Clinics in Medicine

ISSN: 2688-6731

Review Article

Primary Small Cell Neuro-Endocrine Carcinoma of the Kidney and Urinary Tract: A Review and Update

*Anthony Kodzo-Grey Venyo**

North Manchester General Hospital, UK

Abstract

Small cell carcinomas are most commonly found in the lung, but rare cases of extrapulmonary sites had also been reported and they include: the oesophagus, the larynx, nasal cavity, gastrointestinal tract, uterine cervix, urinary bladder, and the breast. It has been iterated that small cell carcinoma of the kidney is an uncommon tumour and that reportedly, small cell neuroendocrine carcinoma of the kidney is a very aggressive tumour as well as there is no standard treatment protocol available due to the small number of cases that had been reported. Diagnosis of Small cell neuroendocrine carcinomas of the kidney and urinary tract can be confirmed based upon the histopathology, immunohistochemistry, as well as flow-cytometry features of biopsy specimens, or excised specimens of the tumour as illustrated in the main article. Small cell carcinomas of the kidney and upper renal tract could be pure tumours or the tumours could co-exist with more common tumours of the kidney including adenocarcinoma of the kidney or transitional cell carcinoma if the tumour is in the upper renal tract. Small cell carcinomas of the kidney and upper renal tract may present with loin pain, haematuria, feeling unwell and other non-specific symptoms. Small cell carcinomas of the urinary bladder would tend to manifest with haematuria, lower urinary tract symptoms and loin pain. Small cell carcinomas of the kidney and urinary tract at the time of initial diagnosis tend to diagnosed as locally advanced or metastatic tumours. On very rare occasions, localized small cell carcinomas of the kidney had been reported at a localized stage and in such situations, aggressive surgical treatment has been the adopted treatment option. With regard to locally advanced and metastatic primary small cell carcinomas of the kidney and urinary tract, the undertaking of surgery, and combination chemotherapy utilizing the chemotherapy regimens that are utilized for small cell neuroendocrine tumours of the lung have been utilized and radiotherapy has been used by some oncologist. The efficacy of radiotherapy in the treatment of advanced and metastatic primary small cell carcinomas of the kidney and urinary tract had not been clearly demonstrated in previously reported literature. There is an urgent global need of a multi-disciplinary team discussion and a global multi-centre trials of various treatment options with regard to the management of localized, locally advanced, and advanced small cell carcinomas of the kidney and urinary tract to ascertain the best treatment options of the tumour as well as for pharmacists and pharmaceutical research workers and oncologists to develop new chemotherapy agents that would safely and effectively destroy small cell neuroendocrine tumours of the kidney and urinary tract.

Keywords: Small cell neuroendocrine carcinoma; Kidney; Renal pelvis; Ureter; Urinary bladder; Localized; Metastatic; Aggressive; Surgery; Chemotherapy; Radiotherapy; Poor survival

Introduction

Chung et al. [1] stated that small cell carcinomas are most commonly found in the lung, but rare cases of extrapulmonary sites had also been reported and they include: the oesophagus, the larynx, nasal cavity, gastrointestinal tract, uterine cervix, urinary bladder, and the breast [2,3]. It has also been iterated that small cell carcinoma of the kidney is uncommon and that reportedly, small cell neuroendocrine carcinoma of the kidney is a very aggressive tumour as well as there is no standard treatment protocol available due to the small number of cases that had been reported [1]. It has also been documented that the median survival rate of primary small cell carcinoma had been reported as up to 8 months [1,4]. It has been stated that as in cases of pulmonary small cell carcinoma, chemotherapy could lead to an improved outcome in patients with extrapulmonary small cell carcinoma [1]. It has also been iterated that even though majority of small cell carcinomas do tend to arise within the tracheobronchial tree, they are increasingly being reported within extra-pulmonary sites including the oesophagus, cervix, parotid gland and in the genitourinary tract like the prostate gland and the urinary bladder [5]. Considering that very few cases of primary small cell carcinomas of the kidney and urinary tract had been reported in the literature, it would be envisaged that majority of clinicians globally would not have encountered or managed a case of primary small cell neuroendocrine carcinoma of the kidney and urinary tract before and they would therefore perhaps not be conversant with the manifestations, the diagnostic features, treatment options and the biological behaviour of this rare neoplasm. The ensuing article on small cell neuroendocrine carcinoma of the kidney and renal tract is divided into two parts: (A) Overview which has discussed general aspects of small cell neuroendocrine carcinoma of the kidney and urinary tract and (B) Miscellaneous narrations from some case reports, case series, and studies related to small cell neuroendocrine carcinoma of the kidney and urinary tract.

Citation: Anthony Kodzo-Grey Venyo. Primary Small Cell Neuro-Endocrine Carcinoma of the Kidney and Urinary Tract: A Review and Update. Clin Med. 2022; 4(1): 1044.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Aug 08th, 2022

***Correspondence:** Anthony Kodzo-Grey Venyo, North Manchester General Hospital, Delaunays Road, Manchester, M8 5RB, UK, E-mail: akodzogrey@yahoo.co.uk

Methods

Various internet data bases were searched including: Google, Google Scholar, Yahoo, and PUBMED. Search words that were used included: Small Cell Neuroendocrine Carcinoma of the Kidney, Small Cell Neuroendocrine Carcinoma of the Urinary Tract, Primary Small Cell Carcinoma of the Kidney, Small Cell Carcinoma of the Urinary Tract, Small Cell Carcinoma of the Urinary Bladder, Small Cell Carcinoma of the Ureter and Renal Pelvis. Fifty-one (51) references were identified which were used to write the article which has been divided into two parts: (A) Overview which has discussed general aspects of small cell neuroendocrine carcinoma of the kidney and urinary tract and (B) Miscellaneous narrations from some case reports, case series, and studies related to small cell neuroendocrine carcinoma of the kidney and urinary tract.

Overview

Definition/general statements [6]:

- Small cell neuroendocrine carcinoma is a terminology that is utilized for a high-grade neuroendocrine tumour that simulates small cell carcinoma of other organs [6].
- It has been documented that small cell neuro-endocrine carcinoma could be either pure Small Cell Neuro Endocrine Carcinoma (SCNC) or it could be admixed with high grade urothelial carcinoma of the kidney / renal tract [6].
- It has been iterated that SCNC of the kidney is uncommon and it does constitute less than one percent (<1% of kidney neoplasms) and that about 50 cases had been reported in the literature [6].
- It has also been documented that SCNC of the kidney has been reported very rarely in association with renal cell carcinoma [7,8].

Epidemiology [6]:

- With regard to epidemiology of SCNC, it has been iterated that the median age of the patients has ranged between 59 years and 65 years, and that SCNC could be seen in association with high-grade urothelial carcinoma of the kidney [9,10].

Pathophysiology: It has been conjectured that SCNC of the kidney likely does arise from a multipotent stem cell [6].

Clinical manifestations [6]:

- It has been iterated that SCNC of the kidney does tend to exhibit the ensuing presentations: haematuria, back pain or abdominal pain [9,10].
- It has been documented that SCNC of the kidney has tended to portend a highly aggressive biological behaviour, and it has often tended to be associated with local or distant metastases [4,10].
- It has been stated that the median survival associated with SCNC of the kidney has been between 8 months and 20 months [4,10].

Laboratory tests

Haematology tests:

- Full blood count and INR are routine tests that are undertaken in the assessment of all patients who manifest with haematuria, loin pain or back pain. Even though the results would not be diagnostic, anyone who is found to be anaemic would be assessed for the cause of anaemia and treated accordingly to improve the general condition of the patient.

Biochemistry:

- Some of the routine biochemistry tests that are undertaken for the full assessment of patients who have small cell carcinoma of the kidney and urinary tract include: Serum urea and electrolytes, EGFR, (renal function tests), liver function tests, bone profile, CRP, blood glucose. If any abnormality is detected, it would be investigated and treated accordingly to improve upon the general condition of the patient.

Urine pathology:

- Urine specimen from voided urine as well as urine specimen obtained at cystoscopy and ureteroscopy could be submitted for cytology examination.

Microbiology:

- Urinalysis, urine microscopy and culture are routine tests that tend to be undertaken in the general assessment of patients and if there is any infection, it would be treated to improve upon the general condition of the patient.

Radiology imaging features [6]

- It has been iterated that the radiology imaging features of SCNC of the kidney do demonstrate the tumour to have a medullary location within the kidney, and that it also tends to be associated with lack of central necrosis within a large tumour [11].

Ultrasound scan

- Ultrasound scan of the kidney and urinary tract is one of the radiology imaging options that tend to be used to identify tumours within the kidney and urinary tract and ultrasound guided biopsies of lesions that are found in the kidney or urinary tract could be undertaken to obtain specimens for histopathology, immunohistochemistry, and flow cytometry studies to confirm the diagnosis.
- Ultrasound scan of the abdomen and pelvis as well as urinary tract can be undertaken as part of the initial assessment of patients in addition to chest x-ray in the initial staging of the disease as well as excluding a primary tumour in the lung perhaps mainly in some less-resourced hospitals in some developing countries but in the developed countries, Computed Tomography (CT) scan of thorax, abdomen, and pelvis and magnetic resonance imaging of thorax, abdomen, and pelvis, have superseded utilization of ultrasound scan.
- In some less resourced areas of the world, where facilities for CT scan and MRI scan are not available, ultrasound scan of abdomen and pelvis and renal tract would tend to be combined with chest x-ray in the follow-up assessment of patients who have undergone treatment for small cell carcinomas of the kidney and renal tract.

Computed Tomography (CT) scan:

- CT-scan of the kidney and urinary tract is one of the radiology imaging options that tend to be used to identify

tumours within the kidney and urinary tract and CT scan guided biopsies of lesions that are found in the kidney or urinary tract could be undertaken to obtain specimens for histopathology, immunohistochemistry, and flow cytometry studies to confirm the diagnosis.

- CT scan of the thorax, abdomen and pelvis as well as urinary tract can be undertaken as part of the initial assessment of patients in the initial staging of the disease as well as excluding a primary tumour in the lung.
- CT scan of thorax, abdomen and pelvis is an option of follow-up assessment imaging that tends to be undertaken in various centres globally to ascertain the progress of the tumour.

Magnetic Resonance Imaging (MRI) scan:

- MRI-scan of the kidney and urinary tract is one of the radiology imaging options that tend to be used to identify tumours within the kidney and urinary tract and MRI-scan guided biopsies of lesions that are found in the kidney or urinary tract could be undertaken to obtain specimens for histopathology, immunohistochemistry, and flow cytometry studies to confirm the diagnosis.
- MRI-scan of the thorax, abdomen and pelvis as well as urinary tract can be undertaken as part of the initial assessment of patients in the initial staging of the disease as well as excluding a primary tumour in the lung.
- MRI scan of thorax, abdomen and pelvis is an option of follow-up assessment imaging that tends to be undertaken in various other centres globally to ascertain the progress of the tumour.

Isotope bone scan

- Bone scan tends to be undertaken to establish if patients who have primary small cell carcinoma of the kidney and urinary tract have developed bone metastasis or not.

Endoscopy procedures

- Cystoscopy (flexible cystoscopy and rigid cystoscopy) and ureteroscopy tend to be undertaken in the assessment of patients who manifest with haematuria and if there a lesion found in the bladder, ureter, or renal pelvis, it would be biopsied, resected plus diathermy undertaken. Histopathology and immunohistochemistry examination of the specimens would establish the diagnosis of small cell carcinoma.
- Urine specimen obtained during cystoscopy and ureteroscopy could be sent for cytology examination.
- Retrograde ureteropyelogram could also demonstrate a lesion in the ureter or renal pelvis.
- Ureterorenoscopy could identify lesions within the ureter and renal pelvis that would provide the chance for the tumours to be identified and specimens obtained for pathology examination.

Treatment

The ensuing summations have been made about the treatment of SCNC of the kidney [6].

- Surgery has tended to be undertaken in the treatment of SCNC of the kidney
- It has been stated that chemotherapy with utilization of platinum-based treatment, could be administered same as in pulmonary small cell carcinoma) ± radiotherapy [4].
- It has been reported that there is slightly improved survival of 17.3 months with the administering of neoadjuvant chemotherapy preceding the nephrectomy [10].

Macroscopic examination features

The gross examination features of SCNC of the kidney have been summarized as follows: [6]

- Macroscopy examination of SCNC of the kidney does tend to demonstrate unifocal, centred tumour within the renal pelvis, which usually has tended to be invading the perinephric adipose tissue [9].
- The median size of primary SCNC of the kidney has been documented to be 11 cm, and the mean size of the tumour has been stated to be 7.1 cm in another study this has been reported to range from 2.3 cm to 23 cm.

Microscopic (histologic) description [6]:

- Similar morphology to small cell carcinoma of the lung
- Diffuse growth of small cells with minimal cytoplasm, nuclear moulding, indistinct nucleoli, high mitotic activity and apoptosis, lympho-vascular invasion, necrosis

Immunohistochemistry staining features:

Positive stains [6]: It has been stated that SCNC does upon Immunohistochemistry staining does tend to exhibit positive staining with utilization of the ensuing tumour markers: [6]

- Pan-cytokeratin.
- Chromogranin
- Synaptophysin
- CD56
- Neuron specific enolase
- CK8/18
- CK19 [9].

Negative stains: It has been stated that SCNC upon Immunohistochemistry staining does tend to exhibit negative staining with utilization of: [6]

- CD45 / LCA

Electron microscopy examination features [6]:

- It has been iterated that electron microscopy examination of specimens of SCNC of the kidney and urinary tract does demonstrate scanty electron dense neurosecretory granules and desmosomes supporting epithelial differentiation [12,13].

Molecular/cytogenetics features of SCNC of the kidney and urinary tract [6]:

- It has been iterated that within the urinary bladder, studies of coexistent urothelial carcinoma and small cell carcinoma had shown very similar loss of heterozygosity and X-inactivation

patterns, which had suggested that urothelial and small cell components are derived from same cells within the urothelium, rather than transformation from a population of normal neuroendocrine cells [14].

Differential diagnoses

Some of the differential diagnoses of SCNC of the kidney and urinary tract have been summarized to include the following [6]:

- Lymphoma: Immunohistochemistry staining of the tumour is stated to be required in order to differentiate between SCNC and lymphoma.
- Metastatic small cell carcinoma of the lung: Radiology imaging, clinical history of primary lung tumour, and absence of high-grade urothelial component
- It has been iterated TTF1 would be unlikely to have a discriminatory value [10,15,16].
- Other small blue cell tumours: These include PNET/Ewing's sarcoma; neuroblastoma, rhabdomyosarcoma, desmoplastic small round cell tumour.
- Poorly differentiated urothelial carcinoma, plasmacytoid carcinoma, lymphoepithelial like carcinoma. Metastatic Merkel cell Carcinoma, and synovial carcinoma.

Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to Small Cell Neuro-Endocrine Carcinoma of the Kidney and Urinary Tract

Capella et al. [17] reported a case of a malignant renal neoplasm with all the morphologic attributes of oat cell (small cell, neuroendocrine carcinoma. The tumour metastasized widely to regional lymph nodes and resulted in the death of the patient. Ultra-structurally, the tumour did contain dense-core endocrine-type secretory granules. It had a cell component that was argyrophilic and which gave a positive immunocytochemical reaction for calcitonin. To the best of their knowledge, this was the first documentation of this tumour type within the kidney.

Tetu et al. [12] reported three cases of primary small cell carcinoma of the kidney with light microscopic, immunohistochemical, and electron microscopic findings. Two patients died as a result of disseminated disease 8 months and 1 year, respectively, after the diagnosis of their tumours and the third was free of tumour after 18 months. Immunohistochemistry staining studies revealed keratin immunostaining of tumour cells in two cases and staining for neuron-specific enolase in the third. The third case also exhibited a few dense neurosecretory granules at the ultrastructural level. Although no strong conclusions regarding histogenesis could be drawn, Tetu et al. [12] stated that the study indicated that small cell carcinoma of the kidney does exist and does not necessarily exhibit a neuroendocrine differentiation. Tetu et al. [12] recommended that small cell carcinoma of the kidney should be considered in the differential diagnosis of malignant renal tumour, especially in cases in which a large necrotic tumour is present. Based on the few cases presented in their study and on the one previously reported case, small cell carcinoma of the kidney did appear to be an aggressive tumour.

Guillou et al. [18] stated that primary small-cell carcinomas of the kidney are rare, and that they are locally aggressive, and rapidly fatal neoplasms in elderly people. Guillou et al. [18] reported an example of combined small-cell and transitional cell carcinoma of the renal pelvis in a 71-year-old woman who had a history of smoking heavily. The cells that pertained to the small-cell component were found to be morphologically mostly of an intermediate type. Immunohistochemically, the tumour cells exhibited positive staining with synaptophysin, carcinoembryonic antigen, and epithelial markers (Lu-5, EAB902, EAB903, and cytokeratin 19), and they were also found to contain scanty neurosecretory granules at the ultrastructural level.

Karadeniz-Bilgili et al. [11] reported the Magnetic Resonance Imaging (MRI) findings of Primary Small-Cell Carcinoma of the Kidney (PSCCK) in a 59-year-old female. The tumour appeared as a 16 cm mass which had arisen from the right kidney. The lesion had diminished signal on T1-weighted images and heterogeneous mixed signal on T2-weighted images. The tumour was found to have primarily involved the renal medulla with persistent thin renal cortex. Despite the tumour's large size, no substantial central necrosis was found present. Karadeniz-Bilgili et al. [11] stated that the predominant medullary location and the lack of central necrosis within the large tumour were considered to be features unusual for renal cell carcinoma and that this should raise the suspicion of another malignancy, the differential diagnosis of which should contain extrapulmonary small-cell carcinoma of the kidney.

Guo et al. [16] studied the clinicopathological features and histologic differential diagnosis of small cell neuroendocrine carcinoma (SmCC) of kidney. Guo et al. [16] retrospectively reviewed the clinicopathological features of 12 cases of SmCC of kidney which had been encountered during the period from 1999 to 2010. Guo et al. [16] summarized the results as follows:

- Six cases of primary and 6 cases of metastatic SmCC which involved the kidney were identified.
- Amongst the primary renal SmCC, 2 were found to be located within the renal parenchyma and 4 within the renal pelvis.
- Chest X-ray demonstrated negative findings.
- Five of the patients underwent radical nephrectomy.
- Upon macroscopic examination, the tumour was noted to be located centrally around the renal pelvis in 4 cases and peripherally within the renal parenchyma in 1 case. On the other hand, 4 of the 6 cases of metastatic SmCC were discovered during treatment for pulmonary SmCC. Two of these patients had manifested with abdominal pain and visible haematuria, with lung and renal tumour masses identified contemporaneously. The diagnosis of all the 6 cases of metastatic SmCC was confirmed by pathology examination of fine needle aspiration biopsy specimens of the tumours.
- Upon microscopy histopathology examination, pure SmCC was demonstrated in the 2 cases of primary renal parenchymal SmCC and 6 cases of metastatic SmCC. The 4 primary renal pelvic SmCC had coexisted with urothelial carcinoma component.
- Upon immunohistochemistry staining studies of the tumours, all cases had exhibited positive staining for cytokeratin, synaptophysin and CD56. All metastatic cases and 4 primary cases were also positively stained for TTF-1.

- Out of six patients who had primary SmCC two died 4 and 9 months after their operation, and two were alive with a follow-up of 25 and 138 months, respectively. Five out of six cases with metastatic SmCC died 3 months to 8 months after their diagnosis. The other 3 cases were failed to attend for follow-up assessment.

Guo et al. [16] made the ensuing conclusions:

- Both primary and metastatic SmCC could be found within the kidney.
- Even though rare, primary SmCC is located either within the renal parenchyma or within the renal pelvis.
- The diagnosis of SmCC does rely upon morphological examination and immunohistochemical study.
- TTF-1 immunostaining would not reliably distinguish primary from metastatic SmCC in kidney.
- Correlation with clinic-radiological findings and demonstration of coexisting urothelial carcinoma component (if any) is helpful with regard to the delineation of the tumour origin.

Banerji et al. [5] reported a 55-year-old gentleman who had right loin pain for six months. He did not have Lower Urinary Tract Symptoms (LUTS), fever or haematuria. On his assessment he was found to have non-visible haematuria and positive urine cytology. He had ultrasound scan which demonstrated right hydroureteronephrosis and a middle calyceal lesion with perinephric stranding. He also had Computed Tomography (CT) scan which showed a small 15 mm × 15 mm pelvicalyceal lesion, along with a mid-ureteric thickening (Figure 1) and many large para-aortic and inter-aorto-caval lymph nodes that measured 5 cm × 4 cm × 3.5 cm, along with a small thrombus within the renal vein, with extension into the Inferior Vena Cava (IVC). Nevertheless, histology did not demonstrate any tumour thrombus.

A working diagnosis of TCC was made and he then underwent a right retrograde pyelogram, ureterorenoscopy which was ensued by the undertaking of right open nephroureterectomy with a bladder cuff. The Retrograde Pyelogram (RGP) demonstrated a complete cut-off of contrast at the mid-ureter with inability of glide wire to be negotiated beyond it (Figure 2). His Ureterorenoscopy (URS) demonstrated a papillary tumour within the mid-ureter.

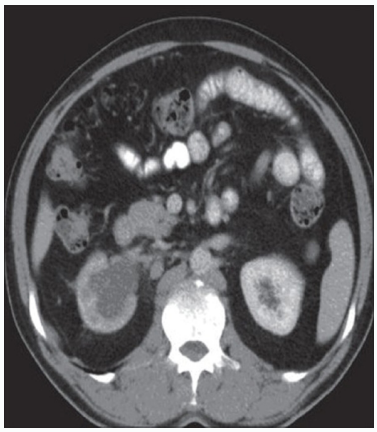

Figure 1: CT showing right hydronephrosis with a small pelvic lesion. Reproduced from: [5] under the creative common's attribution license.

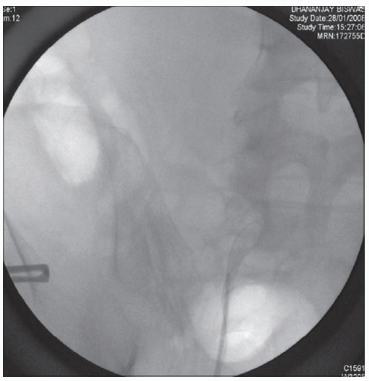

Figure 2: RGP image reproduced from [5] under the creative common's attribution license.

Intraoperatively the mid-ureter was found to be densely adherent to the retroperitoneum and there were large inter-aortocaval and pre-caval nodes, which were also removed.

Upon gross pathology examination, the kidney demonstrated a well-defined tumour in the interpolar region (Figure 3) that measured 1 cm × 1 cm × 2 cm with a firm grey white cut surface and a separate tiny nodule, 0.5 cm, 0.2 cm away from the tumour. The adjacent renal parenchyma did appear to be unremarkable. The ureter was found to contain a tumour (Figure 4) that measured 7 cm × 1 cm × 1.5 cm filling the lumen, 12 cm away from the renal hilum with a similar cut surface. Areas of necrosis and haemorrhage were also found.

The renal pelvis was found to be infiltrated by the tumour which had comprised of dispersed single cells and sheets of small to medium-sized cells with round, hyperchromatic mitotically active nuclei and scant eosinophilic cytoplasm (Figure 5). There were binucleate forms with apoptosis. The tumour cells were found to be separated by fibro-collagenous tissue septa. The tumour was found to be infiltrating the perihilar adipose tissue and renal medulla.

The wall of the ureter was found to be infiltrated by tumour as was described above with areas of necrosis. There were nests of polygonal cells which contained vesicular nuclei, prominent nucleoli and clear cytoplasm (Figure 6). The hilar veins had no histological evidence of tumour thrombus.

Separately sent inter-aortocaval lymph nodes upon examination, demonstrated reactive hyperplasia and no tumour. Immunohistochemistry staining with tumour markers showed cytoplasmic positivity for neuron specific enolase (NSE) and synaptophysin (Figure 7) within the small cell component and the neoplastic cells exhibited negative staining for cytokeratin.

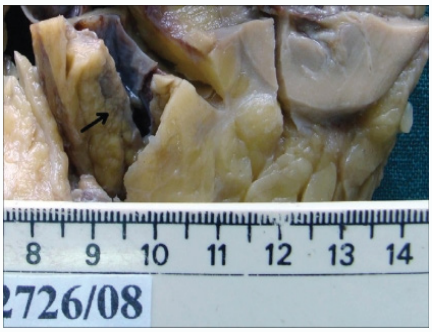

Figure 3: Tumour in the renal pelvis. Reproduced from [5] under the creative common's attribution license.

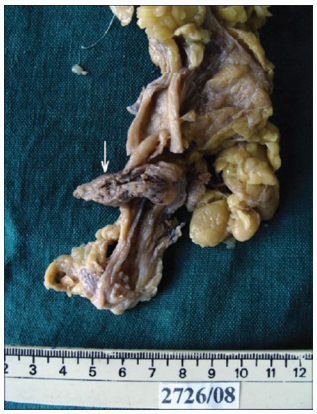

Figure 4: Tumour in the ureter. Reproduced from [5] under the creative common's attribution license.

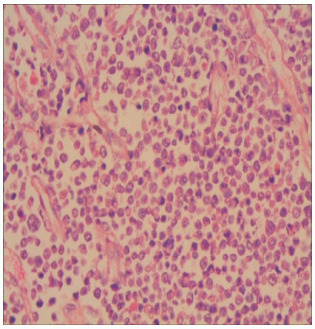

Figure 5: Small cell neuroendocrine tumour in the renal pelvis (H&E, x400). Reproduced from [5] under the creative common's attribution license.

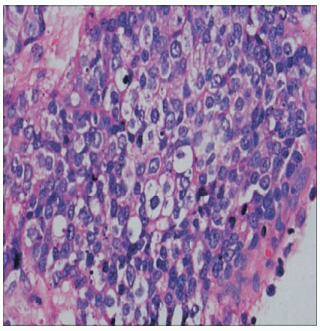

Figure 6: High-grade transitional cell carcinoma in the ureter (H&E, x400). Reproduced [5] under the creative common's attribution license.

Banerji et al. [5] made the ensuing summations:

- Primary malignant small cell neuroendocrine tumours do comprise a group of highly malignant tumours, which hitherto tend to be difficult to characterize, both clinically and upon histopathology examination.
- Neuroendocrine tumours within the urinary tract had been described in the literature and they do range from carcinoid tumours to small cell carcinomas.
- These tumours tend to be more common within the renal pelvis, although there had been reports of neuroendocrine tumours occurring within the renal parenchyma, ureter and urinary bladder [19].

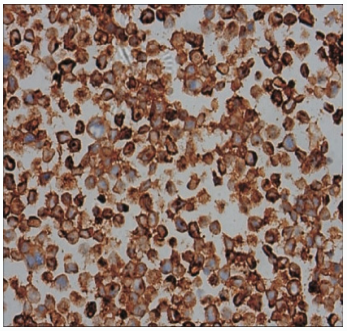

Figure 7: Small cell neuroendocrine carcinoma - tumour cells positive for Synaptophysin (x400). Reproduced from [5] under the creative common's attribution license.

- The histogenesis of these tumours does remain controversial and does warrant further studies. One view is that they are of urothelial origin with neuroendocrine differentiation and the other view is that they do originate from the neuroendocrine cells that present within the renal pelvis.
- Some of the authors had postulated that these tumours do originate from the entrapped neural crest in the kidney during embryogenesis [20].
- These tumours do arise from undifferentiated stem cells with multipotential differentiation towards urothelial or squamous cell lineage and when these elements are present, they tend to be of high grade [21,22].
- This type of tumour is characterized by an aggressive clinical course with the development of early metastasis. The overall survival rate for patients who have small cell carcinoma of the urinary bladder with local disease had been reported as low as 8% [23]. The usual sites of metastasis include the lymph nodes and bone.
- The differential diagnoses do include malignant lymphoma, lymphoepithelioma like carcinoma, plasmacytoid carcinoma, poorly differentiated urothelial carcinoma and primitive neuroectodermal tumour, from which this tumour could be differentiated by utilization of immunohistochemical markers [24].
- Their patient had a tumour within the renal pelvis with a small satellite tumour that was adjacent to it and another tumour within the ureter, both showing histological and immunohistochemical features of neuroendocrine origin. Furthermore, the tumour within the ureter did contain focal nests of high-grade urothelial carcinoma. To their knowledge, their case was the first case in the literature of multicentric high-grade neuroendocrine tumour in the urothelial tract with concomitant high-grade urothelial carcinoma of the ureter.
- It is well known that the kidney could be the site of tumours that have endocrine-paracrine differentiation.
- Tumours of the diffuse endocrine system that are collectively known as carcinoids, had been reported in the literature [25,26].
- It is, nevertheless, much more important to exclude a primary

lung tumour metastasizing to the kidney. Chest X-ray and CT thorax were normal thus ruling out primary pulmonary malignancy.

- The key to the diagnosis of the small cell component is ultrastructure demonstration of secretory neuroendocrine granules and immunohistochemistry staining studies for synaptophysin and neuron-specific enolase.
- In view of the rarity of genitourinary small cell neuroendocrine neoplasms, there are no well-defined protocols for utilization of adjuvant therapy.
- The discussion at the multidisciplinary meeting was that gemcitabine and carboplatin would be offered for six cycles for their patient.
- There had been studies that had proven utilization of carboplatinum, etoposide and vincristine for small cell carcinoma of the lung [27].
- It would be reasonable to expect improved survivals with utilization of platinum-based chemotherapy in combination with irinotecan [28], in view of the fact that there is histological similarity to small cell carcinoma of the lung.

La Rosa et al. [29] iterated that Poorly Differentiated Neuroendocrine Carcinomas (PDNECs) of the kidney are extremely rare high-grade cancers which had accounted for only 42 cases reported in the literature. La Rosa et al. [29] described describe the morphological, immunohistochemical, ultrastructural, and for the first time, cytogenetic features of a renal PDNEC. In addition, La Rosa et al. [29] reviewed the literature and compared the published clinicopathological data with their morphological and genetic results. La Rosa et al. [29] stated that the tumour did arise within the kidney parenchyma and it had showed the typical histological features of a pure small cell PDNEC. Fluorescence *in situ* hybridization study showed a complex chromosomal assessment indicative of a high degree of chromosome instability with gain of multiple chromosomes, loss of p53, and amplification of *myc gene*. La Rosa et al. [29] iterated the following:

- These results had suggested that renal PDNEC has a different genetic background to renal clear cell carcinoma, and it is mainly characterized by the loss of the short arm of chromosome.
- Conversely, genetic alterations do seem to simulate those of type 2 papillary renal cell carcinoma.
- Their review of the literature had demonstrated that PDNECs are associated with poor prognosis and that parenchymal tumours do demonstrate some differences from those arising within the renal pelvis, in that parenchymal tumour are purely neuroendocrine while pelvic tumours tend to be mostly mixed neuroendocrine-exocrine neoplasms.

Morgan et al. [30] described the histological, immunohistochemical, and ultrastructural features of a primary small cell neuroendocrine carcinoma of the renal parenchyma. They iterated that the tumour cells had exhibited positive staining for cytokeratin, neuron-specific enolase, and Leu 7, and they also exhibited negative staining for Grimelius- and chromogranin. They additionally exhibited positivity with anti-MIC2 antibody. By electron microscopy examination, tonofibrils, primitive desmosomes, and dense-core granules with a neuroendocrine appearance were found to be present. Morgan et al. [30] stated that their case was only the 7th recorded example of such a tumour at this site, which showed an aggressive course that was characterized by widespread bony metastases.

Si et al. [9] stated that small cell carcinoma of the kidney is distinctively rare. Si et al. [9] searched pathology files in 2 institutions and they found 14 cases of renal small cell carcinoma. Si et al. [9] summarized the results as follows:

The patients' mean age at diagnosis was 59 years and the ages had ranged between 22 years and 75 years and 8 were women, and 6 were men. Si et al. [9] reported the following results:

- The patients usually manifested visible haematuria in 6 cases, and abdominal pain in 5 cases.
- The mean tumour size was 7.1 cm which ranged between 3.5 cm and 14.0 cm.
- The small cell carcinoma was pure in 9 cases and mixed with high-grade urothelial carcinoma in 5 cases.
- None was associated with any type of renal cell carcinoma.
- Tumour necrosis was present in all cases, and lympho-vascular invasion was identified in 6 cases.
- The tumour had invaded the perinephric adipose tissue in 13 cases and it was confined to the kidney in only 1 case.
- Lymph node metastases were identified in all patients who had undergone lymph node dissection in 5 out 5 cases.
- Upon immunostainings, the small cell carcinoma cells exhibited positive staining for pan-cytokeratin in 11 out of 12, chromogranin in 6 out of 9 cases, and synaptophysin in 8 out of 9 cases.
- Follow-up data were available for 13 patients, and 11 of them died of small cell carcinoma at a mean of 15 months and the time of their death had ranged between 4 months and 31 months after diagnosis of their tumours.
- Out of the 2 surviving patients, 1 was alive at 5 months after diagnosis of the tumour, and the other, whose disease was confined to the kidney, was reported to be alive with no evidence of disease at 137 months.

Si et al. [9] made the ensuing summations:

- Renal small cell carcinoma is a highly aggressive disease which often manifests at an advanced stage with widespread metastases.
- Patients usually tend to have a poor clinical outcome despite multimodal therapy.
- The frequent coexistence of small cell carcinoma with urothelial carcinoma does suggest that renal small cell carcinomas could evolve from a pre-existing urothelial carcinoma.

Lee et al. [31] reported that in July, 2011, a 59-year-old woman, who had undergone kidney transplantation 10 years earlier, had manifested with left flank soreness for several weeks. Following her transplantation surgery, she had regularly taken immunosuppressive agents, which included: tacrolimus, mycophenolate mofetil and

prednisolone. She denied other associated symptoms or signs such as visible haematuria, left flank palpable mass and abdominal pain. She denied any history of smoking. Her routine laboratory examinations, which included renal function tests, were unremarkable. Nevertheless, she had ultrasound scan which showed a left heterogenous kidney tumour and abdominal Computed Tomography (CT) scan which demonstrated a large, complex heterogenous mass with central necrosis occupying the left kidney with no associated retroperitoneal lymphadenopathy. Therefore, renal cell carcinoma was initially suspected (Figure 8). She subsequently had retrograde pyelography which showed a filling defect over the left ureteropelvic junction.

She then underwent left nephroureterectomy with bladder cuff resection. The pathology results were subsequently reported as showing SCC under light microscopic examination and immunohistochemical staining. Light microscopy examination of the tumour also demonstrated that the tumour had comprised of small cells that were round to fusiform in shape with scanty cytoplasm, fine granular nuclear chromatin, absence of nucleoli and high mitotic activity (Figure 9). Immunohistochemical staining studies showed that the tumour cells had exhibited positive staining for chromogranin, synaptophysin, CD56 and Thyroid Transcription Factor-1 (TTF-1) (Figure 10). Metastatic workup which included chest radiograph and bone scan was negative. No primary or metastatic lung lesions were observed. The pathology stage of the tumour was T4N0M0 [American Joint Committee on Cancer (AJCC) stage IV]. She next received a combination adjuvant chemotherapy regimen of carboplatin 450 mg/m^2 and etoposide 100 mg/m^2 every month. At her 8-month postoperative follow-up assessment, the patient demonstrated no recurrent or metastatic disease.

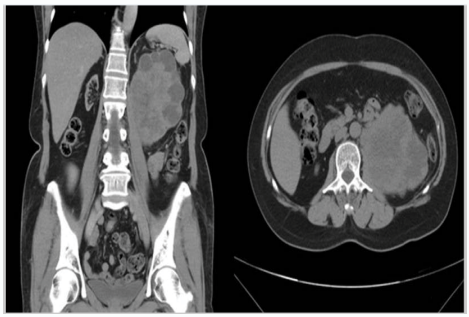

Figure 8: Non-contrast abdominal CT showing a large, complex heterogenous mass with central necrosis originating in the left kidney. Reproduced from [31] under the creative common's attribution license.

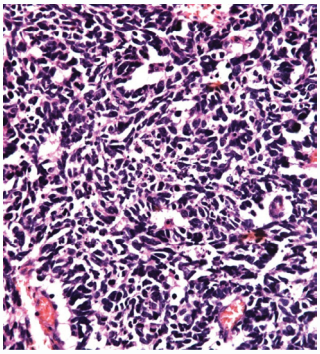

Figure 9: Haematoxylin and eosin staining showing small cells, round to fusiform in shape with scanty cytoplasm, fine granular nuclear chromatin, absence of nucleoli and high mitotic activity (400x). Reproduced from [31] under the creative common's attribution license.

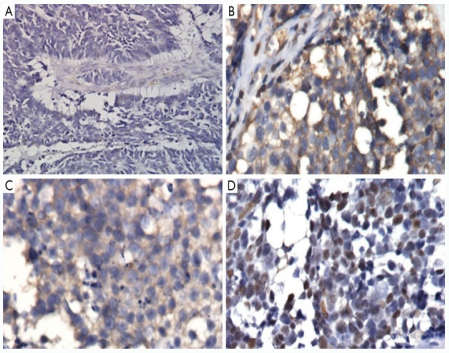

Figure 10: Positive reactions of cancer cells with chromogranin (A): CD56 (B): synaptophysin (C): and TTF-1 (D): revealed by immunohistochemical staining. Reproduced from [31] under the creative common's attribution license.

Lee et al. [31] made the ensuing relevant iterations in their discussion of the case:

- It has been reported that renal SCC does occur at various ages but usually within the sixth decade of life with slightly female predominant, including younger than the age of 40 years [9].
- Therefore, vigilance is required in order to enable early detection of the tumour.
- Unlike SCC of the lung, in which smoking has been confirmed as a risk factor, the specific risk factors for primary renal SCC had remained uncertain. For example, a literature review by Sachin et al. did find out that only 23% of surveyed SCC patients had a history of smoking [32].
- It is difficult to differentiate renal SCC from other kinds of cancers just from clinical manifestations alone.
- The commonest symptoms include flank pain and haematuria. Nevertheless, by the time these clinical symptoms occur, the tumour has tended usually to be already large with evidence of extensive spread or distant metastasis [4].
- In view of the aggressive clinical course of renal SCC with early dissemination and frequent recurrence, the prognosis has tended usually to be poor.
- Based upon these observations, some researchers had concluded that SCC could be associated with a high incidence of occult metastases and even localized disease [4].
- Despite the wide spectrum of methods that are utilized for the diagnosis of SCC, few provide adequate specificity.
- The final results do depend upon pathology and immunohistochemical examination.
- Clinically, radiology image studies, such as ultrasound scan, abdominal Computed Tomography (CT) scan and Magnetic Resonance Image (MRI) scan, have important roles in the detection of the tumour when early-stage SCC is suspected. Since the tumours usually tend to be composed of necrotic areas, they do show predominant hyperechoicity with anechoic areas upon ultrasound scanning, hypo-vascularity with avascular regions on angiography and heterogenous enhanced masses with hypodense areas on abdominal CT [33]. Under MRI scan, renal SCC typically does tend to

demonstrate diminished signals upon T1-weighted images and heterogenous mixed signals on T2- weighted images [11].

- Because primary renal SCC is rare, clinicians need to survey the possibility of metastases from lung which is the most common primary SCC site including chest X-ray or CT.
- Light microscopy examination does show that the tumour is composed of small cells, round to fusiform in shape with scanty cytoplasm, fine granular nuclear chromatin and absent or inconspicuous nucleoli. Mitotic activity also tends to be high [34].
- Immunohistochemistry staining study is an important diagnostic tool, in view of the fact that one or more general neuroendocrine markers such as synaptophysin, Neuron Specific Enolase (NSE) and chromogranin A are positive in SCC [29].
- Like SCC of the lung, renal SCC is staged as either limited or extensive.
- Another useful staging system is the TNM system which was utilized used in their study. Notably, the staging is not associated with survival rate and prognosis.
- Two postulates of the histopathogenesis of urinary tract SCC had been promulgated. One postulate had indicated that it could arise from the neuroendocrine cells within the urinary tract because of immunohistochemical neuroendocrine feature finding. The postulate is that it transforms from pluripotent epithelial reserve cells that are capable of differentiating into various cell types.
- It had been iterated that clinically, SCC of the renal pelvis could coexist with urothelial carcinoma, adenocarcinoma or squamous cell carcinoma [9]. This phenomenon does support the latter postulate [35].
- Renal SCC could be located within the parenchyma or renal pelvis which presents some differences between each other.
- A SCC emerging in the parenchyma is purely a neuroendocrine carcinoma while a SCC emerging in the renal pelvis does occur in combination with non-neuroendocrine carcinoma such as urothelial carcinoma, squamous cell carcinoma or glandular carcinoma [29].
- In their reported case, even though it is difficult to distinguish from parenchyma or renal pelvis origin grossly due to the huge tumour, the pathologist did not discover contemporaneous non-neuroendocrine carcinoma.
- Based upon the above postulate, the renal SCC in their reported case could have originated from parenchyma.
- In view of the rarity of renal SCC and its aggressive characteristics, definitive treatment protocols had not been established. Nevertheless, in view of the fact that surgery alone does not improve upon the survival rate, many clinicians do suggest a multimodality therapy including surgery, chemotherapy and radiotherapy.
- For SCC of lung, a combination of a platinum-based chemotherapeutic agent and etoposide is one of the most utilized regimens. Platinum-based chemotherapy reportedly does tend to achieve a higher survival rate in comparison with other forms of chemotherapy [32].
- The effectiveness of radiotherapy had not been clearly established in view of the widely varying results that had been reported in the literature.
- The most common metastatic or recurrent sites include: bone, liver, lung and brain. Therefore, careful survey of the abdomen, chest and even the brain need to be considered in the follow-up assessments of patients.
- For early diagnosis of metastases, 6 months of close monitoring of patients has been recommended [33].
- According to Sachin et al. immunoreactivity with vimentin and Carcinoembryonic Antigen (CEA) does tend to indicate poor prognosis and development of early metastases with potentially poor survival rate [36,37].
- Even though the precise mechanism is unclear, they hypothesized that their reported patient developed an increased risk of carcinoma formation after taking immunosuppressant for many years.

Lee et al. [31] made the following conclusions:

- Because primary renal SCC does manifest with an advanced tumour stage and a short median survival period, early intervention and close follow-up of the patients are recommended.
- In addition to surgical nephrectomy, utilization of platinum-based chemotherapy has been iterated to be associated with prolonged survival [4].

González-Lois et al. [25] reported a 76-year-old lady who had manifested with a constitutional syndrome of several months' duration that was complicated with visible haematuria during the preceding one month. The patient's medical history was found to be non-contributory. She had ultrasound scan of abdomen which demonstrated a large mass of about 15 cm which had displaced the left kidney. She had a contrast-enhanced computed tomographic scan which showed the mass arising from the posterolateral surface of her left kidney. The tumour had exhibited nonuniform enhancement to a lesser degree in comparison with normal parenchyma and had displayed a central low-density area of necrotic tissue. The interface between the tumour and the encompassing normal renal parenchyma was well defined (Figure 11A).

The tumour was found to exhibit nonuniform enhancement to a lesser degree in normal parenchyma. The central low-density area consists of necrotic tissue (arrows). The interface between the tumour and the surrounding normal renal parenchyma is well defined (arrowheads). (Figure 11B), Macroscopic features of the renal tumour. Note the central necrotic area and the straight limit between the tumour and renal parenchyma. The pelvis is free of involvement. (Figure 11C), the tumour shows a diffuse pattern of growth, which is arranged focally in ill-defined nests surrounded by thin capillary-filled connective tracts. A detailed view of the neoplastic cells shows the tumor's monotonous appearance: round to oval nuclei with inconspicuous nucleoli and granular chromatin ("salt and pepper"); the cells have scanty pale cytoplasm (haematoxylin-eosin, original magnification x400). (Figure 11D), Positive diffuse staining for synaptophysin (original magnification x400).

A left nephrectomy was undertaken with the clinical diagnosis of a primary renal tumour in view of the absence of any other masses in the extension study. Macroscopy pathology examination of the specimen demonstrated that within the left kidney, a mass that measured 15 cm × 5 cm × 2 cm had replaced almost all normal parenchyma and had penetrated the renal capsule. Neither the hilar structures nor the renal pelvis, were involved. The tumour was noted to contain necrotic and haemorrhagic areas (Figure 11B). Microscopy histopathology examination of the specimen showed that the proliferation of tumour was well defined from the parenchyma and had been separated from it by a connective pseudo-capsule. Nevertheless, there were many microscopic demonstrations of capsular and vascular invasion. The tumour grew with demonstration of a predominantly diffuse pattern, that exhibited extensive necrosis, but in other areas it had formed nests encompassed by delicate connective tracts within a neuro-endocrine like or organoid pattern. The tumour comprised of small cells that had a round to fusiform shape, scant cytoplasm, finely granular nuclear chromatin, and absent or inconspicuous nucleoli (Figure 11C). Nuclear moldings were frequently demonstrated, and the mitotic rate was very high. Silver impregnations did not show argyrophilia or argent-affinity. Electron microscopy examination of the tumour did not contribute to the demonstration of the neuroendocrine phenotype of the tumour, likely due to the formalin fixation time. It did demonstrate features of epithelial differentiation, such as abundant well-formed desmosomes. The tumour did not exhibit positive staining for leukocyte common antigen, it did exhibit weak positive staining for cytoplasmic positivity for vimentin and epithelial membrane antigen, and had displayed strong positivity for AE1-AE3, CAM 5.2, neuron-specific enolase, synaptophysin (Figure 11D), and chromogranin. Flow Cytometry studies had demonstrated DNA analysis which showed an aneuploid peak with a quotient between the G1 phases of both cell populations of 1.61 and an S-phase fraction of aneuploid population of 12.5%. The variation coefficients were 7.54 and 8.85 for the G1 phases of diploid and aneuploid populations, respectively. Twenty-seven months after surgery, the patient was alive and free of tumour. González-Lois et al. [25] made the ensuing summations:

- Small cell carcinomas are mainly misdiagnosed as other small round cell tumours including: neuroblastoma, Ewing sarcoma, embryonal rhabdomyosarcoma, and lymphoma.
- The differential diagnosis was made with the first 3 entities by the age of the patient and with the last by immunohistochemical staining features.
- Even though not all SCCs do express epithelial markers, they do react strongly with CD56 and the leukocyte common antigen expression was negative. Nevertheless, has been iterated that it is much more important always to exclude the existence of a primary lung tumour metastatic to the kidney [38].
- Genitourinary SCCs had been reported more often within the prostate gland and urinary bladder; however, they are very rare within the kidney; and less than 30 cases had been reported in the literature up to the time of publication of their article.
- In 8 previously reported cases the tumour had lacked associated features of a transitional or even squamous component of the tumour.
- The 9 patients including their reported case were 37 years to

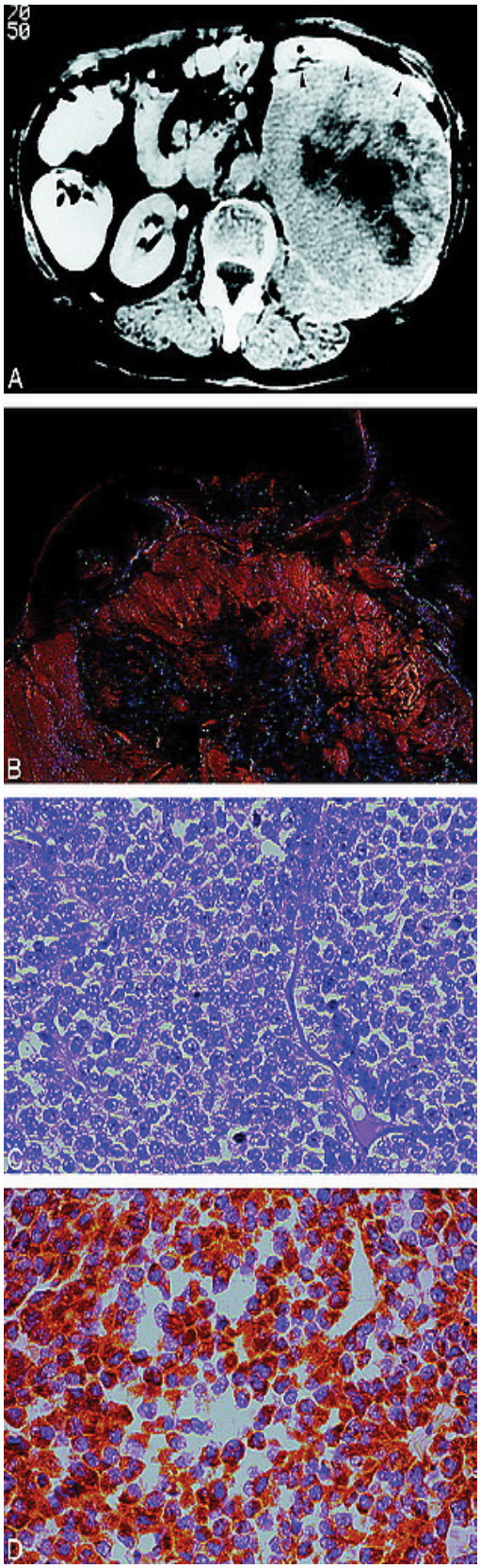

Figure 11: Contrast-enhanced computed tomographic scan shows a large mass arising from the posterolateral surface of the left kidney. The kidney is displaced anteromedially (asterisk). Reproduced from [25] under the creative common's attribution license.

83 years old and their median age was 63.2 years, and 6 of the patients that amounted to 75% of the 8 cases were women and 2 cases that amounted to 25% of the cases were men and in 1 case this information was not available. The median greatest size of the tumours in these cases was 10.9 cm.

- It has been well known that the kidney could be the site of tumours that have endocrine-paracrine differentiation.
- Juxtaglomerular cell tumours with renin secretion and tumours of the diffuse endocrine system, collectively known as carcinoids, had been reported in the literature.
- The previously reported cases had generally involved middle-aged women who had manifested clinically with a constitutional syndrome and renal haematuria, and who had a large mass that measured more than 10 cm and often had metastasis at the time of their diagnosis.
- Small cell carcinoma which had occurred within in the lung or at any other location has tended usually to be a lethal tumour with only a few months of life expectancy. Thus, it does seem very important to analyse tumour features of SCC as related to patient outcome, for example, cellular proliferation markers (Ki-67, p53) or DNA cytometric analysis.
- Even though lung SCCs had been studied briefly by cytometric analysis in a large series [39], these methods had been found to be inapplicable upon endoscopy or cytological specimens. Small cell carcinomas had been studied by these means in many other locations, for example, hypercalcaemic SCC of the ovary which had diploid DNA pattern when it is more aggressive) [40].
- DNA ploidy of SCCs had also been studied within the digestive tract and aneuploidy was found in half of the cases [41], in 5 of 8 cases within the ovary [42], and finally within the cervix, aneuploidy was considered to be a constant feature in cervical SCC) [43].
- In view of the rarity of genitourinary SCC, treatment protocols had not been performed.
- The largest series in the world literature that included 106 genitourinary SCCs, 8 of renal location, had concluded that radical surgery and cisplatin chemotherapy had correlated with improved survival rates and also that the only predictor for poor outcome was metastatic disease at presentation [17].
- In their case, there was no metastasis at manifestation, and this finding had correlated with a long survival time of 27 months.

González-Lois et al. [25] concluded that they had presented an extraordinary case of primary SCC of the kidney and that the clinicopathological features of their case were similar to the 8 previously reported cases they had reviewed.

Teegavarapu et al. [10] made the ensuing iterations:

- Renal Neuroendocrine Tumours (NET), that comprise of carcinoid tumours and small cell carcinomas, are a rare group of neoplasms.
- The rarity of these tumours does pose a diagnostic and therapeutic challenge.
- Their purpose was to characterize the cases that had been treated within a tertiary cancer centre and to evaluate patients' outcomes with the available treatment modalities.

Teegavarapu et al. [10] undertook a retrospective study of patients who had renal NET and who were seen at The University of Texas MD Anderson Cancer Centre between January 1, 2001, and January 1, 2011. The patient and tumour data were analysed by descriptive statistical methods. Teegavarapu et al. [10] summarized the results as follows:

- Three cases of carcinoid tumours and six cases of small cell carcinoma were identified.
- The median age at diagnosis was 53 years for patients who had carcinoid tumours and 65 years for patients who had small cell carcinoma.
- The most common manifesting symptoms included: back pain, flank pain, and haematuria.
- The morphological appearance of the tumour cells and their immunohistochemical reactivity for neuroendocrine markers and cytokeratin had helped establish the diagnosis.
- Nephrectomy was the mainstay of treatment for the carcinoid tumours, which yielded good long-term results, even in the presence of metastases.
- Surgery and chemotherapy were used as treatment for small cell carcinoma of the kidney. The median overall survival for patients who had small cell carcinoma of the kidney was 17.3 months.

Teegavarapu et al. [10] made the ensuing conclusions:

- Renal carcinoid tumours are indolent and they tend to be associated with prolonged survival, while small cell carcinomas of the kidney are aggressive tumours that are associated with relatively short overall survival.
- Even though palliative in nature, cytotoxic chemotherapy is the mainstay of therapy and is best given prior to the undertaking of surgery.

Badiu et al. [44] stated the following:

- Neuroendocrine renal carcinoma does represent less than 1% of all primary tumours of the kidney.
- Most frequently poorly differentiated carcinoma has tended to be diagnosed in advanced stages and they have tended to portend an aggressive evolution and limited survival rate.
- Neuroendocrine carcinomas that arise from the renal pelvis tend to be frequently associated with squamous cell carcinoma or adenocarcinoma.

Badiu et al. [44] reported the case of a 65-year-old female patient, who was known for 3 years before with an undefined retroperitoneal lymph node metastasis, which had been diagnosed at the time of the case as a left large cell neuroendocrine renal carcinoma, who initially had lymph node metastasis. They stated that until the report of their case, 118 cases of primary neuroendocrine renal carcinomas had been reported. A limited number of poorly differentiated neuroendocrine carcinomas had been reported. Badiu et al. [44] stated the following:

- Due to the clinical and biological findings, the aggressive

evolution with early metastasis of lung and bone, their patient was included in the group of poorly differentiated carcinomas.

- In these cases, multimodal treatment was a gold standard.
- Following surgical treatment and palliative chemotherapy with platinum salts, they had obtained a partial remission of the disease and the control of symptoms in their 65-year-old female patient.

Badiu et al. [44] concluded that regarding large cell neuroendocrine carcinoma, the surgical treatment remains the treatment of choice. Chemotherapy can determine limited results, improve the quality of life and enhance the overall survival rate.

La Rosa et al. [29] stated the following:

- Poorly Differentiated Neuroendocrine Carcinomas (PDNECs) of the kidney are very rare high-grade cancers which had accounted for only 42 cases reported in the literature.
- In their article, they had described the morphological, immunohistochemical, ultrastructural, and for the first time, cytogenetic features of a renal PDNEC. In addition, they had reviewed the literature and compared the published clinicopathological data with our morphological and genetic results.
- The tumour arose within the kidney parenchyma and had shown the typical histological features of a pure small cell PDNEC.
- Fluorescence in situ hybridization study had illustrated a complex chromosomal assessment indicative of a high degree of chromosome instability with gain of multiple chromosomes, loss of p53, and amplification of *myc gene*.
- These results had suggested that renal PDNEC has a different genetic background to renal clear cell carcinoma, and this is mainly characterized by the loss of the short arm of chromosome 3. Conversely, genetic alterations seem to simulate those of type 2 papillary renal cell carcinoma.
- Their review of the literature had demonstrated that PDNECs tend to be associated with poor prognosis and that parenchymal tumours do demonstrate some differences from those arising within the pelvis, in that parenchymal tumours are purely neuroendocrine while pelvic tumours tend to be mostly mixed neuroendocrine-exocrine tumours.

Si et al. [9] stated that small cell carcinoma of the kidney is very rare. Si et al. [9] searched pathology files in 2 institutions and found 14 cases of renal small cell carcinoma. The patients' mean age at diagnosis was 59 years and the ages had ranged between 22 years and 75 years; 8 of the patients were women, and 6 were men. The patients usually had manifested with visible haematuria in 6 cases and abdominal pain in 5 cases. The mean tumour size was 7.1 cm and the tumour size had ranged between 3.5 cm and 14.0 cm. The small cell carcinoma was pure in 9 cases and mixed with high-grade urothelial carcinoma in 5 cases. None of the tumours was associated with any type of renal cell carcinoma. Tumour necrosis was present in all cases, and lympho-vascular invasion was found in 6 cases. The tumour had invaded the perinephric adipose tissue in 13 cases and the tumour was confined to the kidney in only 1 case. Lymph node metastases were found in all patients who had undergone lymph node dissection in 5 out of 5 cases. Upon immunohistochemistry staining, the small cell carcinoma cells had exhibited positive staining for pancytokeratin in 11 out of 12 cases, chromogranin in 6 out of 9 cases, and synaptophysin in 8 out of 9 cases. Follow-up data were available for 13 patients, and 11 died of small cell carcinoma at a mean of 15 months and the time of death had ranged between 4 months and 31 months, after diagnosis of the tumours. Of the 2 surviving patients, 1 was alive at 5 months after diagnosis, and the other, whose disease was confined to the kidney, was alive with no evidence of disease at 137 months. Si et al. [9] made the ensuing summations:

- Renal small cell carcinoma is a highly aggressive disease that often manifests at an advanced stage with widespread metastases.
- Patients usually tend to have a poor clinical outcome despite multimodal therapy.
- The frequent coexistence of small cell carcinoma with urothelial carcinoma does suggest that renal small cell carcinomas could evolve from a pre-existing urothelial carcinoma.

Majhail et al. [4] reported two patients who had small cell carcinoma of the kidney and had provided a systematic review of the literature to detail the clinical characteristics and therapy of this rare tumour. Majhail et al. [4] undertook a MEDLINE and CANCERLIT literature search from 1966 to 2002 for articles on small cell carcinoma of the kidney. They reviewed twenty-two patients with small cell carcinoma of the kidney and renal pelvis. Majhail et al. [4] summarized the results as follows:

- The median age at diagnosis of the patients was 62 years and there was a female preponderance (male to female ratio, 1:3.4).
- Abdominal pain which was reported 70% of cases was the most commonly reported manifestation.
- Distant metastases were found in 32% of the patients at the time of diagnosis.
- Surgery and systemic chemotherapy were the primary treatment modalities utilized in that nephrectomy alone was undertaken in 9 patients; nephrectomy and chemotherapy were utilized in 10 patients; chemotherapy alone was utilized in 3 patients.
- The median survival was 8 months and the survival had ranged between less than 1 month to 101 months.
- The use of platinum-based chemotherapy was predictive of an improved overall survival in that the median survival was 20 months in patients had received a platinum-containing regimen compared with 8 months in those who did not receive platinum; P=0.02).

Majhail et al. [4] made the following conclusions:

- Small cell carcinoma of the kidney is an extremely rare neoplasm that simulates its counterparts arising from the tracheo-bronchial and other extrapulmonary sites in its aggressive behaviour and high propensity for locoregional and distant dissemination.
- Clinical manifestation is usually late in the course of the disease.

- The use of platinum-based chemotherapy had been associated with tumour regression and prolonged survival.

Makito et al. [45] reported a 47-year-old man who had a retroperitoneal tumour that measured 18 cm in maximum diameter of the left kidney which was diagnosed with Computed Tomography (CT)-guided needle biopsy as small cell carcinoma. Microscopy immunohistochemistry staining examination of the biopsy specimens showed the tumour cells that exhibited immunohistochemical reaction for neural cell adhesion molecule antibodies. The patient who had advanced renal small cell carcinoma and multiple metastatic lesions was treated with utilization of the first-line combination chemotherapy of cisplatin, etoposide and ifosphamide, which was ensued by a partial response of the primary renal tumour and a complete response of his liver metastasis, and with the second-line chemotherapy of cisplatin and irinotecan, which demonstrated a complete response of Virchow's nodal metastasis. Thereafter, in spite of salvage chemotherapy with utilization of amrubicin hydrochloride for persistent and refractory renal small cell carcinoma, he died 32 months after the first manifestation as a result of local progression. Nevertheless, combination chemotherapy of these anticancer agents had made his prognosis more favorable than was expected before his treatment. Makito et al. [45] made the ensuing iterations:

- The extrapulmonary small cell carcinomas have generally been known to be more aggressive and malignant in comparison with the lung small cell carcinomas, and small cell carcinoma that arises from the kidney is an extremely rare malignant neoplasm, with only 34 cases reported in the English or Japanese literature at the time of publication of their article.
- The prognosis of renal small cell carcinomas at the time of publication of their article was limited as compared with the lung small cell carcinomas, and therefore a cumulative investigation of a larger number of cases that are treated with multidisciplinary modalities including combination chemotherapy is necessary [1].
- Up to 5% of all small cell carcinomas do tend to develop at extrapulmonary sites.
- Primary small cell carcinomas that originate within the kidney are extremely rare tumours.
- They had reported a case of primary small cell carcinoma of the kidney.
- A nephrectomy was undertaken on a 52-year-old female patient in order to remove a large tumour that was located within the right kidney.
- The histology and immunohistochemistry studies of the resected tumour demonstrated a pure small cell carcinoma with invasion into the renal capsule.
- The patient did receive post-operative adjuvant chemotherapy with etoposide and cisplatin.
- The patient was monitored with regular check-ups and he had remained stable with no recurrence at 28 months after the initial diagnosis of his tumour.

Lee et al. [33] stated that primary Small Cell Carcinoma (SCC) of the kidney is uncommon, and the factors that are associated with the survival of these patients were yet to be elucidated. Lee et al. [33] collected data on patients who were admitted to their hospital for SCC of the kidney over the preceding 22 years and of those in studies in the literature. Lee et al. [33] summarized the clinical characteristics with utilization of descriptive statistics. The associations of these factors with survival were evaluated by Lee et al. [33] utilizing Cox regression models, and the hazard ratio of death was calculated. Lee et al. [33] summarized the results as follows:

- This study had included 45 patients of whom 8 patients were admitted to their hospital and 37 patients from studies in the literature who had SCC of the kidney.
- The overall median survival time was 9.9 months and the survival time had ranged from 6.9 months to 31.6 months.
- Data on demographics, clinical symptoms, tumour staging, and tumour characteristics recorded at the time of diagnosis were found not to be associated with survival.
- Among the different treatment modalities that were applied, cisplatin-based chemotherapy had afforded a strong survival advantage (hazard ratio=0.35, p=0.022).
- However, patients who had early local recurrence (hazard ratio=19.13, p=0.012) and early distant metastasis (hazard ratio=10.93, p=0.003) after primary treatment demonstrated significantly poor survival.

Lee et al. [33] made the ensuing conclusions

- Patients who had primary SCC of the kidney manifested presented with large, advanced-stage tumours and they showed poor survival.
- Early detection of the tumour, utilization of cisplatin-based chemotherapy, and careful follow-up for local recurrence or frequent metastasis within 6 months pursuant to the primary treatment might be important for improving the overall patient survival.

Radhi et al. [46] reported a 34-year-old Bahraini lady, who had a three-month history of generalized body aches, night fever and left flank pain. She had CT scan of abdomen which showed a left renal mass. On September 20, 2000, the patient underwent left radical nephrectomy. During the operation, an extensive, left renal tumour, which was predominantly medullary and hilar in location with extension into the inferior vena cava and which had involved the hilar nodes, was excised. The left nephrectomy specimen was found to contain a tumour that measured 13 cm × 10 cm × 8 cm which was predominantly occupying the renal pelvis and which had infiltrated the upper pole of the kidney. The tumour was noted to be soft, uniformly grey-white coloured and it showed areas of necrosis as well as haemorrhage. The cortex was observed to be clearly demarcated and distinctly discernible at many points. The renal vessels and perinephric fat were observed to be infiltrated by the tumour. Formalin fixed, paraffin embedded tissue sections of the tumour were stained with haematoxylin and eosin, Periodic Acid Schiff (PAS), and Mason Fontana's silver stain. Many sections were submitted for immunohistochemistry staining studies with tumour markers, which included Carcinoembryonic Antigen (CEA), desmin, S100, monoclonal Neuron Specific Enolase (NSE), Leukocyte Common Antigen, (LCA), cytokeratin and Epithelial Membrane Antigen (EMA). Sections from different sites of the tumour demonstrated similar findings. The lesion was found to be composed of infiltrating round, oval or small spindle-cells with scanty

cytoplasm and dark nuclei. Within some areas of the tumour, broad bands of collagen had separated the sheets of cells, while in other areas the cells were noted to be closely packed with no appreciable stroma. The cells contained prominent nucleoli and frequent mitosis at 10-15/High Power Fields. Wide areas of haemorrhage and necrosis were observed and no recognizable structures of identifiable mesenchymal elements were visualized. The tumour had extended into the perinephric fat and had involved the renal vessels. Special stains and immunohistochemistry staining studies of the tumour had revealed acid Schiff positive cytoplasm, argyrophilic granules, and positive S100 and NSE reactions. Other tumour markers were noted to be negative for the tumour including CEA, cytokeratin, EMA, Desmin, and LCA. One month subsequently, the patient was read-mitted because of haemoptysis and pain in the left lower extremity. She had CT scans, which demonstrated liver metastases, retroperitoneal lymphadenopathy, small left pleural effusion and few ill-defined pulmonary lesions. She had isotope bone scan, which showed bone metastases. She had routine complete haematology blood tests which showed normocytic normochromic anaemia. She also had biochemistry blood tests, which showed total proteins 76 g/l, albumin 21 g/l, globulins 55 g/l, total bilirubin 19 μmol/l, alkaline phosphatase 563 U/l, gamma glutamyl transpeptidase 851 U/l, calcium 2.87 mmol/l, phosphorus 1.5 mmol/l, magnesium 0.76 mmol/l and urea 9.7 mmol/l. The results of her plasma creatinine and electrolytes were within normal limits. During her admission, she received two cycles of chemotherapy: combination of vincristine, Adriamycin and cyclophosphomide. Her general condition remarkably improved and the haemoptysis and her leg-pains disappeared.

Ouzzane et al. [47] reported two cases of small cell carcinoma of the urinary tract and they performed a systematic literature search from 1970 to 2010 for articles on UUT-SCC. They reported that they had reviewed overall, 40 patients with UUT-SCC and they had generated a database to analyse the clinical characteristics, pathological features and therapy outcomes and to attempt the identification of prognostic factors. Ouzzane et al. [47] summarized the results as follows:

- For the 39 cases that had available data, the median age was 66.5years and male-female ratio was 2:1. An Asian ethnic background was more common with 59% Asian ethnic involvement.
- Surgery was utilized as the standard treatment given to all patients.
- In 67% of the cases, SCC was found to have coexisted with another malignant component, including urothelial carcinoma in 62% of the patients.
- The overall median survival was 15months and the 1-, 2- and 3-year survival rates were noted to be 58.4%, 38.1% and 23.8%, respectively.
- Of all cases, 53.8% of the patients had developed detectable metastasis in a median delay of 13 months.
- The pathological stage of the tumour was the only significant prognostic factor that was found (p=0.01).
- The patients who had received adjuvant chemotherapy seemed to have a higher median survival comparatively to those who did not receive chemotherapy but this was found not to be statistically significant (24 *vs.* 12 months, p=0.56).

Ouzzane et al. [47] made the ensuing conclusions:

- UUT-SCC is an extremely rare tumour, which is characterized by an aggressive clinical course.
- Local or distant metastases are frequent and the survival is poor.
- Pathological stage had appeared to be a prognostic factor for the overall survival.

Asmis et al. [48] reviewed patients who had Genitourinary (GU) Small Cell Carcinoma (SCC) treated at a regional cancer centre, in view of its rarity and aggressive nature, as well as GU SCC had remained a therapeutic challenge. Asmis et al. [48] reviewed the charts of patients who were managed at a regional cancer centre between 1991 and 2002 for any GU diagnosis was manually in order to identify GU SCC. They extracted the demographic, staging, treatment and outcome data. The Veterans administration small cell lung cancer staging classification of 'limited' or 'extensive' disease was adapted for SCC of the prostate and bladder (with 'limited' defined as disease localized to the true and false pelvis, and 'extensive' as disease beyond the pelvis. Asmis et al. [48] summarized the results as follows:

- In all, 555, 858 and 5066 new cases of primary renal, bladder and prostate cancer, respectively, had been identified.
- Out of these patients, 22 had GU SCC that included 12 involving the urinary bladder and 10 involving the prostate gland; there were no cases of SCC of the kidney.
- Eight of 12 patients had urinary bladder SCC had limited disease; five of the 12 patients were alive and all of them had limited disease at the time of their diagnosis, and the median survival was 19.8 months. The surviving patients had received similar treatment, with Trans-Urethral Resection of The Bladder Tumour (TURBT), platinum-based chemotherapy, etoposide which had involved 4 cycles to 6 cycles of chemotherapy, and radical radiotherapy which had involved 56 Gy-60 Gy of radiation.
- Two of 10 patients who had SCC of the prostate gland, had limited-stage disease, but all of the 10 patients died, and their median survival was 9.5 months.
- The survival by stage for both types of tumours combined was 59 months for limited disease and 8 months for extensive disease.

Asmis et al. [48] concluded that these results had indicates that GU SCC is an aggressive cancer; limited-stage SCC of the bladder or prostate, when treated with platinum/etoposide chemotherapy and radical radiotherapy, has a more favourable outcome in comparison with that of extensive GU SCC.

Mukesh et al. [49] reported the clinical experience and management of patients who had Small Cell Carcinoma (SCC) of the urinary bladder, who were treated in the Anglia Cancer network from 1992 to 2007, and they reviewed published studies, as SCC in view of the fact that it is a rare condition, accounting for <1% of all bladder tumours, and there was no established treatment strategy for managing these patients. Mukesh et al. [49] analysed retrospectively data from all patients diagnosed who had SCC of the urinary bladder between 1992 and 2007, with an emphasis on stage, treatment and overall survival. Mukesh et al. [49] summarized the results as follows:

- Twenty patients were identified with primary urinary bladder SCC and the male to female ratio was 3:1; the mean age of the patients was 68 years; and the mean follow-up of the patients was 15.8 months.
- Nine patients that amounted 45% of the patients had extensive-stage disease at the time of diagnosis.
- Four patients received best supportive care, three had undergone a radical cystectomy, one patient had radical radiotherapy and six patients underwent sequential chemo-radiotherapy.
- In all, 13 patients were treated with chemotherapy, with six receiving cyclophosphamide, doxorubicin and vincristine, three received carboplatin and etoposide, and the remaining patients received alternative platinum-based regimens.
- For 12 patients who had assessable disease, six patients had a complete response, three patients had a partial response and three patients had progressive disease after chemotherapy. No patient had received prophylactic cranial irradiation (PCI).
- At the time of analysis, 14 patients that amounted to 70% of the patients had died, with one patient that amounted to 5% of the patients developing brain metastasis. The median survival was 33 months for patients receiving chemotherapy in comparison with 3 months with no chemotherapy.

Mukesh et al. [49] made the following conclusions:

- SCC of the urinary bladder does bladder tends to occur in an older population, and more commonly in men.
- SCC of the urinary bladder is an aggressive tumour with a propensity for early metastasis.
- The response rate to chemotherapy is high but the overall prognosis is poor.
- Brain secondaries are less common in comparison with for SCC of the lung and at the time of publication of their article, the role of PCI was unclear.
- As there was no standard of care for these patients, they were treated according to local protocols.
- Further efforts should be made in order to develop more effective treatments and the role of PCI should be assessed in the setting of a clinical trial, in conjunction with other extrapulmonary SCCs.

Choong et al. [50] iterated that Small Cell Carcinoma (SCC) of the urinary bladder accounts for 0.35% to 0.70% of all urinary bladder tumours and that there was no standard approach to the management of SCC of the urinary bladder. Choong et al. [50] undertook a retrospective study at Mayo Clinic (Rochester, MN) to characterize the clinical and pathologic features of patients with SCC of the urinary bladder diagnosed between 1975 and 2003 with emphasis on management. Choong et al. [50] summarized the results as follows:

- Forty-four patients had been identified who had primary urinary bladder SCC, out of these patients, 61.4% had pure SCC.
- The male to female ratio was 3:1, the mean age of the patients was 66.9 years, and the mean follow-up was 3.2 years.
- Twelve patients that amounted to 27.3% of the patients, had Stage II disease, 13 patients that amounted to 29.6% of the patients, had Stage III disease, and 19 patients that amounted to 43.2% of the patients, had Stage IV disease.
- The overall median survival of the patients was 1.7 years.
- The 5-year survival rates for patients who had Stage II, III, and IV disease were 63.6%, 15.4%, and 10.5%, respectively.
- Six of eight patients who had Stage II urinary bladder SCC achieved a cure with radical cystectomy.
- Five patients who had Stage IV disease had obvious metastases and they received chemotherapy.
- Fourteen patients had undergone radical cystectomy and they were diagnosed later with locally advanced disease (T4b) or lymph node metastasis (N1-N3; Stage IV disease).
- Only 2 out of 19 patients who had Stage IV disease who had received adjuvant chemotherapy were alive at 5 years.

Choong et al. [50] made the ensuing conclusions:

- Patients who have urinary bladder SCC should undergo radical cystectomy except when metastatic disease is present (M1), in which case, systemic chemotherapy would be indicated.
- Adjuvant treatment is not indicated for patients who have Stage II disease after radical cystectomy but adjuvant treatment should be considered for patients who have Stage III and IV disease. Chemotherapy should be a platinum-based regimen.

Bex et al. [51] evaluated the feasibility and efficacy of a therapeutic algorithm for the management of small cell carcinoma of the urinary bladder that is derived from the treatment of small cell lung cancer. Bex et al. [51] studied during a 10-year period, 25 patients who comprised of 23 men and 2 women; and whose median age was 64 years, with 8 [32%] older than 75 years) and who had small cell carcinoma of the urinary bladder which were defined as having Limited Disease (LD) or Extensive Disease (ED) in analogy to the classification of small cell lung cancer. Bex et al. [51] stated that patients who had LD were eligible for chemotherapy and sequential radiotherapy. They also stated that patients who were unfit for chemotherapy were offered complete transurethral resection and radiotherapy or cystectomy for large symptomatic tumours. Patients who had ED were offered palliative chemotherapy. Bex et al. [51] summarized the results as follows:

- Out of the 25 patients, 17 patients that amounted to 68% of the patients had LD and 8 patients that amounted to 32% of the patients had ED.
- Without regard to stage, the median survival of those had received chemotherapy was found to be 15 months versus 4 months for those who did not.
- The median survival rate for those who had LD was 12 months versus 5 months for those who had ED.
- Nine patients that amounted to 52.9% of the patients who had LD could not undergo chemoradiotherapy because of comorbidity and reduced performance in 7 patients, progression of the tumour in 1 patient), or drug-related death in 1 patient.

- Five of those patients underwent TUR and radiotherapy and two had undergone cystectomy.

Bex et al. [51] made the ensuing conclusions:

- The prognosis of small cell carcinoma of the urinary bladder is poor.
- This treatment algorithm does offer urinary bladder sparing for most patients, with few long-term remissions in patients who have small, confined tumours.
- None of the patients died of locoregional tumour progression, which had supported that cystectomy is not the treatment of choice for those who have LD.
- With a significant proportion of elderly patients who had comorbidities, chemoradiotherapy was not feasible in more than one half of the patients who had LD.

Mackey et al. [7] assessed the prognostic impact of genitourinary small cell carcinoma tumour and patient characteristics, and therapy. Mackey et al. [7] retrospectively reviewed the records of 180 patients who had genitourinary small cell carcinoma in which patient and tumour characteristics, therapy, follow-up duration and survival status had been documented. Mackey et al. [7] analysed patient age, sex, primary site, histological features, tumour size, stage, locoregional therapy, systemic chemotherapy and hormonal manipulations for association with survival. Mackey et al. [7] summarized the results as follows:

- There were 106 cases of urinary bladder, 60 prostate, 8 renal and 6 ureteral small-cell -carcinoma
- The median survival was 10.5 months overall, and 7 and 13 months for prostate and urinary bladder small cell carcinoma, respectively ($p<0.0001$ log rank analysis).
- In all of the cases, metastatic disease at manifestation ($p<0.008$, risk ratio 1.9) had predicted poor survival on multivariate analysis.
- The undertaking of radical surgery ($p<0.0001$, risk ratio 0.34) and cisplatin chemotherapy ($p<0.0001$, risk ratio 0.20) were the only factors that had predicted improved survival upon multivariate analysis.
- For prostatic small cell carcinoma primary surgical therapy ($p<0.012$, risk ratio 0.46) was found to be the only parameter which had predicted survival upon univariate analysis.
- For urinary bladder small cell carcinoma only cisplatin chemotherapy ($p<0.0001$, risk ratio 0.15) had predicted survival upon multivariate analysis.

Mackey et al. [7] made the ensuing conclusions:

- Genitourinary small cell carcinoma has a poor prognosis, which is worse in prostatic disease in comparison with urinary bladder disease.
- Patient and tumour characteristics were found not to be determinants of survival when prostatic and bladder small cell carcinoma were analysed individually.
- For prostatic disease only primary surgical treatment was found to be associated with prolonged survival, while for bladder disease cisplatin chemotherapy was associated with a favorable prognosis.
- They would recommend considering primary surgical therapy for prostatic and cisplatin-based chemotherapy for bladder small cell carcinoma.

Conclusions

- Primary Small Cell Carcinomas of the Kidney are rare tumours which tend to manifest with an advanced tumour stage and a short median survival period, and hence early intervention and close follow-up of the patients are recommended.
- In addition to surgical nephrectomy, utilization of platinum-based chemotherapy has been iterated to be associated with longer survival in some cases.
- Primary Small Carcinomas of the Urinary Tract are also rare tumours that most often tend to be diagnosed at an advanced stage and these tumours generally have tended to portend an aggressive biological behaviour even though utilization of combination chemotherapy regimens that have been utilized in some cases of locally advanced or metastatic lesions had prolonged survival of some patients but on the whole, no chemotherapy regimen has been found to provide complete destruction and cure of patients who have primary small cell neuroendocrine carcinoma of the kidney and urinary tract.
- Because primary adenocarcinomas of the kidney tend to be more commonly encountered and very small adenocarcinomas tend portend a slow growing biological behaviour, these tumours have tended to be managed in a number of centres by active surveillance with periodic radiology imaging and those tumours that are found to be growing bigger are then treated surgically; nevertheless, if an individual has a small renal mass that is due to small cell carcinoma, this tumour could quickly grow into a locally advanced or metastatic and aggressive tumour over a short period of time. Perhaps if all cases of small kidney tumours are subjected to radiology image-guided biopsies for pathology examination at the initial phase of the active surveillance programme, then few cases of small cell carcinomas would be detected at an early localized stage so that an aggressive nephrectomy procedure could be undertaken to ensure good long-term survival of patients and those patients who have small adenocarcinomas of the kidney could continue with the active surveillance approach.
- Primary small cell carcinomas of the kidney and upper renal tract could be pure small cell carcinomas or they may be contemporaneously associated with other tumours like adenocarcinoma or transitional cell carcinoma and in cases of mixed tumours, the small cell carcinoma components tend to portend a more aggressive biological behaviour.
- Because primary small cell carcinomas of the lung are the most commonly found small cell carcinomas, it is important for all clinicians to undertake full assessment of all their patients who have small cell carcinomas of the kidney and urinary tract to be sure they do not have metastatic tumours from primary tumours of the lung.
- In order to provide effective and curative treatment for patients who have primary locally advanced and metastatic primary small cell carcinomas of the kidney and urinary tract, there is an urgent need for a global multicentre trial of various

chemotherapy regimens as well as development of new chemotherapy medicaments by oncologists, pharmaceutical research workers and scientists that would safely and effectively destroy all small cell carcinomas and small cell neuroendocrine carcinomas of the kidney and urinary tract.

References

1. Chung CH, Park CY. Small cell carcinoma of the kidney. Korean J Intern Med. 2006;21(3):191-3.
2. Kim JH, Lee SH, Park J, Kim HY, Lee SI, Nam EM, et al. Extrapulmonary small-cell carcinoma: a single-institution experience. Jpn J Clin Oncol. 2004;34(5):250-4.
3. Richardson RL, Weiland LH. Undifferentiated small cell carcinomas in extrapulmonary sites. Semin Oncol. 1982;9(4):484-96.
4. Majhail NS, Elson P, Bukowski RM. Therapy and outcome of small cell carcinoma of the kidney: report of two cases and a systematic review of the literature. Cancer. 2003;97(6):1436-41.
5. Banerji JS, Korula A, Panicker JB. Multicentric small cell neuroendocrine neoplasm of the renal pelvis and ureter with concomitant focal high-grade urothelial carcinoma of the ureter: a case report. Indian J Urol. 2008;24(4):571-4.
6. Andeen NK, Tretiakova M. Bladder, ureter & renal pelvis. Neuroendocrine neoplasms. Small cell neuroendocrine carcinoma. Pathologyoutlines. 2022.
7. Mackey JR, Au HJ, Hugh J, Venner P. Genitourinary small cell carcinoma: determination of clinical and therapeutic factors associated with survival. J Urol. 1998;159(5):1624-9.
8. Clark PG. Ethical dimensions of quality of life in aging: autonomy vs. collectivism in the United States and Canada. Gerontologist. 1991;31(5):631-9.
9. Si Q, Dancer J, Stanton ML, Tamboli P, Ro JY, Czerniak BA, et al. Small cell carcinoma of the kidney: a clinicopathologic study of 14 cases. Hum Pathol. 2011;42(11):1792-8.
10. Teegavarapu PS, Rao P, Matrana M, Cauley DH, Wood CG, Tannir NM. Neuroendocrine tumors of the kidney: a single institution experience. Clin Genitourin Cancer. 2014;12(6):422-7.
11. Karadeniz-Bilgili MY, Semelka RC, Hyslop WB, Pamuklar E, Rivero H, Firat Z, et al. MRI findings of primary small-cell carcinoma of kidney. Magn Reson Imaging. 2005;23(3):515-7.
12. Têtu B, Ro JY, Ayala AG, Ordóñez NG, Johnson DE. Small cell carcinoma of the kidney. a clinicopathologic, immunohistochemical, and ultrastructural study. Cancer. 1987;60(8):1809-14.
13. Kuroda N, Imamura Y, Hamashima T, Ohe C, Mikami S, Nagashima Y, et al. Review of small cell carcinoma of the kidney with focus on clinical and pathobiological aspects. Pol J Pathol. 2014;65(1):15-9.
14. Cheng L, Jones TD, McCarthy RP, Eble JN, Wang M, MacLennan GT, et al. Molecular genetic evidence for a common clonal origin of urinary bladder small cell carcinoma and coexisting urothelial carcinoma. Am J Pathol. 2005;166(5):1533-9.
15. Ordóñez NG. Value of thyroid transcription factor-1 immunostaining in tumor diagnosis: a review and update. Appl Immunohistochem Mol Morphol. 2012;20(5):429-44.
16. Guo AT, Huang H, Wei LX. [Pathologic diagnosis and differential diagnosis of small cell neuroendocrine carcinoma of kidney]. Zhonghua Bing Li Xue Za Zhi. 2012;41(8):538-42.
17. Capella C, Eusebi V, Rosai J. Primary oat cell carcinoma of the kidney. Am J Surg Pathol. 1984;8(11):855-61.
18. Guillou L, Duvoisin B, Chobaz C, Chapuis G, Costa J. Combined small-cell and transitional cell carcinoma of the renal pelvis. a light microscopic, immunohistochemical, and ultrastructural study of a case with literature review. Arch Pathol Lab Med. 1993;117(3):239-43.
19. Ibrahim NB, Briggs JC, Corbishley CM. Extrapulmonary oat cell carcinoma. Cancer. 1984;54(8):1645-61.
20. Guy L, Bégin LR, Oligny LL, Brock GB, Chevalier S, Aprikian AG. Searching for an intrinsic neuroendocrine cell in the kidney: an immunohistochemical study of the fetal, infantile and adult kidney. Pathol Res Pract. 1999;195(1):25-30.
21. Raslan WF, Ro JY, Ordonez NG, Amin MB, Troncoso P, Sella A, et al. Primary carcinoid of the kidney: immunohistochemical and ultrastructural studies of five patients. Cancer. 1993;72(9):2660-6.
22. Kim TS, Seong DH, Ro JY. Small cell carcinoma of the ureter with squamous cell and transitional cell carcinomatous components associated with ureteral stone. J Korean Med Sci. 2001;16(6):796-800.
23. Blomjous CE, Vos W, De Voogt HJ, Van der Valk P, Meijer CJ. Small cell carcinoma of the urinary bladder: a clinicopathologic, morphometric, immunohistochemical and ultrastructural study of 18 cases. Cancer. 1989;64(6):1347-57.
24. Parham DM, Roloson GJ, Feely M, Green DM, Bridge JA, Beckwith JB. Primary malignant neuroepithelial tumors of the kidney: a clinicopathologic analysis of 146 adult and paediatric cases from the national Wilm's tumor study group pathology centre. Am J Surg Pathol. 2001;25(2):133-46.
25. González-Lois C, Madero S, Redondo P, Alonso I, Salas A, Montalbán MA. Small cell carcinoma of the kidney: a case report and review of literature. Arch Pathol Lab Med. 2001;125(6):796-8.
26. Unger PD, Russell A, Thung SN, Gordon RE. Primary renal carcinoid. Arch Pathol Lab Med. 1990;114:68-71.
27. Lee YC, McCrystal MR, Christmas TI. Chemotherapy for small cell lung carcinoma: the greenlane hospital experience 1993-1995. NZ Med J. 1998;111(1078):451-2,453-4.
28. Okamoto H, Naoki K, Narita Y, Hida N, Kunikane H, Watanabe K. A combination chemotherapy of carboplatin and irinotecan with granulocyte colony stimulating factor (G-CSF) support in elderly patients with small cell lung cancer. Lung Cancer. 2006;53(2):197-203.
29. Rosa SL, Bernasconi B, Micello D, Finzi G, Capella C. Primary small cell neuroendocrine carcinoma of the kidney: morphological, immunohistochemical, ultrastructural, and cytogenetic study of a case and review of the literature. Endocr Pathol. 2009;20(1):24-34.
30. Morgan KG, Banerjee SS, Eyden BP, Barnard RJ. Primary small cell neuroendocrine carcinoma of the kidney. Ultrastruct Pathol. 1996;20(2):141-4.
31. Lee HY, Wu WJ, Tsai KB, Shen JT, Jang MY, Wang HS, et al. Primary small cell carcinoma of kidney after renal transplantation: a case report and literature review. Chin J Cancer Res. 2013;25(5):608-11.
32. Patil S, Kaza RCM, Kakkar AK, Chamberlain RS. Small cell carcinoma of the renal pelvis: a case report and review of the literature. ISRN Urol. 2011;2011:786505.
33. Lee SY, Hsu HH, Lin HY, Chen YC, Wong YC, Wang LJ, et al. Factors associated with the survival of patients with primary small cell carcinoma of the kidney. Int J Clin Oncol. 2013;18(1):139-47.
34. Martin SM, Gonzalez JRC, Lagarto EG, Arteaga CM, Garcia-Ripoll JRT, del Busto EF. Primary small cell carcinoma of the ureter. Int J Urol. 2007;14(8):771-3.
35. Kho VKS, Chan PH. Primary small cell carcinoma of the upper urinary tract. J Chin Med Assoc. 2010;73(3):173-6.
36. Chuang CK, Liao SK. A retrospective immunohistochemical and clinicopathological study of small cell carcinomas of the urinary tract. Chang Gung Med J. 2003;26(1):26-33.
37. Goslin RH, Skarin AT, Zamcheck N. Carcinoembryonic antigen. a useful monitor of therapy of small cell lung cancer. JAMA. 1981;246(19):2173-6.
38. Rosai J. Respiratory tract. In: Patterson AS, Gery L, Weis CS, Joiner P, Barrett S, Fuchs T, Eds. Ackerman's surgical pathology. 8th ed. St Louis, Mo: Mosby-Year Book Inc. 1996;383-4.
39. Virén MM, Ojala AT, Kataja VV, Mattila JJ, Koivisto PA, Nikkanen VT. Flow cytometric analysis of tumor DNA profile related to response to treatment and survival in small-cell lung cancer. Med Oncol. 1997;14(1):35-8.
40. Eichhorn JH, Bell DA, Young RH, Swymer CM, Flotte TJ, Preffer RI, et al. DNA

content and proliferative activity in ovarian small cell carcinomas of the hypercalcemic type. Implications for diagnosis, prognosis, and histogenesis. Am J Clin Pathol. 1992;98(6):579-86.

41. Kimura H, Konishi K, Maeda K, Yabushita K, Tsuji M, Miwa A. Highly aggressive behavior and poor prognosis of small-cell carcinoma in the alimentary tract: flow-cytometric analysis and immunohistochemical staining for the p53 protein and proliferating cell nuclear antigen. Dig Surg. 1999;16(2):152-7.

42. Eichhorn JH, Young RH, Scully RE. Primary ovarian small cell carcinoma of pulmonary type. A clinicopathologic, immunohistologic, and flow cytometric analysis of 11 cases. Am J Surg Pathol. 1992;16(10):926-38.

43. Miller B, Dockter M, el Torky M, Photopulos G. Small cell carcinoma of the cervix: a clinical and flow-cytometric study. Gynecol Oncol. 1991;42(1):27-33.

44. Badiu CD, Nita GR, Ciuhu AN, Manea C, Smarandache CG, Georgescu DG, et al. Neuroendocrine renal carcinoma - therapeutic and diagnostic issues. Acta Endocrinol (Buchar). 2016;12(3):355-61.

45. Miyake M, Fujimoto K, Tanaka M, Matsushita C, Tanaka N, Hirao Y. A case of small cell carcinoma of the kidney. Hinyokika Kiyo. 2007;53(4):235-40.

46. Radhi A, Ratnakar KS, Durazi MA, Khalifa F. Primitive neuroectodermal tumor or small cell carcinoma of the kidney, a rare neoplasm: case report. Saudi J Kidney Dis Transpl. 2002;13(4):506-10.

47. Ouzzane A, Ghoneim TP, Udo K, Verhasselt-Crinquette M, Puech P, Betrouni N, et al. Small cell carcinoma of the upper urinary tract (UUT-SCC): report of a rare entity and systematic review of the literature. Cancer Treat Rev. 2011;37(5):366-72.

48. Asmis TR, Reaume MN, Dahrouge S, Malone S. Genitourinary small cell carcinoma: a retrospective review of treatment and survival patterns at the Ottawa hospital regional cancer center. BJU Int. 2006;97(4):711-5.

49. Mukesh M, Cook N, Hollingdale AE, Ainsworth NL, Russell SG. Small cell carcinoma of the urinary bladder: a 15-year retrospective review of treatment and survival in the anglian cancer network. BJU Int. 2009;103(6):747-52.

50. Choong NWW, Quevedo JF, Kaur JS. Small cell carcinoma of the urinary bladder the mayo clinic experience. Cancer. 2005;103(6):1172-8.

51. Bex A, Nieuwenhuijzen JA, Kerst M, Pos F, van Boven H, Meinhardt W, et al. Small cell carcinoma of bladder: a single-center prospective study of 25 cases treated in analogy to small cell lung cancer. Urology. 2005;65(2):295-9.