Honda M, Momohara C, Komori K and Fujioka H: Synchronous triple urogenital cancer (renal cancer, bladder cancer, prostatic cancer): A case report. Hinyokika Kiyo 48: 239-242, 2002 (In Japanese).
43. Satoh H, Momma T, Saito S and Hirose S: A case of synchronous triple primary carcinomas of the kidney, bladder and prostate. Hinyokika Kiyo 49: 261-264, 2003 (In Japanese).
44. Arikan-Sengul C, Pehlivan Y, Sevinc A, Karakok M, Kalender ME and Camci C: A case of metachronous triple primary urogenital cancer: Urinary bladder, prostate, and renal cancer. Onkologie 32: 122-124, 2009.
45. Nishikawa K, Soga N, Kato M, Masui S, Hasegawa Y, Yamada Y, Kise H, Arima K and Sugimura Y: Case of bladder cancer following adjuvant external beam radiation for prostate cancer. Hinyokika Kiyo 55: 39-41, 2009 (In Japanese).
46. Pérez MPM, Bazán AA, Dorrego JMA, Herrero, Ledo JC and de la Peña Barthel J: Simultaneous cystectomy and nephroureterectomy due to synchronous upper urinary tract tumors and invasive bladder cancer: Open and laparoscopic approaches. Curr Urol 6: 76-81, 2012.
47. Tiwari P, Tripathi A, Bansal P, Vijay M, Gupta A and Kundu AK: Synchronous primary cancers of urinary bladder and kidney and prostate. Saudi J Kidney Dis Transpl 23: 786-789, 2012.
48. Okumura A, Tsuritani S, Takagawa K and Fuse H: Case of heterochronous triple urogenital cancer (renal cell carcinoma, bladder cancer, prostatic cancer). Nihon Hinyokika Gakkai Zasshi 104: 702-705, 2013 (In Japanese).
49. Kurose H, Ueda K, Nakiri M, Matsuo M, Suekane S and Igawa T: Synchronous primary triple urogenital malignant tumors of kidney, prostate and bladder. Urol Case Rep 33: 101277, 2020.
50. Zhang G, Liao H, Liu L, Tang D and Zhang F: A case report of synchronous triple cancers in the urinary and male reproductive system. Chin J Urol 44: 861-862, 2023 (In Chinese).
51. Kinbara H, Suzuki S, Nakano S, Yamakawa K, Hioki T, Okabe S, Sugimura Y, Tajima K, Tochigi H and Kawamura J: A case of renal cell carcinoma and bladder carcinoma associated with von Hippel-Lindau disease. Hinyokika Kiyo 36: 823-826, 1990 (In Japanese).
52. Nakano S, Suzuki S, Kinbara H, Maeda Y, Yanagawa M, Tajima K, Tochigi H, Kawamura J, Hounoki S and Yamamoto I: A case of double cancer: Renal cell carcinoma and transitional cell carcinoma of urinary bladder. Hinyokika Kiyo 36: 831-835, 1990 (In Japanese).
53. Soda T, Nishimura K, Kobayashi Y, Kato T, Tokugawa S, Kishikawa H, Ihara H and Ichikawa Y: A case of synchronous contralateral renal cell carcinoma and urothelial carcinoma. Hinyokika Kiyo 55: 491-494, 2009 (In Japanese).
54. Ando M, Arisawa C and Okano T: A case of renal cell carcinoma associated with synchronous contralateral renal pelvic cancer and bladder tumor. Int J Urol 3: 310-312, 1996.
55. Lian Y, Wang D, Chen Q, Zhang Y, Shangguan Z, Jiang M, Hu K and Hao W: A clinical analysis for 9 cases of multiple primary malignant neoplasms associated with renal cell carcinoma. Oncol Prog 18: 815-818, 2020 (In Chinese).
56. Tsujimura A, Takahara S and Koide T: A case of synchronous ipsilateral renal cell carcinoma and transitional cell carcinoma. Hinyokika Kiyo 37: 1303-1306, 1991 (In Japanese).
57. Chuang HC, Chuang CK and Ng KF: Simultaneous development of renal cell carcinoma and multifocal urothelial carcinoma. Chang Gung Med J 31: 515-519, 2008.
58. Morikawa Y, Shiomi K, Ishihara Y and Matsuura N: Triple primary cancers involving kidney, urinary bladder, and liver in a dye worker. Am J Ind Med 31: 44-49, 1997.

59. Kamota S, Harabayashi T, Suzuki S, Takeyama Y, Mitsui T, Mouri G, Hashimoto A, Nakamura M, Shinohara N, Nonomura K and Koyanagi T: Ureteral and bladder metastases of renal cell carcinoma following synchronous renal cell carcinoma and bladder cancer; a case report. Nihon Hinyokika Gakkai Zasshi 94: 705-708, 2003 (In Japanese).
60. Gönül II, Cakr A, Sözen S, Ataoglu O and Alkibay T: A case of tubulocystic carcinoma simultaneously occurring with clear cell type renal cell carcinoma and micropapillary urothelial carcinoma of bladder. South Med J 102: 754-757, 2009.
61. Wang Y, Yu Z, He H, Wang X, Ge H and Xie X: Cancerization of ureteral inverted papilloma complicated with ipsilateral renal cell cancer and bladder transitional cell carcinoma: One case report. J Chin Oncol 22: 691-692, 2016 (In Chinese).
62. Xu G, Bu S and Wang X: A case report of four primary malignant tumors. Cancer Res Prev Treat 46: 1141-1142, 2019 (In Chinese).
63. Akan S and Ediz C: A rare association in a patient with non-muscle invasive bladder cancer: Ureteral fibroepithelial polyp and ipsilateral renal cell carcinoma: A case report. J Med Case Rep 15: 475, 2021.
64. Mitchell K, El Naili R, Pillai L, Lopez EM, Riordan J, Marsh W, Luchey A and Hajiran A: Triple threat: Three primary malignancies simultaneously involving three genitourinary organs. Case Rep Urol 2023: 3242986, 2023.
65. Huang J, Deng S, Li Q, Li J, Li W, Zhang X and Xue S: Multiple primary malignancies of the bladder, rectum and kidney: A case report. Chin J Urol 44: 383-384, 2023 (In Chinese).
66. Lobo N, Afferi L, Moschini M, Mostafid H, Porten S, Psutka SP, Gupta S, Smith AB, Williams SB and Lotan Y: Epidemiology, screening, and prevention of bladder cancer. Eur Urol Oncol 5: 628-639, 2022.
67. Dyrskjøt L, Hansel DE, Efstathiou JA, Knowles MA, Galsky MD, Teoh J and Theodorescu D: Bladder cancer. Nat Rev Dis Primers 9: 58, 2023.
68. Aminoltejari K and Black PC: Radical cystectomy: A review of techniques, developments and controversies. Transl Androl Urol 9: 3073-3081, 2020.
69. Khan MS, Gan C, Ahmed K, Ismail AF, Watkins J, Summers JA, Peacock JL, Rimington P and Dasgupta P: A single-centre early phase randomised controlled three-arm trial of open, robotic, and laparoscopic radical cystectomy (CORAL). Eur Urol 69: 613-621, 2016.
70. Dindo D, Demartines N and Clavien PA: Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240: 205-213, 2004.
71. Griffiths G, Hall R, Sylvester R, Raghavan D and Parmar MK: International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 29: 2171-2177, 2011.
72. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration: Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 48: 202-206, 2005.
73. van der Heijden MS, Sonpavde G, Powles T, Necchi A, Burotto M, Schenker M, Sade JP, Bamias A, Beuzeboc P, Bedke J, *et al*: Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. N Engl J Med 389: 1778-1789, 2023.
74. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, *et al*: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 41: 3881-3890, 2023.
75. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, Kalofonos H, Radulović S, Demey W, Ullén A, *et al*: Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 383: 1218-1230, 2020.
76. Massari F, Santoni M, Takeshita H, Okada Y, Tapia JC, Basso U, Maruzzo M, Scagliarini S, Büttner T, Fornarini G, *et al*: Global real-world experiences with pembrolizumab in advanced urothelial carcinoma after platinum-based chemotherapy: The ARON-2 study. Cancer Immunol Immunother 73: 106, 2024.
77. Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, Lotan Y, Meeks JJ, Michalski JM, Morgan TM, *et al*: Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. J Urol 198: 552-559, 2017.
78. Powles T, Bellmunt J, Comperat E, De Santis M, Huddart R, Loriot Y, Necchi A, Valderrama BP, Ravaud A, Shariat SF, *et al*: ESMO clinical practice guideline interim update on first-line therapy in advanced urothelial carcinoma. Ann Oncol 35: 485-490, 2024.
79. Benjamin DJ, Rezazadeh KA and Prasad V: The overall survival benefit in EV-302: Is enfortumab vedotin plus pembrolizumab the new frontline standard of care for metastatic urothelial carcinoma? Eur Urol Oncol 7: 313-315, 2024.
80. Cirillo L, Innocenti S and Becherucci F: Global epidemiology of kidney cancer. Nephrol Dial Transplant 39: 920-928, 2024.
81. Deng J, Tu S, Li L, Li G and Zhang Y: Diagnostic, predictive and prognostic molecular biomarkers in clear cell renal cell carcinoma: A retrospective study. Cancer Rep (Hoboken) 7: e2116, 2024.
82. Safiri S, Hassanzadeh K, Jolfayi AG, Mousavi SE, Asghari KM, Nejadghaderi SA, Naghdi-Sedeh N, Noori M, Sullman MJM, Collins GS and Kolahi AA: Kidney cancer in the Middle East and North Africa region: A 30-year analysis (1990-2019). Sci Rep 14: 13710, 2024.
83. Hunt JD, van der Hel OL, Mcmillan GP, Boffetta P and Brennan P: Renal cell carcinoma in relation to cigarette smoking: Meta-analysis of 24 studies. Int J Cancer 114: 101-108, 2005.
84. Chow WH, Dong LM and Devesa SS: Epidemiology and risk factors for kidney cancer. Nat Rev Urol 7: 245-257, 2010.
85. Roskoski R Jr: Combination immune checkpoint and targeted protein kinase inhibitors for the treatment of renal cell carcinomas. Pharmacol Res 203: 107181, 2024.
86. Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, Heng DY, Larkin J and Ficarra V: Renal cell carcinoma. Nat Rev Dis Primers 3: 17009, 2017.
87. Goswamy R, Kalemoglu E, Master V and Bilen MA: Perioperative systemic treatments in renal cell carcinoma. Front Oncol 14: 1362172, 2024.
88. Gao B, Gorgen ARH, Bhatt R, Tano ZE, Morgan KL, Vo K, Zarandi SS, Ali SN, Jiang P, Patel RM, *et al*: Avoiding 'Needless' nephrectomy: What is the role of small renal mass biopsy in 2024? Urol Oncol 42: 236-244, 2024.
89. Johnson DC, Vukina J, Smith AB, Meyer AM, Wheeler SB, Kuo TM, Tan HJ, Woods ME, Raynor MC, Wallen EM, *et al*: Preoperatively misclassified, surgically removed benign renal masses: A systematic review of surgical series and United States population level burden estimate. J Urol 193: 30-35, 2015.
90. Warren S: Multiple primary malignant tumors, a survey of the literature and a statistical study. Am J Cancer 16: 1358-1414, 1932
91. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T and Omlin A: Multiple primary tumours: Challenges and approaches, a review. ESMO Open 2: e000172, 2017.
92. Gul ZG, Liaw CW and Mehrazin R: Gender differences in incidence, diagnosis, treatments, and outcomes in clinically localized bladder and renal cancer. Urology 151: 176-181, 2021.
93. Czene K and Hemminki K: Familial papillary renal cell tumors and subsequent cancers: A nationwide epidemiological study from Sweden. J Urol 169: 1271-1275, 2003.
94. Rabbani F, Reuter VE, Katz J and Russo P: Second primary malignancies associated with renal cell carcinoma: Influence of histologic type. Urology 56: 399-403, 2000.
95. Antonelli A, Calza S, Arrighi N, Zani D, Corti S, Cozzoli A, Zanotelli T, Cunico SC and Simeone C: Clinical features and prognosis of patients with renal cancer and a second malignancy. Urol Oncol 30: 294-300, 2012.
96. Lonati C, Simeone C, Suardi N, Spiess PE, Necchi A and Moschini M: Genitourinary manifestations of Lynch syndrome in the urological practice. Asian J Urol 9: 443-450, 2022.
97. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, *et al*: Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 96: 261-268, 2004.
98. Nassour AJ, Jain A, Hui N, Siopis G, Symons J and Woo H: Relative risk of bladder and kidney cancer in lynch syndrome: Systematic review and meta-analysis. Cancers (Basel) 15: 506, 2023.
99. Wu KY, Cheong IS, Lai JN, Hu CY, Hung KC, Chen YT, Chiu LT, Tsai HT, Jou YC, Tzai TS and Tsai YS: Risk of secondary primary malignancies in survivors of upper tract urothelial carcinoma: A nationwide population-based analysis. Cancer Epidemiol 89: 102536, 2024.