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Metastatic Renal cell Carcinoma (Clear Cell Carcinoma) to the Urinary Bladder

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Abstract

Metastatic renal cell carcinomas to the urinary bladder (MRCCTUB) are rarely encountered. Literature review on MRCCTUB was done by using various internet data bases to identify literature on MRCCTUB using the following search words: renal cell carcinoma metastatic to bladder; clear cell carcinoma metastatic to bladder. The review revealed that less than 100 cases of MRCCTUB have been reported in the English literature. MRCCTUBs may be synchronous or metachronous. MRCCTUBs may present with haematuria or lower urinary tract symptoms. Radiological imaging reveals a bladder mass. Cystoscopy reveals a non-papillary, solid, polypoid, pedunculated mass which may be yellowish. Metastatic renal cell carcinoma of the urinary bladder exhibits the following features: Delicate fibro-vascular stroma with abundant sinusoidal vessels, polygonal cells with abundant clear cytoplasm and nuclei. They may resemble urothelial carcinoma with clear cell features. MRCCTUBs on immunohistochemistry stain: (a) Positively with CAM 5.2, vimentin, Leu-M1 (CD15) (b) negatively with CK7, CK20, 34betaE12, CEA, S100, HMB45, chromogranin. The prognosis of MRCCTUs, have been generally poor and may depend upon whether they are solitary metastases or associated with metastases to other organs. MRCCTUs have on a number of occasions been confined to the bladder mucosa and these have been treated by trans-urethral resection. There is anecdotal information to suggest that intravesical BCG may help prevent local bladder recurrence. Systemic therapies have been used to treat disseminated disease with on the whole poor outcome. There is no consensus of opinion regarding the best treatment option. MRCCTUs are rare and there is no consensus opinion regarding their treatment in relation to other disseminated metastases. There is need for all cases of MRCCTUs to be entered in a multi-centric trial. Urologists and Oncologists should report cases of MRCCTUs they encounter.

Key Words: Metastatic renal cell carcinoma to bladder; metastatic clear cell carcinoma to bladder; metastatic renal clear cell carcinoma to bladder; CAM 5.2, vimentin, Leu-M1 (CD15); metastasectomy.

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Introduction

Metastatic Renal cell carcinoma (Renal clear cell carcinoma / clear cell carcinoma) to the urinary bladder is a rarely encountered tumour which may be found contemporaneously in association with the renal tumour or they may me diagnosed many years after the primary renal tumour had been treated. The diagnosis of this rare carcinoma may be difficult to establish sometimes. In view of the rarity of this carcinoma many clinicians would not have encountered the disease and they would be unfamiliar its biological behavior. The ensuing literature review has been presented in two sections: the first section contains a general overview of various aspects of the carcinoma and the second part contains miscellaneous narrations and discussions from reported cases which have been aimed at illustrating various aspects of the biological behavior of the carcinoma and various approaches to the treatment of a number of cases.

Methods

Various internet data bases were used to identify literature using the following search words:

renal cell carcinoma metastatic to bladder; clear cell carcinoma metastatic to bladder. 64 references were identified in the English literature, which were found useful to base the review on. Some case reports were found in the non-English literature which did not provide much detailed information to the author because of language barrier.

Literature Review

General Overview (A): Metastases to the urinary bladder, are occasionally encountered; some of the usual sites of the primary carcinomas include: the breast and melanoma, lung, pancreas, ovary and stomach. [1] Urinary bladder metastases tend to be associated with disseminated disease and the urothelium is most often spared. [1] Additionally urinary bladder metastases may also arise from local extension of carcinomas of prostate, uterine cervix or rectum [1]. It is difficult to differentiate adenocarcinoma of the urinary bladder morphologically from extension of colonic adenocarcinoma [1].

Incidence: Less than 100 cases of Renal cell carcinoma metastases to the urinary bladder have been reported in the literature.
Ages: Metastatic renal cell carcinomas of the urinary bladder have been reported in patients aged between 35 years and 76 years.
Presentation: Patients with metastatic renal cell carcinoma of urinary bladder present with visible haematuria or urinary obstruction symptoms [1].

In view of the fact that metastases also present in other organs their presentation may depend upon which other organs have been involved by the carcinoma.

Mode of development of metastasis: Metastatic clear cell renal carcinoma of the urinary bladder may be a result of haematogenous spread, retrograde spread from renal vein or renal hilar lymphatics or direct intraluminal transit [1]
Macroscopic features: Cystoscopy usually reveals a non-papillary, polypoid, pedunculated lesion which could be yellowish or pale yellow.
Microscopic description: Metastatic renal cell carcinoma of the urinary bladder exhibits the following features [1]:

- Delicate fibro-vascular stroma with abundant sinusoidal vessels
- Nests of polygonal cells with abundant clear cytoplasm and nuclei ranging from small and hyperchromatic with inconspicuous nucleoli to large irregular nuclei with prominent nucleoli.
- They may resemble urothelial carcinomas with clear cell features

Immunohistochemical staining characteristics [1]
Positive stains
Metastatic clear cell (renal cell) carcinoma of the urinary bladder on immunohistochemical staining stain positively with:

- CAM 5.2,
- vimentin,
- Leu-M1 (CD15)

Negative stains
Metastatic clear cell (renal cell) carcinoma of the urinary bladder on immunohistochemical staining stain negatively with:

- CK7
- CK20
- 34betaE12
- CEA
- S100
- HMB45,
- chromogranin

Radiological Imaging
Computed tomography (CT) scan, Ultrasound scan and Magnetic resonance Imaging (MRI) scan would show a mass in the urinary bladder as well as a synchronous tumour in the kidney but these scans are non-specific and would not diagnose clear cell carcinoma (the diagnosis is based upon the histological and immunohistochemical characteristics of the tumour; see figures 1 to 4, 5, 6 and 7)

Differential diagnoses
Differential diagnoses of metastatic clear cell renal carcinoma of the urinary bladder include:
● Colorectal carcinoma (extension): this tumour is immunohistochemically, positively stained for CK20, villin, beta-catenin (nuclear) [1]
● Prostatic adenocarinoma (extension): this tumour is positively stained for PSA, PSAP, AMACR, Leu7 [1]
● Urothelial carcinoma with glandular differentiation which is positively stained for CK7, CK20, 34betaE12, Uroplakin, Thrombomodulin [1]

Prognosis: The prognosis of metastatic clear cell carcinoma of the urinary bladder is poor. [1] [2]

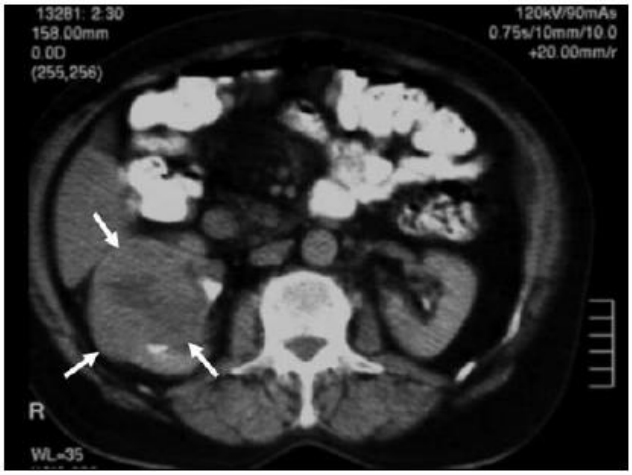

Figure 1: Showing a solid renal mass at the mid-portion of the right kidney (arrows). Reproduced from [24] Tuna A, Tuna B, Seçil M, Sahin A, Yorukoglu K. Solitary Synchronous Metastasis to the Urinary Bladder from Renal Cell Carcinoma. Turkish Journal of Pathology DOI: 10.5146/tjpath.2010.01001 with permission from the Editor in Chief of the Journal on behalf of the Journal.

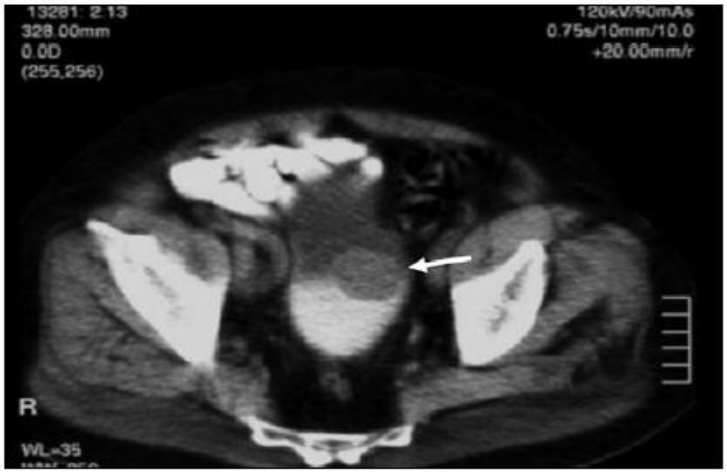

Figure 2: Showing a polypoid mass originating from the left lateral wall of the bladder (arrow) Reproduced from [24] Tuna A, Tuna B, Seçil M, Sahin A, Yorukoglu K. Solitary Synchronous Metastasis to the Urinary Bladder from Renal Cell Carcinoma. Turkish Journal of Pathology DOI: 10.5146/tjpath.2010.01001 with permission from the Editor in Chief of the Journal on behalf of the Journal.

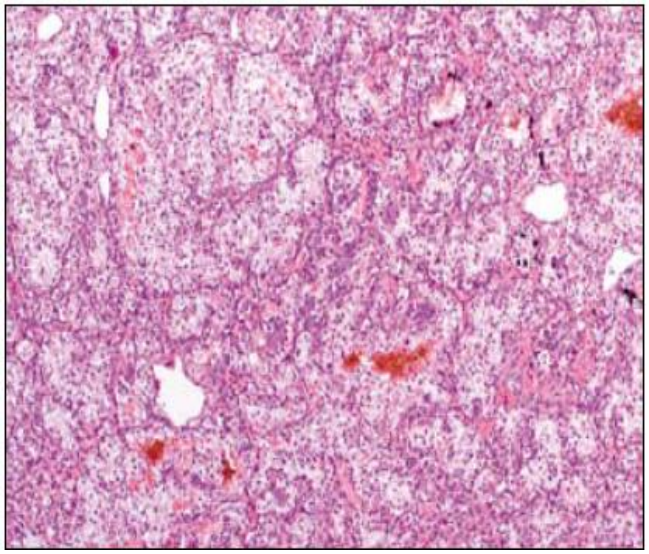

Figure 3: showing renal cell carcinoma (Hematoxylin and eosin stain x 100); Reproduced from [24] Tuna A, Tuna B, Seçil M, Sahin A, Yorukoglu K. Solitary Synchronous Metastasis to the Urinary Bladder from Renal Cell Carcinoma. Turkish Journal of Pathology DOI: 10.5146/tjpath.2010.01001 with permission from the Editor in Chief of the Journal on behalf of the Journal.

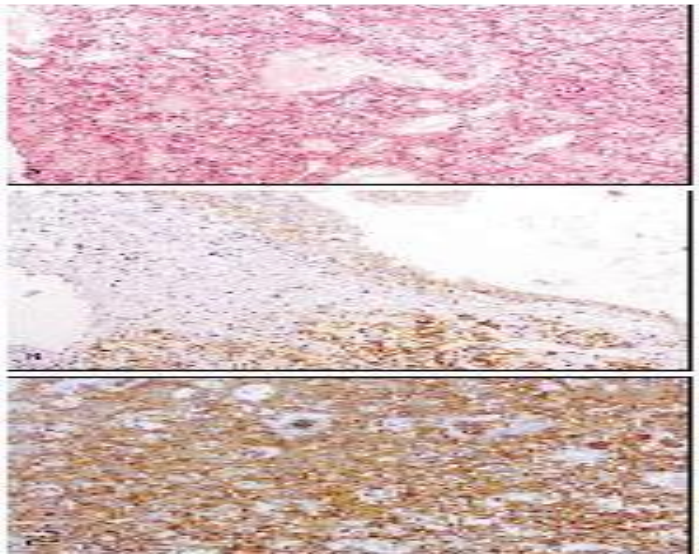

Figure 4: Metastatic renal cell carcinoma in the bladder (A: H&E x 100); B: Keratin immunoreactivity, and C: Vimentin immunoreactivity x 200 Reproduced from [24] Tuna A, Tuna B, Seçil M, Sahin A, Yorukoglu K. Solitary Synchronous Metastasis to the Urinary Bladder from Renal Cell Carcinoma. Turkish Journal of Pathology DOI: 10.5146/tjpath.2010.01001 with permission from the editor in Chief of the Journal on behalf of the Journal.

Miscellaneous narrations and discussions from some of the reported cases of metastatic clear-cell carcinoma of the urinary bladder (B)

Sim et al. [2] reported seven cases of Clear Cell carcinoma of the kidney (RCC) metastatic to the urinary bladder that occurred in 6 men and 1 woman who were aged between 35 to 69 years old. The most common presenting symptom was the reappearance of haematuria, which developed from 2 to 131 months (mean, 41.3 months) after the removal of the primary clear cell carcinoma of the kidney. In all of the patients, the metastatic RCC involved multiple organs; no case had an isolated metastasis to the bladder. The prognosis was poor, and five patients died of disease between 4 and 24 months (mean, 12.8 months) after diagnosis of the metastasis to the urinary bladder. The remaining two patients were lost to follow-up. All of the tumours were conventional clear or "granular" cell RCCs, with nuclear grades of 2 or 3. In five patients, the metastases were confined to the lamina propria, but in two patients, the tumours involved the muscularis propria as well. Sim et al [2] stated that:

- A comparative immunohistochemical study showed that metastatic RCCs were positive for CAM5.2, vimentin, and Leu-M1, and negative for cytokeratin 20, cytokeratin 7, 34betaE12, carcinoembryonic antigen, S-100 protein, HMB45, and chromogranin.
- Classic and clear cell TCCs were positive for all of the cytokeratins, and carcinoembryonic antigen (CEA) and negative for vimentin.
- Paragangliomas were positive for chromogranin and showed scattered positivity for the S-100 protein in the sustentacular cells.
- Metastatic melanomas were positive for S-100 protein and HMB45.
- The histologic appearance of RCC, particularly the delicate fibrovascular stroma with abundant sinusoidal vessels, is a feature that can be used to recognize the tumour. When there is difficulty diagnosing metastatic RCC, TCC, or other tumours in the bladder, the immunohistochemical findings can assist in the differential diagnosis.

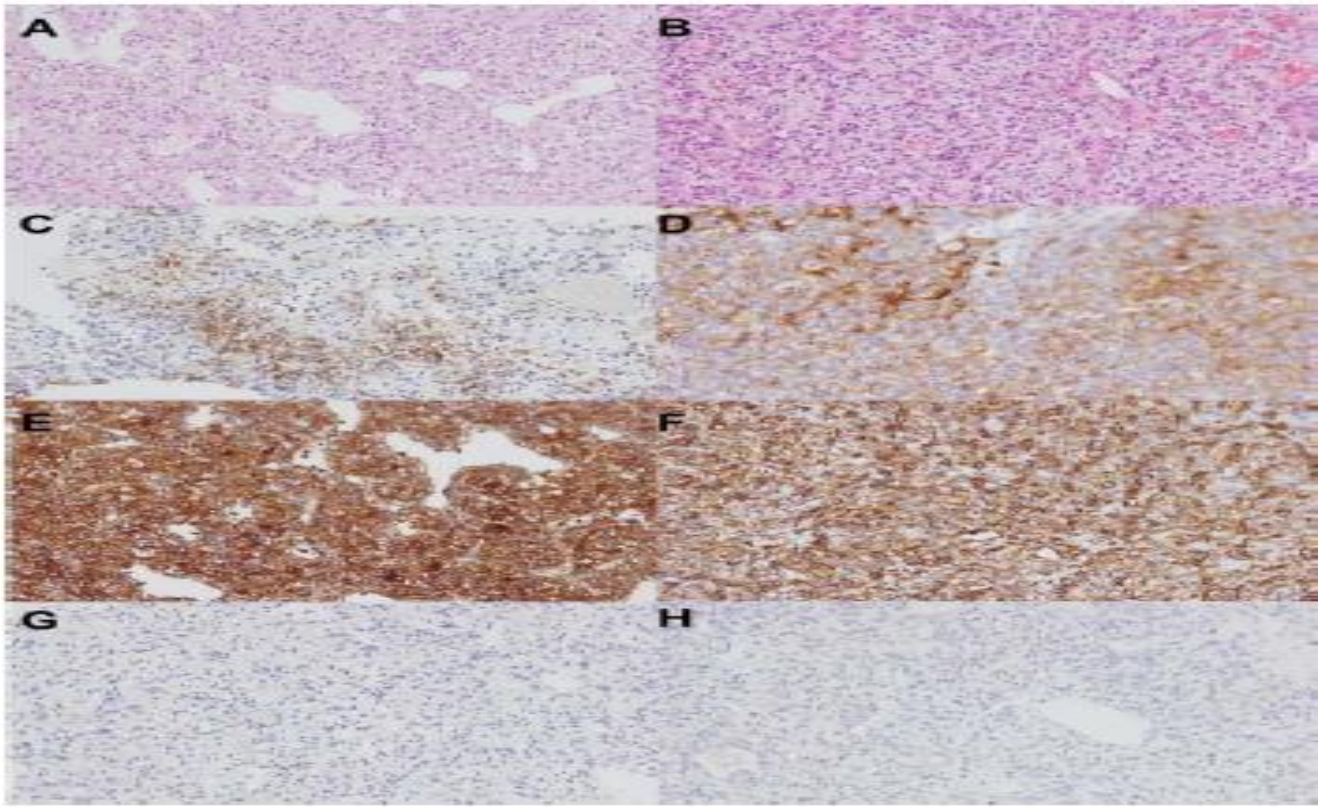

Figure 5 A, B, C, D, E, F, G, H. Microscopic examination of kidney and bladder tumours. (A). Kidney tumour shows clear cell cytoplasm with large, irregular nuclei and prominent nucleoli (magnification x 100 hematoxylin and eosin stain), (B). Bladder tumour shows clear cell cytoplasm with large irregular nuclei and prominent nucleoli (magnification x 100 Hematoxylin and eosin stain). Both of the tissues revealed positive reactivity for CD 10 and vimentin; ((C), and (E): kidney), (D), and (F): bladder). However, they revealed negative reactivity for uroplakin ((G): kidney; (H): bladder). Reproduced from Jang et al, [49] Renal cell carcinoma with synchronous metastases to lung and bladder. Case Reports in Clinical Medicine. 2013; 2(2): 95 – 97 with permission from Case Reports in Clinical Medicine granted under copyright © 2013 as Won Seok Jang et al. This is an open access article distributed under Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

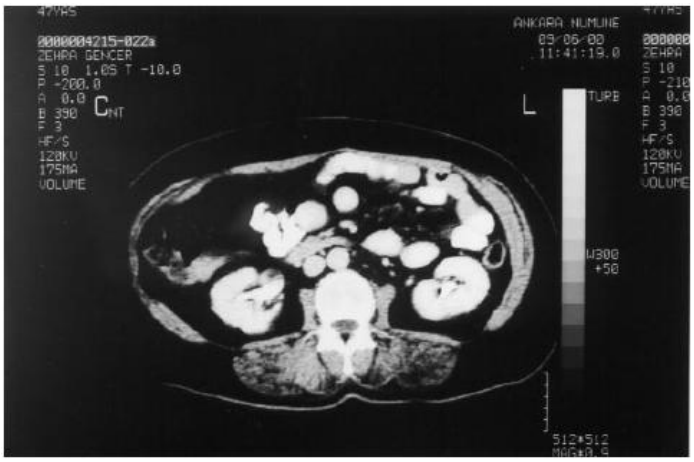

Figure 6: CT-Scan of patient (27 months after nephron sparring surgery for renal cell carcinoma) demonstrates the operated left kidney without any local recurrence. Reproduced from Aki F T, Gökkaya S, Adsan Ö, Erdogan S, Seçkin S A Solitary Metachronous Metastasis after Nephron Sparring Surgery for Renal Cell Carcinoma: A Case Report. Turk J. Med Sci 2002; 32: 425 – 426 with permission from the journal.

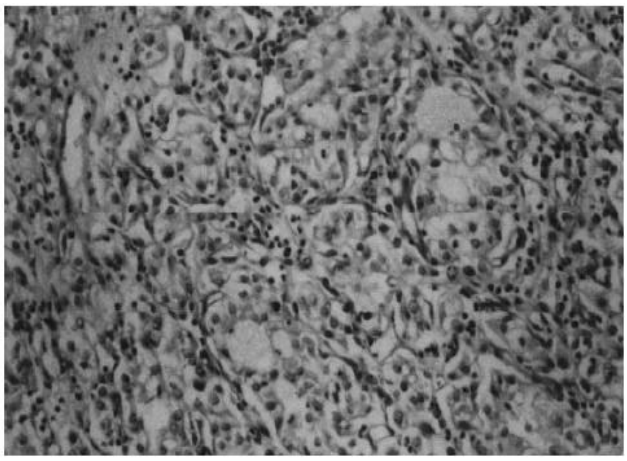

Figure 7: Metastatic renal cell carcinoma of the bladder Reproduced from Aki F T, Gökkaya S, Adsan Ö, Erdogan S, Seçkin S. A Solitary Metachronous Metastasis after Nephron Sparring Surgery for Renal Cell Carcinoma: A Case Report. Turk J. Med Sci 2002; 32: 425 – 426 with permission from the journal.

Kruck et al, [3] reported a 57-year-old man who underwent transurethral resection of the bladder tumour (TURBT) for visible haematuria. The pathological examination revealed a metastatic Renal Cell Carcinoma (RCC) lesion located within the detrusor muscle of the bladder wall, which did not reach into the lamina propria mucosa. He subsequently underwent lumbar retroperitoneal radical nephrectomy with hilar lymphadenectomy for renal tumour and the final pathological classification reported a pT1b, pN0, cM1 RCC, Fuhrman Grading 3. The patient was discharged on the 10th postoperative day. He received primarily planned systemic therapy of mTOR inhibition by temsirolismus. Temsirolismus administration was initiated three weeks post-operatively. The restaging showed a progressive pulmonary and bone metastatic disease without recurrence of the bladder lesion ten weeks after the start of systemic therapy. Due to lack of evidence-based second line treatment after mTOR based therapy failure, the therapy was switched to sunitinib malate 50 mg daily on a 4-weeks-on/2-weeks-off schedule. The patient's general condition deteriorated with ascites, general anasarca and paralytic ileus 6 weeks after the start of sunitinib malate. Systemic treatment was stopped and he received palliative home care until his death two weeks later.

Krishnamoothy et al, [4] reported a 53-year-old lady who presented with total painless visible haematuria and a mass in the region of right kidney. Her urine cytology was negative for malignant cells. She had ultrasound scan and computed tomography (CT) scan of abdomen which showed a solid lesion in the right kidney and this extended to the renal pelvis and upper ureter. There was no evidence of distant metastasis. She underwent right radical nephron-ureterectomy with excision of a cuff of bladder. The histological examination of the tumour showed clear cell variety of renal cell carcinoma, stage pT3, N0, M0. She developed total painless visible haematuria at 6 months after surgery. Her urine cytology was negative for malignant cells. She had CT scan of abdomen which revealed a solid mass of about 3 cm in the right lateral wall of her urinary bladder (Fig. No.2). She underwent transurethral resection of the tumour. The histopathology examination revealed clear cell variety of renal cell carcinoma involving the urinary bladder mucosa. There was no deep muscle infiltration. Post-operatively, she was given alpha interferon + 5-Fluorouracil as adjuvant therapy for three months. She did not have any recurrence after 6 months of further follow up.

Doo et al. [5] reported a 73-year-old woman who complained of visible hematuria. Her urine analysis showed numerous red blood cells. She underwent a cystoscopy that revealed a sessile mass on the right

lateral bladder wall. She had computerized tomography of her abdomen and pelvis which showed an enhancing lesion on the right lateral bladder wall. A heterogenous enhancing mass in the lower pole of the left kidney with left renal vein thrombosis, multiple small enhancing nodules in the pancreas parenchyma, and nodular thickening of both adrenal glands were also found. She also had Chest computed tomography (CT) which showed haematogenous lung metastasis and left mediastinal and hilar lymph node metastasis. Transurethral resection of bladder tumour was undertaken for histological examination.

At the operation, the tumour was resected widely and its base was additionally resected. Pathological examination of the resected specimen revealed that the tumour base was free of tumour and the tumour was a metastatic RCC of the clear cell type. The patient received therapy with Sorafenib 200 mg owing to the multiple metastatic sites. Five weeks after the therapy, she fell down in the bathroom, sustained an intracranial hemorrhage, and died of accompanying hyponatremia and aspiration pneumonia.

Doo et al.[5] stated: "Some authors had stated that"

- Less than 2% of bladder cancers represent metastases from distant primary cancers **[6], [7]**
- Metastatic bladder cancers usually come from gastric adenocarcinoma, melanoma, and adenocarcinoma of the breast and colon. RCC is an uncommon source of bladder metastases, with fewer than 40 such reported cases. Metastatic urinary bladder carcinomas may be synchronous or metachronous [8].
- Frequent metastatic sites of RCC are the regional lymph nodes, lung, liver, bone, adrenal gland, brain, and skin.
- Reported metastatic sites in the genitourinary tract include the ipsilateral ureter, contralateral ureter, ureteric stump, bladder, and prostatic fossa [6], [7].
- Some authors [6] [8] had stated that patients with RCC metastatic to the bladder typically present with gross hematuria. In the majority of cases, there is a well-established history of RCC. However, infrequently, the primary renal tumor may present initially as a bleeding bladder lesion [6], [8].
- The mechanisms of the spread of RCC to the bladder are debatable. Several postulates have been proposed, including haematogenous metastasis through the general circulation, retrograde spread of the tumour from the renal vein or renal hilar lymphatics down the peri-ureteral veins or lymphatics which connect with pelvic organs, and direct intra-luminal transit of tumour cells with seeding of the distal urothelium [6], [7], [8], [9], [10], [11].
- RCC usually metastasizes through the bloodstream, leading to the synchronous discovery of a widespread area of metastasis.
- Treatment options for RCC, especially when metastatic, are limited owing to the poor treatment response to chemotherapy and radiation therapy. Conventional surgical treatment remains controversial regarding the establishment of good criteria for its application and often results in poor treatment effects.
- Prior to the development of target treatment agents, immunotherapy had been widely used. Target therapy is now accepted as the standard therapy for metastatic RCC because of the superior effect of sunitinib and sorafenib, which target vascular endothelial growth factor receptor and platelet-derived growth factor receptor.
- For cases in which RCC is metastatic at the time of diagnosis (synchronous metastases), as in their patient's case, the decision of whether to perform nephrectomy is debatable. In cases of severe symptoms from the primary carcinoma, palliative nephrectomy can be performed, and nephrectomy is performed with an expectation of spontaneous regression or to improve the treatment effect and survival rate by reducing the total volume of primary carcinoma when systemic treatment such as immune therapy or chemotherapy is given. In doing so, careful consideration should be given to the patient's performance status, position and degree of remote metastasis, types and degree of differentiation of carcinoma cells, size of carcinoma, patient's age, and gender.
- For the treatment of metastatic tumours in the bladder, trans-urethral resection, partial cystectomy, and radical cystectomy have been used. Even though genitourinary metastases are generally considered to have a poor prognosis, long-term survival is occasionally reported [11].
- The outcome has been reported to be good when only a single metastasis exists in the bladder, and follow-up without additional systemic treatment is possible after the surgical removal of the metastatic lesion in the bladder [12]. Furthermore, in cases when carcinoma has metastasized to other organs at the time when RCC metastasis is

found in the bladder, additional systemic treatment such as immune therapy is required.

Kamota et al [13] reported a 73-year-old man who presented with visible haematuria. He had ultrasound scan and computerized tomography scan which showed small bladder tumours and a left renal mass which was protruding into the renal pelvis. Trans-urethral resection of bladder tumour, and ureteroscopic tumour biopsy were performed, and pathological- examination of the specimens revealed transitional cell carcinoma in the bladder and renal cell carcinoma in the kidney. He underwent left radical nephrectomy. A 4-month post-operative check cystoscopy revealed a solitary non-papillary tumour in the bladder. Trans-urethral resection of the tumour was undertaken and the histo-pathological diagnosis was metastasis from renal cell carcinoma. At that time, multiple metastases to ureteral stump and lung were found. He had undergone palliative treatment because of his poor general condition until he died 26 months post-operatively.

Melegari et al. [14] reported a 65-year-old patient who was affected by bladder transitional cell carcinoma (TCC), RCC and adenocarcinoma of the prostate. They stated that the bladder TCC was diagnosed elsewhere in 1993; the patient underwent trans-urethral resection of bladder tumour (TCC stage Tx grade G2). He received no adjuvant therapy and continued to attend for regular endoscopic follow-up. The bladder tumour recurred twice: in 1997 (TCC T1G1) and in 2006 (TCC T1G2 associated with carcinoma in situ). He was administered bacillus Calmette-Guérin for 36 months, following the Southwest Oncology Group schedule [10].

In 2005, when he presented for the first time a pT2N0M0 prostate cancer was diagnosed (combined Gleason score 8 [4+4]; prostate specific antigen 37.7 ng/ml). An abdominal computed tomography scan revealed incidental presence of a left kidney cancer. Thus, he underwent a left radical nephrectomy and lymphadenectomy for an RCC pT3a pN0, Fuhrman grade III. The tumour was <10 cm in diameter and was necrotic. He later on underwent radiotherapy for carcinoma of the prostate cancer (66 Gy). There was no evidence of prostate cancer recurrence in three years of regular follow-up.

In February 2009, he underwent check cystoscopy as surveillance for the TCC and a 5-mm lesion was found. This lesion was endoscopically resected and its histology was that of clear cell RCC. The diagnosis of RCC metastases was confirmed by comparison with the histology of the resected primary kidney cancer. Immunohistochemistry was positive for cytokeratin (ck) AE1/AE3, ck 7, ck 20, cluster of differentiation (CD10) and beta catenin, and negative for c kit, PSA and FAP (fibroblast activation protein).

Melegari et al. [14] stated that:

- Renal cell carcinoma rarely metastasizes to the bladder.
- Kagota et al [15] reported 30 cases in Japan; few other cases had been described in the literature [12] [16].
- In view of the infrequency of this site for RCC metastases, the management of these lesions described in the literature has varied considerably.
- With regard to the management of single renal cell carcinoma metastases, as reported in 2005 by the Tongaonkar group (Thyavihally et al [17]), complete resection either by excision or radiotherapy is justified and can contribute to long-term survival.
- The first metastasectomy was undertaken by Barney [18] in 1939 in a patient who had a lung secondary tumour, and who died 23 years later of coronary artery disease.
- Russo and O'Brien [19] in 2008 stated that the decision to perform metastasectomy is usually made according to various prognostic criteria: the site and number of metastases, the completeness of resection of the primary tumour, the performance status and the disease-free interval from treatment of the primary tumour to the diagnosis of metastatic disease.
- Partial cystectomy [15], endoscopic resection [15] [19] and endoscopic resection followed by interleukin-2 systemic therapy [20] had all been employed to treat bladder metastases.
- Complete resection of the RCC single metastases is associated with five-year survival rates between 35% and 60%. Mean survival time after a single metastasectomy is 45 months **[17**]. The longer the disease-free interval, the longer the survival and synchronous metastases seems to correlate to a worse prognosis than metachronous metastases.
- Most authors are of the opinion that patients with metastatic RCC should be offered metastasectomy if the likelihood that complete resection of all sites of disease is high. Even though more data are required to reach a conclusion and the curative impact of metastasectomy can be still considered uncertain,

surgical intervention can provide effective palliation for symptomatic metastatic disease in such sites as bone, brain and adrenal gland [21] [22].

- The site of metastases could be related to the survival: patients with lung and bone metastases had a better outcome (median survival 62 months) than those with liver and brain metastases (median survival 22 months), perhaps because of differences in the feasibility of a radical excision [17].
- In the case of urinary bladder metastases, the three-year survival rate was 80% in the case of single metastases and 20% for patients with more than one site involved. Approximately 50% of patients with multiple metastases have a life expectancy of less than one year following diagnosis; no difference was found between synchronous and metachronous metastases in terms of overall survival. The mean time to diagnosis of urinary bladder metastases is 28 months after nephrectomy (range 0 to 131 months) [23].
- In their case, the diagnosis of bladder metastases was metachronous, 36 months after nephrectomy was performed. According to the Mayo Clinic scoring system for renal cancer, this patient was at high risk of metastases (62.9% at three years).

Matsuo et al, [23] reported a case of renal cell carcinoma with solitary metachronous metastasis to the urinary bladder, which occurred 6 years after radical nephrectomy. The patient underwent partial cystectomy and survived for 60 months. Matsuo et al, [23] reviewed other cases like their case in published reports, and they found that the 3-year survival rate for patients with this type of cancer with solitary metastasis to the urinary bladder was 80%. Matsuo et al [23] stated that the follow-up duration of their case was the longest in the published studies. Matsuo et al [23] suggested that:

Tuna et al. [24] reported a 57-year-old man who presented with painless visible haematuria. He has ultrasound scan which showed a solitary large mass in the urinary bladder and a right renal mass. He had a CT scan which showed a large tumour in the mid portion of the right kidney and a polypoid tumour in the left lateral wall of the urinary bladder (see figures 1 and 2). There was no evidence of tumour anywhere else on the CT scan. He had cystoscopy which revealed a non-papillary bladder tumour. He underwent trans-urethral resection of bladder tumour (TURBT) and right radical nephrectomy. Histological examination revealed that the renal tumour was clear cell carcinoma Fuhrman grade 2, pT2 (see figure 3). Histological examination further revealed that the urinary bladder tumour was clear cell carcinoma similar to the right renal tumour. The morphology of the urinary bladder tumour was similar to that of the right kidney tumour (Positive immunohistochemical staining for pan-cytokeratin, cytokeratin 7, CD10, Vimentin, and negatively stained for cytokeratin 20, chromogranin, and high molecular weight keratin) (see figures 4 A, B, C). The urinary bladder tumours were of the same grade (Fuhrman grade 2) as the primary renal tumour. The case was therefore diagnosed as solitary synchronous metastasis to the urinary bladder from a primary renal cell carcinoma (RCC). The patient received adjunctive post-operative therapy (interferon alpha 2a; 9 million unit 3/week). He was well until 24 months later when he developed right adrenal gland metastasis for which he underwent right adrenalectomy and histological examination confirmed a diagnosis of metastatic renal cell carcinoma in the adrenal gland. At the time of publication of the paper the patient remained well without any further metastasis at 36 months follow-up.

Wada et al. [25] reported a 65-year-old man who presented with visible haematuria in 2004. He had computed tomography (CT) scan which showed a left renal mass. He underwent laparoscopic radical nephrectomy. The pathological examination was clear cell carcinoma which was staged as pT2N0M0 and it was graded G2 - G3. Four years later he had CT scan which showed a right adrenal tumour. He then underwent laparoscopic adrenalectomy. Histological examination of the specimen showed metastasis of renal clear cell carcinoma. In 2009, he developed visible haematuria for which he underwent cystoscopy and this revealed a 2 cm solitary, non-papillary tumour at the anterior wall of the urinary bladder. At the same time computed tomography scan had revealed a small, 6mm, solitary liver metastasis in his liver. He underwent trans-urethral resection of the bladder tumour (TURBT) and resection of the liver tumour. Histological examination revealed clear cell carcinoma both in the urinary bladder and liver masses. Nine months after his last operation he was alive with no evidence of tumour recurrence. Wada et al. [25] they had reviewed the literature and found that at the time of their publication their case was the 34th case of bladder metastasis from renal cell carcinoma in the Japanese literature.

Nakanishi et al. [26] reported a 48-year-old woman was found to have on ultrasound scan a small urinary bladder tumour and a right renal mass. She

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had cystoscopy which revealed a solitary non papillary tumour at the right side of the retro-trigone. She also had computed tomography scan which revealed a large tumour in the right kidney. She underwent trans-urethral resection of bladder tumour (TURBT) and histological examination of the tumour showed clear cell carcinoma. There was no other distant metastasis. She subsequently, underwent right radical nephrectomy and histological examination clear cell carcinoma. Nakanishi et al. [26] considered their case to be a case of a solitary metastatic bladder tumour from renal cell carcinoma.

Tanikawa et al. [27] reported a 48-year-old man who presented with visible haematuria, who had three years earlier on undergone right radical nephrectomy histology of which was consistent with clear cell carcinoma pT1N0M0. She had cystoscopy which revealed a solitary non-papillary tumour in the middle of the inter-ureteric ridge. He underwent trans-urethral resection of tumour. Histological examination of the specimen showed renal cell carcinoma (clear cell sub-type). Tanikawa et al. [27] stated that the tumour was considered to be a metastatic tumour from the renal cell carcinoma which was treated three years earlier and that their case may represent a so-called latent distant metastasis.

Shiraishi et al. [20] reported a 78-year-old man, who at the age of 64 years who had undergone right radical nephrectomy. He had cystoscopy which revealed a solitary, spherical tumour 1.5 cm in size protruding into the urinary bladder. He underwent trans-urethral resection of the bladder tumour and histological examination of the resected specimen showed the lesion was clear cell carcinoma. He was administered interleukin-2 and was alive 12 months after his bladder tumour recurrence.

Gallmetzer et al. [28] reported a case of solitary, synchronous bladder metastasis which was treated by trans-urethral resection. They stated that at 12. They also stated that:

- Metastases to the urinary bladder from renal cell carcinoma are poor and did not seem to be related to the type of treatment.
- Most patients die within 1 year of diagnosis.

Mayer et al. 16] reported one case of synchronous metastasis of renal cell carcinoma (RCC) to the ipsi-lateral ureter and one case of solitary synchronous metastasis of RCC to the urinary bladder.

Dogra et al. [29] reported an unusual case of Von Hipple Lindau (VHL) syndrome with bilateral multicentric renal cell carcinoma with synchronous solitary urinary metastasis. They stated that to the best of their knowledge their case was the first reported in the literature with the aforementioned combination of tumours.

Joshi et al. [30] reported a 56-year-old man who was referred in 1996 for recurrence of renal cell carcinoma (RCC) metastatic to the urinary bladder. The patient's primary tumour was treated by means of left radical nephrectomy in 1994 for a tumour which was staged pT3bN0M0. His initial recurrent tumour, a 2-cm nodular lesion was found at cystoscopy one year later after microscopic haematuria was detected. He underwent trans-urethral resection of the tumour (TURBT) and the histology of the tumour exhibited identical morphology to the 1994 renal mass, confirming metastatic renal cell carcinoma. Joshi et al. [30] stated that a rare primary clear cell adenocarcinoma of the urinary bladder was excluded in view of the prominent vascular pattern, the lack of tubular differentiation, and the absence of mucin. Histologically, the tumour was found to have invaded the lamina propria (pT1). His metastatic work-up included isotope bone scan, computed tomography scans of the chest, abdomen, pelvis and brain which were all negative for recurrent tumour. Three years later, he developed visible haematuria investigation of which led the detection of a second recurrent bladder tumour. A 2.5 cm pedunculated solid mass with vascular features was found on the posterior wall of the urinary bladder. He had re-staging imaging which did not show any evidence of other disease sites. He underwent partial cystectomy. Joshi et al. [30] stated that pathological examination of the specimen showed a non-invasive tumour which had similar cell pattern and architecture as was previously observed which suggested recurrent metastatic renal cell carcinoma. After three years of surveillance, the patient had remained free of disease. Joshi et al. [30] stated that Hoffman [31] reported the first case of RCC metastases to the urinary bladder in 1907. The patient like the majority of others described in the literature, had associated wide spread tumour dissemination.

Ziade et al. [32] in 1994 reported the fourth case of synchronous urinary bladder metastases from renal cell carcinoma. They stated that the first these

cases the bladder tumour followed a left kidney tumour and in three, a brain metastasis was also found.

Ceccherini et al. [33] reported clear cell adenocarcinoma which affected the urinary bladder, kidney and ureter. They stated that involvement of the urinary bladder, kidney and ureter by clear cell carcinoma in the same patient is an unusual distribution which is rare. [34] Chinegwundoh et al. [34] in 1997 also reported a case of bladder metastasis from renal cell carcinoma.

Sambur et al. [35] in 2000, reported a 49-year-old man who was incidentally found on Ct scan to have had a 10 x 13.6 x 8 – cm heterogeneous right renal mass. He underwent laparoscopic right nephrectomy. Histological examination of the specimen confirmed that the tumour was a renal cell carcinoma which was staged as T3 N0 MX. Four months after the surgery a small lesion was found on his chest CT scan which had increased in size at one year follow-up and histological examination of mediastinal biopsy of the confirmed metastatic renal cell carcinoma. He underwent interleukin 2 chemotherapy as an outpatient for 6 months. His lung lesion resolved, and subsequently, he did not have any active disease in his chest or abdomen based upon follow-up CT scans. At 2 years and 2 months after his laparoscopic nephrectomy when he was aged 51 years, he developed visible haematuria. He had ultrasound scan of the renal tract which revealed a seroma in the right renal space (the site of the previous surgery), a heterogeneous, well defined, and elongated mass attached to the right anterior bladder wall which extended into the lumen of the urinary bladder. Colour Doppler imaging (CDI) identified flow in vessels within the bladder wall mass near its attachment to the bladder wall. Pulsed Doppler imaging with special analysis of flow in this vessel showed an arterial waveform with increased flow during diastole and a resistive index (RI) of approximately 0.30. A normal left ureteral jet was visualized. Detection of vessels within the mass with high diastolic flow suggested a neoplasm with a possible adherent thrombus. He underwent cystoscopy which revealed a lesion in the anterior wall of the bladder and this appeared somewhat yellow and quite vascular and quite vascular. There was also moderate amount of blood clot in the bladder. Trans-urethral resection of the bladder tumour (TURBT) was subsequently done. During the procedure, the mass was well visualized after the clot was removed. The bladder mass was rounded, pedunculated, and pale yellow. The base of the lesion was very vascular with large parasitic vessels coursing from the bladder mucosa into the base of the mass. The mass was completely resected, with normal-appearing muscle at the base of resection. Pathological examination of the specimen showed that the resected mass was represented clear cell-type metastatic renal cell carcinoma. Immunohistochemical stains of the tumour were positive for epithelial membrane antigen, vimentin, and pan-cytokeratin and negative for cytokeratin 7, a profile which supported a diagnosis of metastatic renal cell carcinoma. The patient had no further haematuria, bladder recurrence, or other metastatic lesions up to the time of publication of the paper which was 2 years after the TURBT. Sambur et al. [35] stated that in their review:

- 14 of the bladder metastases resulted from left-sided carcinoma, whereas only 11 of the metastases occurred from right-sided carcinoma [2], [6], [10], [[23], [34], [36], [37], [38], [39], [40], [41], [42], [43] [44], [45], [46], [47] [48]. The remaining cases either did not report the site from which the carcinoma originated or were written in non-English language, and they were unable to determine the originating side.
- The main mechanism of spread to the urothelium is not clear, however, direct spread through contamination of the colleting system is one explanation.
- Abeshouse [39] postulated 4 possible routes of metastases which include (a) direct expansion of the tumour, (b) seeding of the tumour cells from the kidney to the urothelium, (c) lymphogenous spread, and (d) retrograde venous embolism of the tumour cells from venous drainage of the kidney to the bladder, which would ccount for left-sided metastasis.

Jang et al. [49] reported a 77-year-old woman who presented with visible haematuria. Her CT scan of chest and abdomen revealed bilateral renal masses, urinary bladder dome mass, and multiple lung metastases. She had trans-urethral resection of the bladder tumour and ultrasound scan guided renal biopsy. Histological examination of the specimens showed clear cell renal cell carcinoma with similar microscopic and immunohistochemical staining characteristics (see figures 5 A, B, C, D, E, F, G, H). She had targeted therapy using pazopanib without surgical resection of primary tumours and metastatic lung lesions. Jang et al. [49] reported their case as synchronous metastases of renal cell carcinoma to the

urinary bladder and lung. At the time of the report of the case, three months after beginning therapy, the patient was alive.

Rotellini et al. [50] reported the case of a man who had earlier on undergone radical nephrectomy for clear cell carcinoma of kidney and who had a bladder tumour with histological features exhibiting polygonal cells with abundant clear cytoplasm which had deeply infiltrated the urinary bladder wall. Rotellini et al. [50] made their diagnosis based upon the morphology, immunohistochemical staining characteristics and the UroVysion FISH analysis.

Tsai et al. [51] reported a 57-year-old woman who presented initially like pyelonephritis and in whom conservative treatment was un-effective. Surgical intervention revealed the presence of concomitant renal cell carcinoma, collecting duct carcinoma, (transitional cell carcinoma) of the kidney. They also reported that metastatic renal cell carcinoma to the urinary bladder, liver, and lung subsequently developed. They further stated that:

- Deceptive inflammatory presentations can occur in aggressive synchronous renal malignancies;
- Recognition of this rare disease entity could prevent delays in diagnosis and treatment.

Kazarans et al. [52] reported a 35-year-old patient with renal cell carcinoma in whom only comparative genomic hybridisation (CGH) could help differentiate between a second primary malignancy in the urinary bladder and atypical urinary bladder metastasis. They stated that:

- In patients who are younger than 40 years, renal cell carcinoma metastases to the urinary bladder are rare.
- Comparative genomic hybridisation (CGH) may be useful to differentiate between metastatic renal cell carcinoma and secondary malignancies of the genitourinary tract, which can occur in all histologic types.

Herrera Puerto et al. [53] reported a patient with adenocarcinoma of the kidney which subsequently metastasized to the urinary bladder. They stated that even though involvement of any organ in this area could lead to secondary invasion of the urinary bladder wall, haematuria which presents in a patient who had previously undergone nephrectomy due to hypernephroma should prompt clinicians to strongly suspect tumour spread to the bladder They also reported that after a follow-up of 1.5 years, there was no evidence of recurrence which in their opinion was a good result.

Tashiro et al. [54] reported a 64-year-old woman who underwent nephrectomy and lymphadenectomy surgery for renal cell carcinoma on July 1, 1981 and histology of the tumour was adenocarcinoma of the clear cell type which was staged Robson's stage 2. She subsequently in November 1981 had biopsy of an inoperable tumour in the lesser curve of her stomach of Boormann's type IV which was based upon histological examination diagnosed as un-differentiated adenocarcinoma. In January 1982 she had cystoscopy for haematuria which revealed a soy bean-sized, smooth, pedicle tumour onto which coagula were partially adherent in the center of the trigone. She underwent trans-urethral resection of the bladder tumour on 3rd March 1982 and the pathological diagnosis of the tumour was adenocarcinoma of the clear cell type with no sub-mucosal infiltration (pTa). The tumour was thus diagnosed as metastatic renal cell carcinoma of the urinary bladder. She died of bleeding from her stomach cancer on June 15 1982. Tashiro et al. [54] were of the opinion that based upon the fact that the tumour had localized in the urinary bladder mucosa, they had strongly suspected implantation through the urinary tract was the metastatic route of the renal cell carcinoma to the bladder.

Vecchioli Scaldazza et al. [55] reported a 56-year-old man with asynchronous isolated metastases to the ureteral stump and bladder from renal cell carcinoma. They stated that the ureteral metastasis was discovered 2 years after he had undergone nephrectomy. He had cystoscopy and magnetic resonance imaging (MRI) scan. He had excision of the ureteral stump with a cuff of the bladder. No other metastasis was observed. Six months later, he underwent trans-urethral resection of a metastatic tumour on the right wall of the bladder. Histological examination of the tumour showed a renal cell adenocarcinoma metastasis. After 6 months, a new bladder metastasis from renal cell carcinoma was found. The nodule on the lower part of the right wall of the bladder wall was removed.

Nair and Little [56] reported a case of bladder tumour which arose as a metastasis of renal carcinoma and which presented as urinary outflow obstruction.

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Rodriguez et al. [57] reported the case of a patient who had undergone surgery for clear cell renal carcinoma 2 years earlier before presenting with metastatic extension to the urinary bladder on follow-up. During follow-up, radiological imaging showed a urinary bladder mass. The patient underwent trans-urethral resection of the bladder tumour and histological examination of the specimen showed clear cell carcinoma which was compatible with a primary renal origin. They stated that the urinary bladder is a rare place for metastasis from kidney tumours and the prognosis would depend upon the time of appearance of such metastases.

Kava et al. [58] reported two patients who presented with visible haematuria within 1 year of their radical nephrectomy. They reported that both patients underwent trans-urethral resection of the tumour metastases. One of the patients developed a metastasis in the head of pancreas 12 months after undergoing TURBT. The second patient developed bilateral femoral and spinal bone metastasis.

Tocco et al. [59] reported the case of a renal cell carcinoma with solitary metastasis to the urinary bladder, which had occurred 3 years after radical nephrectomy in a 68-year-old male patient. The patient underwent cystoscopy which revealed a solid and rounded urinary bladder lesion with a fine footstalk. Trans-urethral resection of bladder tumour was performed and the pathological diagnosis was eosinophil cell and clear cell carcinoma. The patient subsequently developed secondary lesions in the infra- and supra-diaphragmatic lymph node area, brain and lung. He received treatment with several systemic chemotherapy agents (Sorafenib, Sutent, Everolimus, IFN-alpha, Oxaliplatin, and Gemcitabine).

Kume et al. [60] reported two cases with renal cell carcinoma which had recurred in the urinary bladder. The first was an 87-year-old woman who had undergone right nephrectomy 17 years earlier. During investigation of hypercalcemia which she had developed, bone metastases and a urinary bladder tumour were found. She had trans-urethral resection of the bladder tumour and histological examination of the tumour revealed that the tumour was clear cell carcinoma which was similar to the right renal tumour. The second patient was a 67-year-old man who had undergone left nephrectomy 4 and half years earlier. Despite having had adjuvant immunotherapy which included interferon alpha, gamma and interleukin-2, 16 months later he developed multiple lung metastases. He developed painless visible haematuria one month before his admission. He underwent cystoscopy and trans-urethral resection of 3 non-papillary pedunculated tumours which were seen at the cystoscopy. Histological examination revealed the bladder tumour was clear cell carcinoma which was similar to the left renal tumour. Kume et al. [60] stated that in both cases the recurrent carcinomas of the urinary bladder were confined to the mucosa and that they were of the opinion that the metastases were caused by implantation.

Miki et al. [61] reported a 74-year-old man who had a CT scan which showed a right renal tumour with para-aortic lymph adenopathy. He underwent radical nephrectomy and left lymph adenectomy in September 2008. He was administered adjuvant therapy and he received Interferon-alpha (6 million international units three times per week). He developed side effects including fatigue; therefore, his immunotherapy was discontinued after 6 months. Nine months after his surgery, he had radiofrequency for pulmonary metastasis. A nodular pedunculated tumour was found on the posterior wall of the urinary bladder when he had a CT scan, and trans-urethral resection of the tumour was performed 18 months after he had undergone nephrectomy / lymphadenectomy. The pathological diagnosis of the bladder tumour was clear cell carcinoma and it was thought that the urinary bladder tumour had originated from the renal cell carcinoma. Miki et al. [61] summarized 43 cases of urinary bladder metastasis of renal cell carcinoma in Japanese patients which had been reported up to 2012 including their patient.

Acino and Hampel [62] in 1988 reported the first case in which the diagnosis of renal cell carcinoma was made following biopsy of an actively bleeding solitary bladder metastasis of clear cell carcinoma of the kidney.

McAchran et al. [63] in 2010 stated that:

- Renal cell carcinoma is an uncommon source of bladder metastases with fewer than 40 reported cases at the time of their publication.
- Such metastases may be synchronous or metachronous and may be discovered years after the original tumour had been identified.
- The incidence of bladder and ureteral metastasis of renal carcinoma is 2% and 1% respectively.

Vecchioli and Giaccomini [64] reported the case of repeated metastases of the ureteral stump and bladder in a 59 year old man. They reported that two years after the patient had undergone nephrectomy his ureteral stump and bladder were involved by two different metastases. Subsequently, other nine metastases developed in the urinary bladder during the ensuing 12 months. Biopsy with coagulation was performed. Vecchioli and Giacomini [64] stated that:

- The urinary bladder metastases ranged from 2 mm and 4 mm.
- Magnetic resonance imaging and isotope bone scans did not reveal any other metastasis
- Thirteen months after the first bladder metastasis, the patient received intravesical Bacillus Calmette-Guerin (BCG)
- They did not find any report in the literature regarding BCG in the treatment of superficial bladder metastases from renal cell carcinoma. Nevertheless, 15 months from the beginning of BCG treatment no metastasis developed from the bladder and the patient had remained disease-free after a follow-up of 19 months.

Aki et al. [65] reported a 53-year-old woman who underwent nephron sparing surgery for a 45 mm x 50 mm tumour in the lower pole of her left kidney which was found on CT scan of abdomen and pelvis which she had when she was investigated for left loin pain. Microscopic examination of the specimen revealed large tumour cells with clear cytoplasm showing glandular differentiation in some areas, otherwise forming nests. A diagnosis of renal cell carcinoma of clear cell type involving the left kidney was made. She remained asymptomatic; however, she had a CT scan of abdomen and pelvis 27 months after her first operation and this showed a polypoid mass on the left lateral wall of the urinary bladder. She underwent complete trans-urethral resection of the bladder tumour. Histological examination of the specimen revealed the tumour was metastatic renal cell carcinoma of the bladder similar to the previously removed renal tumour (see figures 6 and 7). The tumour was confined to the mucosa and did not involve the lamina propria or muscularis propria (pTa); however, in the paper Aki et al reported it as pT1. The patient remained well with no evidence of metastasis after 6 months of follow-up with no additional treatment. Aki et al. [65] stated that:

- Bladder recurrence more than 2 years after nephron-sparing surgery for a pT1 renal tumour without any symptoms would suggest that, even small renal cell carcinomas, have the capability of late distant recurrences and bladder recurrences may occur without any symptoms or signs meaning that metastases investigation should include the urinary bladder.
- In general the prognosis is poor and survival is less than 1 year.
- In the literature have varied from trans urethral surgery to cystectomy [10] [34]
- Resection of solitary metastatic lesion prolonged survival but additional therapies were usually unsatisfactory. [10]
- Their patient underwent trans-urethral resection and fulguration and was followed up closely without any adjuvant therapy.
- The long-term disease outcome is unknown, as in the literature no long-term survivors are mentioned.

Conclusions

MRCCTUs are rare and there is no consensus opinion regarding their treatment in relation to other disseminated metastases. However, trans-urethral resection of the bladder tumours have been used to treat the local disease and anecdotal use of intravesical BCG has been reported. The prognosis of solitary bladder metastasis would appear to be better in comparison with bladder metastasis associated with other disseminated metastases. There is need for all cases of MRCCTUs to be entered into a multi-centric trial. Urologists and Oncologists should report cases of MRCCTUs they encounter.

Conflict of Interest: None

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