



Primary Small Cell Carcinoma of the Kidney: A Review of the Literature

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ABSTRACT

Primary small cell carcinoma of the kidney is an extremely rare neoplasm. Less than 100 cases of primary small cell carcinoma of the kidney have so far been reported in the literature. In view of this most practitioners globally would not be accustomed to the biological behaviour of this neoplasm. There is therefore the need to review the literature on primary small cell carcinoma of the kidney. To review the literature on primary small cell carcinoma of the kidney, various internet search engines were used to form a foundation for the literature review including: Google; Google scholar; educus; Up To Date; Pub Med. The median age at diagnosis of small cell carcinoma of the kidney was 62 years and there was a female preponderance. Abdominal pain and haematuria are common symptoms of small cell carcinoma of the kidney. At the time of initial diagnosis slightly less than a third of the patients have distant metastasis. Surgery in the form of nephrectomy and systemic chemotherapy, have been the main forms of treatment modalities which include: nephrectomy alone; nephrectomy and chemotherapy; chemotherapy alone. The median survival in one series was about 8 months and this has ranged on the whole from between 1 month to 101 months. In another series the overall median survival was 9.9 months (range 6.9 to 31.6 months). Data on demographics, clinical symptoms, tumour staging and tumour characteristics recorded at the time of diagnosis was not found to be related to survival. The use of cisplatin-based chemotherapy was in some cases observed to be predictive of better overall survival. Small cell carcinoma of the kidney is an extremely rare neoplasm which mimics small cell carcinoma of the tracheobronchial tree and other extra-pulmonary sites, its aggressive biological behaviour and its high ability to result in the development of loco-regional and distant dissemination. The development of symptoms or clinical presentation tends to be usually late in the course of the disease. Utilization of platinum-based chemotherapeutic regimen has been found to be associated with tumour regression and prolonged survival. Small cell carcinomas of the genitourinary tract have been more commonly reported in the urinary bladder in comparison with primary small cell carcinoma of the kidney which is very rare. In view of the rarity of primary small cell carcinoma of the kidney its natural history, diagnosis and management is not well known. Despite the use of cisplatin-based chemotherapeutic regimen in the treatment of small cell carcinoma of the kidney there is not enough documentation of any treatment modality that would prolong life for a very long time. There is therefore the need for Urologists and oncologists throughout the world to come together in order to undertake a multicentre trial of chemotherapeutic modalities in the management of small cell carcinoma of the kidney in order to find ways of further improving the prognosis of such a rare carcinoma.

Key Words: Small-cell carcinoma, Kidney, Nephrectomy, Cisplatin-based-chemotherapy

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Introduction

Small cell carcinoma is a malignant neoplasm which is composed of small cells which have a diffuse growth pattern. Small cell carcinoma has the immunohistochemical and ultra-structural characteristics of both neuro-endocrine and epithelial cells. Small cell carcinomas comprise of 10% to 20% of malignant neoplasms of the lung, which is the most frequent site where such tumours are found. Small cell carcinomas have been described in extra-pulmonary sites and less than 100 cases of primary small cell carcinomas of the kidney have been reported.

Small cell carcinoma has been defined as a high-grade epithelial neoplasm with neuro-endocrine -differentiation at both immunohistochemical and ultra-structural levels. [1] The

constituent tumour cells in small cell carcinomas tend to be less than 3 times the size lymphocytes, their nucleoli are inconspicuous, and they tend to have scant cytoplasm. Mitotic activities in small cell carcinomas are quite often high. [2] From time to time primary small cell carcinomas affecting extra-pulmonary sites are being reported. This paper has reviewed the literature on small cell carcinomas of the kidney that have so far been reported.

Literature Review Incidence

Most of the small cell carcinomas that are encountered in medical practice arise in the tracheobronchial tree and the occurrence of small cell carcinoma in the urinary tract is rare, occurring at a rate of 0.48% in the urinary bladder. [3] A number of authors [4] [5] [6] [7] [8] [9] [10] stated that extra-pulmonary small cell carcinomas have been reported increasingly, perhaps as a result developments in immunohistochemical staining techniques, but those involving the kidney are still rare and by 1997 only 10 known cases of small cell carcinoma of the kidney had been reported.

Extrapulmonary small cell carcinomas have been reported in various organs, inclusive of the oesophagus, stomach,

pancreas, gallbladder, uterine cervix, kidney, urinary bladder and prostate and also in the upper urinary tract [12], [13], [14], [15], [16], as well as concurrently in the urinary bladder and ureter. [17] Extra-pulmonary small cell carcinoma was first described by Duguid and Kennedy in 1930 [18]. To the knowledge of the author less than 50 cases of small cell carcinoma of the kidney have so far been reported in the literature. Gonzalez-Lois and associates reported the 9th case of small cell carcinoma of the kidney in 2001 [1] Cheng and associates [19] reported the 21st case of small-cell carcinoma of the kidney in 2011.

Presentation

Patients with small cell carcinoma may present with haematuria [1] [19] [20] [21], loin pain [19] [21], abdominal pain [20], iron deficiency anaemia [21] Cheng and associates [19] stated that the clinical symptoms of a renal small cell carcinoma are not distinguishable from those of renal cell carcinoma. Other authors [11] [18] [22] stated that abdominal pain and haematuria are the most common clinical features. A number of authors [11] [18] iterated that:

- The biological behaviour of this rare tumour seems quite aggressive
- Early dissemination and frequent recurrences are common in small cell carcinomas of kidney
- About 32% of patients had distant metastasis at the time of initial diagnosis of small cell carcinomas of the kidney [11] [18].

Radiological investigations

Some of the radiological investigations that have been used to identify a renal mass in the investigation of small cell carcinoma of the kidney include: ultrasound scan of renal tract / abdomen and pelvis [1] computed tomography scan of abdomen and pelvis [1], [19]. [21] These scans tend to reveal a heterogeneous renal tumour mass. These radiological investigations would only confirm the presence, nature, and size of the tumour as well as presence or absence of lymph node enlargement, metastatic masses (see figure A which shows an example of a contrast-enhanced computed tomography scan of a reported small cell carcinoma of the left kidney).

Cheng and associates [19] recommended that:

- Imaging studies including chest X-ray, and chest and abdominal computed tomography (CT) scan should be carried out but it is still difficult to distinguish small cell carcinoma of the kidney from renal cell carcinoma.
- A whole-body bone scan should also be done to detect early dissemination Karadeniz-Bilgili and associates [23] stated that:
- Magnetic resonance imaging of extra-pulmonary small cell carcinoma shows a diminished signal on T1-weighted images and a heterogeneous mixed signal on T2-weighted images.
- The predominant medullary location and lack of central necrosis constitute features of extra-pulmonary small cell carcinoma, which are unusual for renal cell carcinoma.

Diagnosis

Diagnosis of small cell carcinoma of the kidney is usually established following microscopic histological examination as well as immunohistological examination of the nephrectomy specimen. Macroscopic examination of a cut section of a kidney containing small cell carcinoma of the kidney

tends to reveal a tumour which has grey-yellow coloration and which may contain bloody and serosanguinous fluid [21]. Microscopic examination of a kidney which contains a small cell carcinoma of the kidney should reveal small cell carcinoma with scant cytoplasm and stippled nuclear chromatin [21]. The tumour cells have also been described as round to spindle-shaped small cells with dense nuclei, inconspicuous nucleoli, and sparse cytoplasm [19]. Immunohistochemical stains of small cell carcinoma of the kidney should reveal tumour cells that stain positively for synaptophysin [1] [19] [21] and Chromogranin A [1] [19] [21] as in reported cases. The tumour cells also stain positively for: AE1-AE3; CAM 5.2; neuron-specific enolase (NSE) [1] [19]; and cytokeratin [19].

A number of authors [11] [18] iterated that:

- The differential diagnoses of extrapulmonary small cell carcinoma (small cell carcinoma of the kidney) include renal cell carcinoma, urothelial carcinoma, renal sarcomas, and other metastatic tumours.
- The final diagnosis of small cell carcinoma of the kidney is based upon the histopathological characteristics of the tumour such as the appearance of round to spindle-shaped small cells with dense nuclei, inconspicuous nucleoli, and sparse cytoplasm. For equivocal cases in which diagnosis of small cell carcinoma cannot be confirmed by the histological microscopic appearances of the tumour immunohistochemical staining with chromogranin A synaptophysin, or non-specific enolase (NSE) may be helpful.

Treatment

Surgery (radical nephrectomy) and chemotherapy have been the principal therapeutic approaches in the treatment of small cell carcinoma of the kidney. Cheng and associates [19] stipulated that in the treatment of extra-pulmonary small cell carcinoma, surgery alone is not enough and that in the published literature a combination of surgical resection and chemotherapy offered better results as reported by a number of authors [11] [18] [22].

Cheng and associates [19] also stated that in view of local extensiveness and early dissemination of this rare tumour, chemotherapy can be helpful. They also stated that the combination of platinum based chemotherapy and etoposide, 5-fluorouracil, gemcitabine may improve over-all survival. It has been stated that the medium overall survival was 8 months in the non-chemotherapy patients and 20 months in patients who received platinum-based combination chemotherapy ($p= 0.02$) [18].

Discussion

Small cell carcinoma is a malignant tumour which is composed of small cells with a diffuse growth pattern. It has ultra-structural and immunohistochemical characteristics of both neuroendocrine and epithelial neoplasms. Small cell carcinomas constitute 10% to 20% malignant tumours in the lung which is the most frequent site that is involved by the tumour [1]. Small cell carcinoma tumour cells are less than 3 times the size of lymphocytes; their nucleoli are inconspicuous; and they have scant cytoplasm; mitotic activity is quite often high [1]. Small cell carcinomas are now being reported in extra-pulmonary sites including the aerodigestive and genito-urinary tracts [1]. Gonzalez-Lois and associates [1] suggested that in all these unusual locations, the diagnosis of small cell carcinoma should rest upon histopathologic, immunohistochemical, and ultra-

structural similarities with respect to the tumour's lung counterpart.

Gonzalez-Lois and associates [1] iterated that:

- Small cell carcinomas are mainly misdiagnosed as other small round tumours (for example neuroblastoma, Ewings sarcoma, embryonal rhabdomyosarcoma, lymphoma).
- The differential diagnosis is with with neuroblastoma, Ewings sarcoma and embryonal rhabdomyosarcoma by the age of the patient and with lymphoma by means of immunohistochemistry. Even though not all small cell carcinomas express epithelial markers, they react strongly with CD56 and leucocyte common antigen expression is negative. Nevertheless, it is much more important always to rule out the existence of primary lung tumour metastasising to the kidney.
- Genito-urinary small cell carcinomas have been reported in more often in the prostate and urinary bladder and the kidney; less than 30 cases have been reported to date in the literature. In 8 previous cases the tumour lacked associated features (a transitional or squamous component). The ages of the 9 cases Inclusive of their reported case ranged from 37 years to 83 years with a median age of 63.2 years. Out of the 8 previously reported cases 6 (75%) were women and 2 (25%) were men (In 1 case this information was not available). The median greatest size of the tumour in these cases was 10.9 cm.

Gonzalez-Lois and associates [1] reported a 76-year old woman who complained of constitutional symptoms of several months duration which was complicated by visible gross haematuria for a month prior to her presentation in hospital. She did not have any voiding symptoms and did not have any significant past medical history. She had an abdominal ultrasound scan which revealed a large mass of about 15 cm displacing the left kidney. She also had a contrast enhanced computed tomography scan which showed the mass to be arising from the posterolateral surface of the left kidney. The tumour exhibited non-uniform enhancement to a lesser degree than normal parenchyma and displayed a central low-density area of necrotic tissue. The interface between the tumour and surrounding normal renal parenchyma was well defined (see figure A). A left nephrectomy was performed with the clinical diagnosis of a primary renal tumour.

Macroscopic examination of left kidney specimen revealed a mass which measured 15 cm x 5 cm x 2 cm and this had replaced almost all the normal parenchyma and penetrated the renal capsule. , neither the structures in the hilum nor the renal pelvis were involved (see figure B).

The formalin-fixed paraffin embedded specimens of the resected tumour were examined histologically using 4-micrometre sections of the tumour which were stained by haematoxylin and eosin stain, reticulin, Masson trichome, periodic acid-Schiff, Masson-Fontana, and Sevier-Munger silver impregnations. The tumour was also studied by means of electron microscopy and immunohistochemical stains against keratins (human cytokeratin, high-molecular-weight MO630, Dakopatts AJS, Glostrup, Denmark), epithelial membrane antigen (E29, Dako), leukocyte common antigen (2811+PD7/28, Dako), vimentin (V9 Dako), neuron-specific enolase(BBS/NC/VI-H14, Dako), synaptophysin (SY38, Dako), and chromogranin A DAK-A3, Dako). Finally flow cytometry was carried out using paraffin-embedded tissue.

Gonzalez-Lois and associates reported the histologic findings as follows (see figure C): the neoplastic proliferation was well defined from the parenchyma which was encompassed by a connective pseudo-capsule. There were numerous microscopic findings of capsular and vascular invasion. The tumour exhibited

a predominantly diffuse pattern, showing extensive necrosis, but in other areas it formed nests surrounded by delicate connective tracts in a neuroendocrine like or organoid pattern. The tumour was composed of small cells with a round to fusiform shape, scant cytoplasm, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. Nuclear moldings were observed frequently, and the mitotic rate was very high. Silver impregnations did not exhibit argyrophilia or argentaffinity. Gonzalez-Lois and associates [1] also reported that electron microscopy showed features of epithelial differentiation, such as abundant well-formed desmosomes but it did not contribute to the demonstration of the neuro-endocrine phenotype of the tumour, likely as a result of formalin fixation time. Gonzalez-Lois reported that immunohistochemical staining of the tumour revealed the following:

- Tumour did not stain for leukocyte common antigen
- Weak cytoplasmic positivity for vimentin
- Weak positivity for epithelial membrane antigen
- Strong positivity for AE1-AE3
- Strong positivity for CAM 5.2
- Strong positivity for neuron-specific enolase
- Strong positivity for synaptophysin (see figure D)
- Strong positivity for chromogranin

Gonzalez-Lois and associates [1] reported the results of flow cytometric studies of the tumour as follows: DNA analysis showed an aneuploidy peak with a quotient between the G1-phase 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 aneuploidy populations respectively. Twenty-seven months after surgery the patient was alive and free of tumour. Chung and Park [21] reported a 52-year-old man who had a 2-week history of right flank pain and intermittent haematuria with iron deficiency anaemia. He had a computed tomography scan of the abdomen which revealed a relatively well defined, large heterogeneous tumour in the right kidney. He also had computed tomography scans of brain and chest as well as bone scan which did not reveal any metastasis. A provisional diagnosis of renal cell carcinoma of the right kidney was made. He underwent a right radical nephrectomy. Macroscopic examination revealed a very large mass which measured 10 cm x 15 cm, from the right kidney. Cut sections of the tumour revealed a tumour that was grey-yellow in colour and this contained bloody and serosanguinous fluid. The tumour penetrated the capsule, but there was no infiltration into the renal pelvis, hilum of the kidney, or adjacent lymph nodes. Histological examination of the specimen revealed a pure small cell carcinoma with scant cytoplasm and stippled nuclear chromatin. Immunohistochemical staining of the specimen revealed that the tumour cells were strongly positive for synaptophysin, weakly positive for chromogranin, and negative for S-100, leukocyte common antigen. Based upon the histological and immunohistochemical findings a diagnosis of pure small cell carcinoma of the kidney was made. The patient received post-operatively six courses of chemotherapy which consisted of etoposide and cisplatin. Pursuant to completion of the chemotherapy, all his oncological investigations, including computed tomography scans of abdomen, pelvis and chest, revealed no recurrence. Out-patient follow-up investigations including laboratory and radiological studies were carried out at regular intervals. The patient remained well without any evidence of recurrence at 28 months following the diagnosis of the primary tumour.

Cheng and associates [19] reported an 82-year-old male patient who presented with gross painless haematuria of one year duration. In addition he had suffered from right-flank and lower-abdominal-quadrant pain for one month. He was a non-smoker. He had an ultrasound scan of abdomen which revealed a right renal mass. He also had computed tomography scan which revealed a heterogeneous contrast-enhanced mass occupying the upper pole of the right kidney. He had a chest X-ray which was normal. He had a right retrograde pyelogram during which the right renal pelvis could not be demonstrated due to difficulty with the contrast medium entering this area. A computed tomography scan revealed a 7.3 cm x 6.0 cm heterogeneous contrast-enhanced mass in the upper pole of the right kidney. A tumour thrombus in the inferior vena cava and clusters of enlarged lymph nodes in the retro-caval and para-aortocaval spaces and the right renal hilum were also demonstrated on the computed tomography scan. A whole-body bone scan showed no evidence of bone metastasis. He underwent trans-peritoneal laparoscopic radical nephrectomy. During the operation, multiple enlarged lymph nodes were noted around the renal hilar area with severe adhesion to the inferior vena cava. Complete lymph-node dissection was too difficult and too dangerous to perform. The pathology report revealed small cell carcinoma with angiolymphatic invasion. Microscopic examination at higher magnification revealed tumour cells with hyperchromatic nuclei and scanty cytoplasm after haematoxylin and eosin staining. Immunohistochemical studies revealed positive reactivity for the following:

- Cytokeratin
- Neuron-specific enolase (NSE)
- Synaptophysin
- Chromogranin A

The final pathologic stage was T3aN1M0, stage IV. He was referred to an oncology centre where he received four cycles of chemotherapy with starting doses of 300 mg/m² carboplatin and 75 mg/m² etoposide. Unfortunately, his follow-up computed tomography scan showed multiple nodal metastases in the para-aortocaval space, peritoneal space, and bilateral common iliac chain 4 months post-operatively. His condition deteriorated and he died in hospital 9 months after the laparoscopic radical nephrectomy. Oiusheng and associates [20] searched the pathology files of two institutions and found 14 cases of renal small cell carcinoma. They reported that the patients' mean age at diagnosis was 59 years (range; 22 years to 75 years), 8 of the patients were women, and 6 were men. Oiusheng and associates [20] also reported that the patients usually presented with haematuria (n=6), and abdominal pain (n=5). The mean tumour size was 7.1 cm (range, 3.5 cm to 14.0 cm). The small cell carcinoma was pure in 9 cases and mixed with high-grade urothelial carcinoma in 5 cases. None was found to be associated with any type of renal cell carcinoma. There was evidence of tumour necrosis in all cases, and lymphovascular invasion was identified in 6 cases. The tumour invaded the peri-nephric adipose tissue in 13 cases and was confined to the kidney in only 1 case. Lymph node metastases were identified in all patients who underwent lymph-node dissection (5/5). On immunohistochemical staining the small cell carcinomas were positive for:

- Pancytokeratin (11/12)
- Chromogranin (6/9)
- Synaptophysin (8/9).

Follow-up data was available for 13 patients, and 11 died of small cell carcinoma at a mean of 15 months (range, 4 months to 31 months) after diagnosis of the tumour. Of the two surviving patients, 1 was alive at 5 months after the diagnosis, and the other whose disease was confined to the kidney was alive without any

evidence of disease at 137 months. Oiusheng and associates [20] concluded that renal small cell carcinoma is a highly aggressive disease which often presents at an advanced stage with widespread metastases. Patients usually have a poor clinical outcome despite multi-modal therapy. The frequent co-existence of small cell carcinoma with urothelial carcinoma suggests that renal small cell carcinoma may evolve from a pre-existing urothelial carcinoma.

Majhail and associates [22] described two patients with small cell carcinoma of the kidney and they also provided a systematic review of the literature to outline the clinical characteristics and therapy of this rare tumour.

Case 1: Majhail and associates [22] reported a 62-year-old Caucasian female, with a history of smoking who presented in May 1993 with a four month history of localized epigastric pain, abdominal bloating, anorexia, and weight loss. On examination a palpable, non-tender, firm, non-pulsatile mass was found in the epigastrium. Computed tomography (CT) scan of the abdomen revealed a 10 cm x 10 cm mass in the upper pole of the right kidney with extension into the right renal vein and the inferior vena cava. The para-aortic and retroperitoneal lymph nodes were significantly enlarged. Metastatic work-up including CT scan of the chest was negative. The patient subsequently underwent a CT-guided aspiration biopsy of the renal mass, which showed a small cell carcinoma of the kidney on cytopathology and immunohistochemistry. The clinical stage was T3b N2 M0 (American Joint Committee on Cancer [AJCC] stage IV). He received six-cycles of combination chemotherapy. He had a CT-scan of the abdomen at the end of six cycles of chemotherapy which revealed a complete response. The patient was alive and remained disease free at a follow-up more than 8 years later.

Case 2

Majhail and associates [22] reported a 58-year-old Caucasian male with a 20-pack-year history of smoking who presented in May 2001 with a one day history of right flank pain and haematuria which started after a fall while playing football. His clinical examination was unremarkable. Contrast-enhanced CT-scan of the abdomen revealed a large mass arising from the upper pole of the right kidney with associated para-aortic lymphadenopathy. Thrombus was seen in the right renal vein and inferior vena cava. An extensive metastatic work-up did not reveal any metastatic deposits. CT scan of the chest was normal. He underwent pre-operative embolization of the right kidney which was followed by right-sided radical nephrectomy in July 2001. Histology and immunohistochemistry of the resected tumour revealed a small cell carcinoma which measured 18 cm x 14 cm x 11 cm. with invasion of the renal capsule, peri-nephric adipose tissue, and adrenal gland. The pathologic stage was T3b N2 M0 (AJCC stage IV). The patient developed fast progressive disease and died 2 months later before systemic chemotherapy could be given.

Majhail and associates [22] reviewed the literature on 22 patients with small cell carcinoma of the kidney and renal pelvis who were treated between the years 1996 and 2002 [1], [5], [7], [8], [9], [10]; [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34]. They reported that the median age at diagnosis was 62 years, and there was a female preponderance with a male to female ratio of 1:3.4 History of tobacco smoking was available in five patients, and of these five patients, three had smoked. The median duration of symptoms was 1.5 months. Majhail and associates [22] found out that the presenting symptoms were as follows:

- Abdominal pain (70%)
- Haematuria (45%)

- Flank mass (15%)
- Weight loss (10%)
- Abdominal pain, haematuria, and flank mass (– classic triad associated with renal cell carcinoma) (10%)
- Four patients ----

Majhail and associates [22] stated that that they found details of loco-regional spread of primary tumour in 18 cases with detailed pathology reports in 17 patients who underwent surgery. They described the characteristics of the tumours as follows:

- The median tumour size was 11 cm (range 4 – 19 cm)
- There was local extension of the tumour in 13 of 18 (72%) patients
- Regional lymph node metastases were found in 10 of 18 (56%) patients.
- Limited stage disease was observed in six out of seven (86%) patients who underwent nephrectomy alone versus 4 out of 11 (36%) patients who received chemotherapy
- Distant metastases were present in 7 out of 22 (32%) patients at the time of diagnosis. Bone metastases were present in 3 patients, and in 3 patients multiple metastases were found.
- 11 out of 21 (52%) patients had evidence of extensive-stage disease at presentation.

With regard to treatment, Majhail and associates [22] stated that Surgery and systemic chemotherapy were the main treatment modalities which were used. Nine patients underwent nephrectomy alone; 10 patients were treated by means of nephrectomy and chemotherapy; 3 patients were treated by means of chemotherapy alone. They also reported that:

- The median survival was 8 months (range, < 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 who received a platinum-based chemotherapeutic regimen in comparison with 8 months in those who did not receive platinum-based treatment, $P = 0.02$.

They concluded that:

- Small cell carcinoma of the kidney is an extremely rare neoplasm which resembles its counterparts arising from the trachea-bronchial tree and other extra-pulmonary sites in its aggressive biological behaviour as well as in its high propensity for loco-regional and distant dissemination.
- The clinical presentation usually tends to be late in the course of the disease.
- The use of platinum-based chemotherapy has been associated with tumour regression and prolonged survival.

A summary of some of the reported cases of small cell carcinoma of the kidney can be found in table 1 which include their references (inclusive of references 35 to 42 not discussed in text). Lee and associates [43] studied the factors associated with survival of small cell carcinoma of the kidney. They collected data on patients who were admitted to their hospital and with small cell carcinoma of the kidney for a period of 22 years preceding their study as well as data from reported studies of small cell carcinoma of the kidney in the literature. They included 45 patients (8 admitted to their hospital and 37 from

studies in the literature with small cell carcinoma of the kidney. They reported that:

- The overall median survival was 9.9 months (range 6.9 to 31.6 months)
- Data on demographics, clinical symptoms, tumour staging, and tumour characteristics recorded at the time of diagnosis were not associated with survival
- Among the different treatment modalities applied, cisplatin-based chemotherapy afforded a strong survival advantage (hazard ratio = 0.35 $p = 0.022$). Nevertheless, patients with early local recurrence (hazard ratio 19.13 $p = 0.012$) and early distant metastasis (hazard ratio 10.93, $p = 0.003$) after primary treatment showed significantly poor survival.

Lee and associates (43) concluded that:

- Patients with small cell carcinoma of the kidney, generally presented with large, advanced stage tumours and showed poor survival
- Early detection of the tumour, use of cisplatin-based chemotherapy, and careful follow-up for local recurrence or frequent metastasis within 6 months after the primary treatment could be important for improving the overall patient survival.

Guo and associates reviewed the clinicopathologic features of 12 cases of small cell carcinoma of the kidney which they had encountered between 1999 and 2010. They reported six cases of primary and 6 cases of metastatic small cell carcinoma involving the kidney. They reported that:

- Amongst the primary renal small cell carcinoma, 2 were located in the renal parenchyma and 4 in the renal pelvis.
- Chest X-ray showed negative findings
- Five of the patients underwent radical nephrectomy.
- Gross examination revealed that the tumour was located centrally around the renal pelvis in 4 cases and peripherally in the renal parenchyma in 1 case.
- On the other hand, four of the 6 cases of metastatic small cell carcinoma were discovered during therapy for pulmonary small cell carcinoma. Two of these manifested with abdominal pain and visible haematuria, with lung and renal tumour detected contemporaneously. The diagnosis of all the six cases of metastatic small cell carcinoma was confirmed by fine needle aspiration biopsy.
- Microscopically, pure small cell carcinoma was demonstrated in the 2 cases of primary renal parenchymal small cell carcinoma and 6 cases of metastatic small cell carcinoma. The 4 primary renal pelvis small cell carcinoma co-existed with urothelial carcinoma component.
- Immunohistochemical studies revealed that all the cases were positive for cytokeratin, synaptophysin and CD56; all metastatic cases and 4 primary cases were positive for TTF-1.
- With regard to outcome following treatment, of the 6 patients with primary small cell carcinoma two died at 4 and 9 months post-operatively and two were alive with a follow-up of 25 months and 138 months, respectively. Five of six cases with metastatic small cell carcinoma died between 3 to 8 months pursuant to the diagnosis. The remaining 3 patients failed to turn up for follow-up.

Table 1: List of some of the reported cases of small cell carcinoma of the kidney

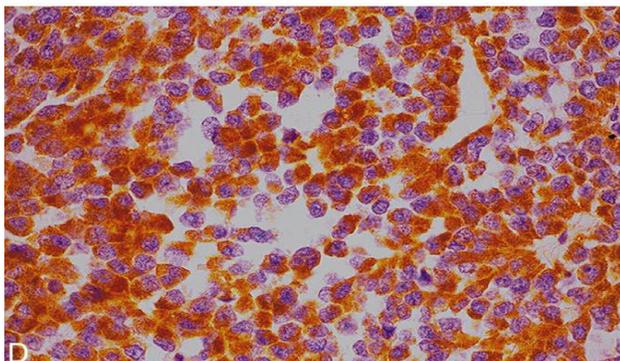
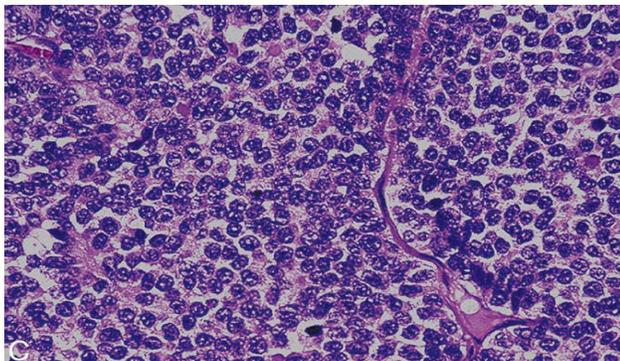
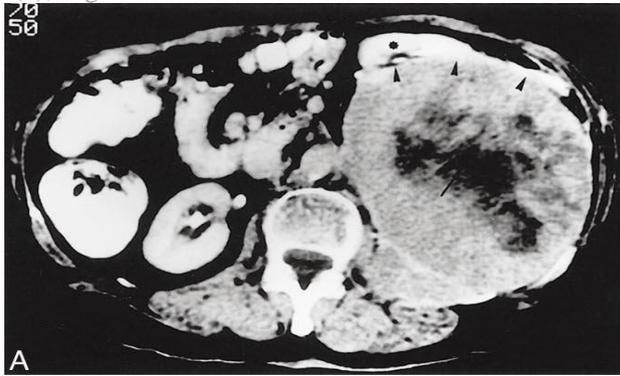
Case No.	Source	Metastasis at Diagnosis	Age/sex	Diameter (cm)	Survival (months)
1.	Capella et al 1984 ⁽²⁴⁾	LN's	66/F	12	0.3
2.	Fetissol as cited in Masuda ⁽³²⁾	NR	60/M	3	NR
3.	Tetu et al 1987 ⁽⁵⁾	IVC, LN's	56/F	10.5	8
4.	Tetu et al 1987 ⁽⁵⁾	No	83/F	14.5	18
5.	Tetu et al 1987 ⁽⁵⁾	RV	64/F	18.5	12
6.	Chang et al 1990 ⁽²⁵⁾	Bone	38/M	3	6
7.	Yu et al 1990 ⁽⁸⁾	Bone; brain	37/M	4	5
8.	Christopher et al 1991 ⁽⁹⁾	Skin; LN's	62/F	NR	10
9.	Kitamura et al 1997 ⁽¹⁰⁾	No	83/F	NR	2
10.	Masuda et al 1998 ⁽³²⁾	IVC; RA	37/M	10	NR
11.	Chuang et al 2000 ⁽²⁶⁾	No	35/F	NR	4
12.	Gonzalez-Lois et al 2001 ⁽¹⁾	LN's	76/F	15	NR
13.	Miyagi et al 2001 ⁽³⁶⁾	IVC; lung; bone; liver	43/M	NR	6
14.	Kilicarsalan et al 2003 ⁽³⁵⁾	LN's	68/M	10	12
15.	Majhail et al 2003 ⁽²²⁾	RV; IVC; LN's	62/F	10	96
16.	Majhail et al. 2003 ⁽²²⁾	RV; IVC; LN's	58/M	18	2
17.	Matsumoto et al 2004 ⁽³⁹⁾	IVC; LN's	79/M	15	6
18.	Takizawa et al 2004 ⁽³⁷⁾	No	18/M	NR	55
19.	Wang et al 2002 ⁽⁴⁰⁾	No	71/M	3.5	6
20.	Xu G, et al 2009 ⁽⁴²⁾	RV; IVC; PA	33/M	15	7 (Alive)
21.	Cheng et al 2011 ⁽¹⁹⁾	RV;IVC; LN's	82/M	7.3	9
22.	Kojima et al (1998) ⁽²⁸⁾	LN's	61/F	Large	3
23.	Morgan et al (1996) ⁽³⁴⁾	Bone			NR
24.	Hattori Y et al 2005 ⁽³⁸⁾	LN's; Spleen	67/M	NR	10 (Alive)
25.	Chung C H et al 2006 ⁽²¹⁾	No	52/F	15	28 (Alive)
26.	Takeshima et al 1996 ⁽⁴¹⁾				
27.	Kojima et al. 1998 [***]	Lymph node	61/F	Large	Died at 3
28.	Radhi et al 2002 [***]	liver; lung; bone	34/F	NR	NR
29.	Karadenis Biligili et al 2005 ⁽²³⁾		59/F	16	NR
30.	Wenhan-Tang et al 2009	LN's	68/F	6	12 (alive)
31.	Miyake et al 2007	Multiple	47/M	47	32
32.	La Rosa et al 2009	Synchronous bladder tumour	90/M	15 cm	Died on arrival
33.	Guo et al 2012				(In Chinese) details not clear only abstract available (see text)
34.	Guo et al 2012				(In Chinese) details not clear only abstract available (see text)

Table 2: Summary of patient and tumour characteristics of 22 patients with small cell carcinoma of the kidney that were reviewed by Majhail and associates

Age	Median	62 years
	Range	22 – 83 years
Gender	Male	5 (23%)
	Female	17 (77%)
Duration of symptoms*	Median	15 months
	Range	1 day to 1 year
Site	Upper pole	8 (36%)
	Lower pole	4 (18%)
	Renal pelvis	5 (23%)
	Not reported	5 (23%)
Side	Right	10 (46%)
	Left	9 (41%)
	Not reported	3 (13%)
Tumour size**	Median	11 cm
	Range	4 – 19 cm
Local extension***	Present	13 (59%)
	Absent	5 (23%)
	Not reported	4 (18%)
Lymph-node metastases	Present	10 (46%)
	Absent	8 (36%)
	Not reported	4 (18%)
Distant metastases at diagnosis	Present	7 (32%)
	Absent	14 (64%)
	Not reported	1 (4%)

Table 2:

Data available for 16 patients*
 Data available for 14 patients**
 Defined as extension of tumour into either the major veins, adrenal gland, peri-nephric tissues, or beyond gerota's fascia***



Figures A, B, C, and D

Figure A.
Contrast-enhanced computed tomographic scan which shows a large mass within the posterolateral surface of the left kidney. The kidney is displaced anteromedially (asterisk). The tumour exhibits non-uniform enhancement to a lesser degree than 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 B.
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 C.
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 tumour'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 3400).

Figure D
Positive diffuse staining for synaptophysin (original magnification 3400)

Taken from: González-Lois C, Santiago Madero S, Redondo P, Alonso I, Salas A. Angeles Montalbán M. Small Cell Carcinoma of the Kidney: A Case Report and Review of the Literature. Arch Pathol Lab Med 2001 June; 125(6): 796 – 798 with permission of the Editor in Chief on behalf of the Editorial team of the Journal (The figures have been reproduced with the author's gratitude and acknowledgement to the editor in Chief and the editorial team of the journal)

Guo and associates [44] concluded that:

- Both primary and metastatic small cell carcinoma can be found in the kidney.
- Although rare, primary small cell carcinoma can be found in the renal parenchyma or in the pelvis.
- The diagnosis of small cell carcinoma relies on morphologic examination and immunohistochemical study.
- TTF-1 immunostaining cannot reliably distinguish primary from metastatic small cell carcinoma in the kidney.
- Correlation with clinicoradiologic findings and demonstration of co-existing urothelial carcinoma component (if any) is helpful in delineation of tumour origin.

La Rosa and associates [45] reported a 90 year-old man without any significant was medical history who was admitted as emergency because of chronic renal failure. He died shortly after admission to hospital. He had a post-mortem examination which revealed a 15 cm x 10 cm x 8 cm grey-white tumour in the parenchyma of the left kidney infiltrating into the per-renal tissue but no evidence of inferior vena cava involvement. In addition there was a small 1 cm papillary tumour in the anterior wall of his urinary bladder. The post-mortem did not reveal any other lesion anywhere else. The tumour showed the typical histological features of a pure small cell neuroendocrine tumour (PDNEC). Fluorescent in situ hybridization study demonstrated a complex chromosomal assessment indicative of a high degree of chromosomal instability with gain of multiple chromosomes, loss of p53, and amplification of myc gene. They iterated that these results suggest that PDNEC has a different genetic background to renal clear cell carcinoma, mainly characterized by the loss of short arm of chromosome 3. Conversely, genetic alterations seem to resemble those of type 2 papillary renal cell carcinoma. They additionally stipulated that their review of the literature demonstrated that PDNECs are associated with poor prognosis and that parenchymal tumours show differences from those arising in the pelvis in that parenchymal tumours are purely neuroendocrine while pelvic tumours are mostly mixed neuroendocrine and endocrine neoplasms.

Conclusions

Small cell carcinoma of the kidney is a very rare neoplasm which resembles its counterparts that arise from the trachea-bronchial tree and other extrapulmonary sites in its aggressive biological behaviour and in its high propensity for loco-regional dissemination as well as in its propensity for development of distant metastases. Usually clinical presentation of small cell carcinoma is late during the course of the disease. Diagnosis of small cell carcinoma is based upon the characteristic histological appearance and immunohistochemical staining characteristics of the tumour. Use of platinum-based chemotherapy has been associated with regression of the tumour and some improvement in survival.

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