Rare Tumours of the Kidney

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Review and Update

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CHAPTER 1

RARE RENAL TUMOURS

INTRODUCTION/ABSTRACT

Rare tumours of the kidney exist and these need to be appreciated in relation to the more common adenocarcinoma of the kidney. Before learning about rare tumours of the kidney, it is important to know about the more common adenocarcinoma of the kidney in order to appreciate the differences. The ensuing article has detailed out features of conventional and more common adenocarcinoma of the kidney.

General Summating Abstract of Renal Cell Carcinomas

Practice Essentials

It has been known for a very long time that Renal cell carcinoma (RCC) is the commonest or most frequently encountered type of kidney cancer in adults as well as that RCC accounts for about 85% of tumours arising from the kidney. [1] [2]

It has been iterated that Renal cell carcinoma (RCC) could remain clinically occult for most of its course and that only 10% of patients who are afflicted by RCC do manifest with the classic triad of flank pain, haematuria, and mass within the flank. [1] Other documented manifestations / symptoms associated with RCC include: [1]

- Weight loss
- Pyrexia / Fever
- The finding of high blood pressure (Hypertension)
- The finding of high calcium levels in blood tests (Hypercalcemia)
- Night sweats
- The feeling of general malaise or feeling unwell without any specific symptoms.
- A varicocele could be noted which usually has tended to be left sided, as a result of obstruction of the testicular vein.

Diagnosis of RCC is generally established ensuing various assessment processes including general assessment of the patients and specific investigations that demonstrate the RCC lesion or lesions within the kidney which is then ensued by confirmation of the diagnosis of RCC by establishment of the pathology examination features of the kidney neoplasm. As part of the general assessment of patients who are suspected to have renal cell carcinoma the ensuing laboratory test investigations tend to be undertaken: [1]

- Urinalysis (UA), urine microscopy, and culture which could be normal in some cases but in RCCs associated with haematuria, there could be non-visible haematuria or visible haematuria.
- Complete blood cell count (CBC or full blood count) with differential count, and in majority of cases the results would tend to be normal but in the scenario of the finding that the patient has anaemia, the anaemia would be assessed and treated appropriately to improve the general condition of the patient.
- CRP and serum urea and electrolytes.
- Renal function tests.
- Liver function tests (LFTs; aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).
- Serum calcium level.

Identification of presence of a lesion or lesions within the kidney, position and size of the lesion(s), contiguity with and invasion of other organs is usually undertaken with the undertaking of radiology imaging studies and these images may include the ensuing:

- Excretory urography (intravenous urography)
- Computed Tomography (CT) scan
- Positron Emission Tomography (PET) scan
- Ultrasound scan
- Arteriography (renal artery angiography)
- Venography
- Magnetic Resonance Imaging (MRI) scan
- Isotope bone scan is undertaken when there is suspicion of bone metastases to confirm the presence of bone metastasis, number of metastases, and position of the metastases.

Management [1]

The principal treatment options for renal cell cancer are as follows:

- Active surveillance of a small localised lesion within the kidney based upon multi-disciplinary team discussion including urologists, radiologists, pathologists, oncologists, and other members of the multi-disciplinary team and the options of management are then discussed with the patient.
- The undertaking of surgery, which could be partial nephrectomy, or radical nephrectomy plus dissection and excision of peri-renal lymph nodes depending upon the size of the tumour, evidence of no lymph node enlargement.
- Molecular-targeted therapy on some occasions.
- Immunotherapy in some cases.
- Radiotherapy.
- Cryotherapy.
- Radiofrequency ablation of renal tumour.
- Irreversible electroporation of renal tumour.
- Selective renal artery angiography and super-selective embolization of the branch if renal artery supplies the tumour.
- Combination therapy using some of the aforementioned options.

Surgical resection of the tumour has generally been undertaken in most centres as curative treatment for localised renal cell carcinoma, and it is also utilised to improve the outcome or for palliation in metastatic disease. **Targeted therapy and immunomodulatory agents are considered to be standards of care in patients who have advanced or metastatic kidney cancer**. Chemotherapy has tended to be undertaken only occasionally, in certain sub-types of kidney cancer. [1] Experimental treatment approaches that are being undertaken in some centres in the world include vaccines and non-myeloablative allogeneic peripheral blood stem cell transplantation. [1]

Even though clear renal cell carcinomas are commonly encountered in the world, new sub-types of renal cell carcinomas are being sporadically reported from various centres in the world and the biological behaviour of these rare tumours had tended to vary in that some of these tumours had been reported to be less aggressive and they tend to be associated with no local recurrence or metastasis pursuant to their initial surgical excision and other sub-types of rare renal cell carcinomas portend an aggressive biological behaviour with a high rate of development of local recurrence and metastasis as well as death of patients. The World Health Organization has been periodically recognising and listing some rare renal cell carcinomas as distinct tumours based upon their histopathology examination features, immunohistochemistry staining features, as well as

their molecular and cytogenetics studies features, and separate tumour entities that are different from the common type of renal cell carcinomas. Considering that these new-subtypes of renal cell carcinomas are not common and the fact that these rare subtypes of tumour had not been included or described in many of the previously published text books of surgery and urology, it would be envisaged that the majority of clinicians all over the world would tend not to be familiar with the manifestations, diagnostic features, management, as well as outcome, pursuant to treatment of these rare sub-types of newly identified renal tumours in order to be able to be sure on the best way to treat these rare tumours. There is therefore the need for an extensive documentation on various miscellaneous rare sub-types of renal cell carcinoma which would constitute one repository of knowledge for readers all over the world to help them have an up-to-date knowledge about the diagnostic features, treatment, follow-up management plan and outcome of these rare tumours before they are included in future text books. Additional treatment options are being developed for the management of common renal cell carcinomas, hence it is important for readers to update their knowledge regarding common renal cell carcinomas before updating their knowledge about the new sub-types of renal cell carcinomas.

REVIEW OF RENAL CELL CARCINOMAS

Background

Renal cell carcinoma (RCC) has been stated to account for about 3% of adult malignancies and 90% to 95% of tumours arising from the kidney. [1] Renal cell carcinoma is stated to be typified by a lack of early warning signs, diverse clinical presentations, and resistance to radiotherapy as well as to chemotherapy. [1] [3] [4] [5]

It has been pointed out that increasingly, renal cell cancers are being identified at an earlier stage, and nephron-sparing surgery, thermal ablation, and surveillance are gaining acceptance as treatment options of choice for smaller tumours. [1] The undertaking of radical nephrectomy is the standard treatment for larger and central kidney tumours. [1]

It has furthermore been pointed out that over recent years, multiple treatment agents have been developed for the systemic therapy of metastatic disease as follows: [1]

- Even though the optimal therapeutic treatment has continued to develop, three agents that target angiogenesis (sunitinib,

bevacizumab/interferon, and pazopanib) and a mammalian target of rapamycin (mTOR)-targeted therapy (temsirolimus) have been approved as front-line agents.

- ❖ For selected patients, cabozantinib or combination therapy with nivolumab plus ipilimumab are also utilised as first-line treatments.
- ❖ Finally, high-dose interleukin-2 (IL-2) and axitinib could be utilised in selected patients.
- ❖ A number of agents are available to be utilised in second and subsequent lines of treatment. These include anti-angiogenic therapy (if not already utilised in first-line treatment), nivolumab, cabozantinib, and mTOR inhibitors.
- ❖ Recommendations related to sequence-approved agents during subsequent treatment are evolving; more work is required.
- ❖ Clinical trials are currently being undertaken to explore future directions, including combinations of approved agents and the optimal sequencing of these agents.

Pathophysiology

Summations made regarding the pathophysiology of renal cell carcinoma include the following: [1]

The tissue of origin for renal cell carcinoma (RCC) is the proximal renal tubular epithelium. Renal cancer develops in a sporadic (non-hereditary) and a hereditary form, and both forms tend to be associated with structural alterations of the short arm of chromosome 3 (3p). Genetic studies of the families at high risk for the development of renal cancer led to the cloning of genes whose alteration results in tumour formation. These genes are either tumour suppressors (*VHL*, *TSC*) or oncogenes (*MET*).

Multiple hereditary syndromes associated with renal cell carcinoma have been identified as follows: [1]

- von Hippel-Lindau (VHL) syndrome
- Hereditary papillary renal carcinoma (HPRC)
- Familial renal oncocytoma (FRO) associated with Birt-Hogg-Dube syndrome (BHDS)
- Succinate dehydrogenase (SDH)–deficient RCC
- Hereditary renal carcinoma (HRC)

von Hippel-Lindau syndrome [1]

von Hippel-Lindau syndrome, or von Hippel-Lindau disease, is an autosomal dominant syndrome which confers predisposition to a variety of tumours, including the ensuing:[1]

- Renal cell carcinoma with clear cell histology features
- Pheochromocytoma
- Pancreatic cysts and islet cell tumours
- Central nervous system (CNS) hemangioblastomas
- Retinal angiomas
- Endolymphatic sac tumours
- Epididymal cystadenomas

Renal cell carcinoma develops in about 40% of patients with von Hippel-Lindau disease and is a major cause of death in these patients. Deletions of chromosome 3p occurs commonly in renal cell carcinoma that is associated with von Hippel-Lindau disease. Chromosome 3p contains many of the genes that are associated with kidney cancer, including *BAP-1* and *PBRM-1,* among others. [1]

The *VHL* gene is mutated in a high percentage of tumours and cell lines from patients who are afflicted with sporadic (non-hereditary) clear cell renal carcinoma. Many kindreds with familial clear cell carcinoma have a constitutional balanced translocation between 3p and either chromosome 6 or chromosome 8. [1]

Mutations of the *VHL* gene emanate in the accumulation of hypoxia-inducible factors (HIFs) which stimulate angiogenesis via vascular endothelial growth factor (VEGF) and its receptor (VEGFR). VEGF and VEGFR are important new treatment targets.[1]

Hereditary papillary renal carcinoma [1]

Hereditary papillary renal carcinoma is stated to be an inherited disorder which is associated with an autosomal dominant inheritance pattern; affected individuals tend to develop bilateral, multifocal papillary renal carcinoma. Germline mutations in the tyrosine kinase domain of the *MET* gene have been identified. [1]

Familial renal oncocytoma and Birt-Hogg-Dube syndrome [1]

It has been stated that individuals who are afflicted by familial renal oncocytoma could develop bilateral, multifocal oncocytoma, or oncocytic neoplasms in the kidney. [1] Birt-Hogg-Dube syndrome is a hereditary cutaneous syndrome. [1] Patients who have Birt-Hogg-Dube syndrome have a dominantly inherited predisposition to develop benign tumours of the hair follicle (for example fibrofolliculomas), predominantly upon the face, neck, and upper trunk, and these individuals are at risk for the development of renal tumours, colonic polyps, or tumours, and pulmonary cysts. [1]

Hereditary renal carcinoma [1]

- It has been pointed out that affected individuals with this inherited medical condition have an increased tendency for the development of oncocytomas, benign kidney tumours that have a low malignant potential. [1]
- It has been advised that renal carcinoma patients, who are diagnosed at 45 years or younger than 45 years and those with family history of kidney cancer, should be provided genetic counselling.

Aetiology of Renal Cell Carcinoma [1]

The aetiology of RCC has been summated as follows: [1]

- A number of environmental and genetic factors have been studied as possible causes for renal cell carcinoma (RCC) and the ensuing iterations have been made.
  - ❖ Cigarette smoking doubles the risk for the development of renal cell carcinoma and contributes to as many as one third of all cases of RCC.
  - ❖ The risk appears to increase with the amount of cigarette smoking in a dose-dependent fashion.
  - ❖ Smoking has also been associated with the development of advanced disease at manifestation.
- Obesity is a risk factor, particularly in women. Increasing body weight has a linear relationship with increasing risk.
- Hypertension is a possible risk factor for the development of RCC.

- It has been iterated that occupational exposure to certain chemicals, such as trichloroethylene, has been linked to an increased risk for the development of renal cell carcinoma. [6]
- Furthermore, the risk of renal cell carcinoma was stated to increase with duration of exposure to benzene, benzidine, cadmium, herbicides, and vinyl chloride. [7]
- A prospective assessment evaluation by Cho et al. [8] had concluded that longer duration of use of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) might increase the risk for the development of renal cell cancer. [8]
- Phenacetin-containing analgesics that are consumed in large amounts might be associated with increased incidence of renal cell carcinoma; and it was iterated that Phenacetin-containing analgesics are no longer approved for utilisation within the United States of America.[1].
- It has been iterated that patients who are undergoing long-term dialysis have an associated increased incidence of acquired cystic disease of the kidney, which is predisposed to the development of renal cell cancer. [1]
- It has also been iterated that in kidney transplant recipients, the development of acquired renal cystic disease is also predisposed the development of renal cell cancer. [1]
- Chronic hepatitis C infection [9] and, according to a meta-analysis of pooled data, kidney stones in males [10] have been documented to be associated with higher incidences of kidney cancer.
- Documented genetic disorders that tend to be associated with renal cell carcinoma include the ensuing: von Hippel-Lindau syndrome, hereditary papillary renal carcinoma, Birt-Hogg-Dube syndrome, and hereditary renal carcinoma. [1]
- The genetic disease of tuberous sclerosis appears to be associated with renal cell carcinoma, even though the exact nature of the association is not clear. [1]

Epidemiology of renal cell carcinoma

The ensuing summations have been made related to the epidemiology of RCC: [1]

- The incidence of kidney cancer within the United States of America (USA) has been rising since the 1990s, reaching 15.4 cases per 100,000 population in 2019. [11]

- From 2010 to 2019, the incidence rate increased by about 1% per year. [1]
- Majority of the increase has been in localized-stage cancers, and the increase appeared to have been due in part to increased incidental identification of asymptomatic tumours because of the wider undertaking of radiology medical imaging. [6]
- In 2023, cancers of the kidney and renal pelvis were the sixth most common cancer in USA men, which accounted for 5% of cases, and the ninth most common in USA women, which accounted for 3% of cases. [1]
- The American Cancer Society estimated that in 2023 there would be 81,800 cases (52,360 in males and 29,440 in females) of malignant tumours of the kidney and renal pelvis diagnosed, with 13,780 deaths (8790 in males and 4990 in females). [6]
- Renal cell carcinoma was expected to account for 80% of this incidence and mortality.
- Within most of Europe, the incidence of kidney cancer decreased or stabilized over the preceding decade, perhaps in part because of reduced tobacco smoking in men. Mortality from kidney cancer also decreased in most of Europe, principally within Scandinavia and other western European countries. In men, the mortality rate per 100,000 population fell from 4.8 in 1990-1994 to 4.1 in 2000-2004; in women, the rate fell from 2.1 to 1.8. [12]
- It has been noted that renal cell carcinoma is more common in people of Northern European ancestry (Scandinavians) and North Americans in comparison with those of Asian or African descent. [1]
- In the United States of America, the incidence of RCC is slightly higher in Blacks than in Whites: 26.2 versus 24.3 per 100,000 population in men, and 13.2 versus 11.9 per 100,000 population in women. [1]
- The highest incidence rates of RCC in the USA are in American Indian/Alaska Native men, at 36.2 cases per 100,000 population. [11]
- It has been iterated that the median age at diagnosis of RCC from 2015 to 2019 was 65 years. In familial clusters, nevertheless, it has been documented that RCC has been reported in younger people. [11]

Prognosis [1]

- It has been iterated that within the United States of America, death rates from kidney and renal pelvis cancer reduced by about 2% per year from 2013 to 2020. [6]
- RCCs have been documented to currently constitute the twelfth leading cause of cancer death. [11]
- The 5-year survival rates of RCCs initially reported by Robson in 1969 were 66% for stage I renal carcinoma, 64% for stage II, 42% for stage III, and only 11% for stage IV. [13] [14] Except for stage I, these survival statistics remained essentially unchanged over a period of many decades. [1]
- Surveillance, Epidemiology, and End Results (SEER) data from 2012–2018 documented the 5-year relative survival for localized kidney and renal pelvic cancer as 93.0% for localized disease, 72.3% for regional disease, and 15.3% for distant disease. [1] [11]

Prognostic systems for metastatic renal cell carcinoma

It has been documented that two similar prognostic systems are commonly utilised to calculate risk in patients with metastatic renal cell carcinoma (RCC). The Memorial Sloan-Kettering Cancer Center (MSKCC)/Motzer score includes the ensuing stipulated criteria: [1] [15]

- Time from diagnosis of RCC to systemic treatment of less than 1 year
- Hemoglobin concentration below the lower limit of normal (LLN)
- Serum calcium concentration > 10 mg/dL (2.5 mmol/L)
- Lactate dehydrogenase (LDH) level more than 1.5 times the upper limit of normal (ULN)
- Performance status (Karnofsky) less than 80%

The International Metastatic RCC Database Consortium (IMDC) risk model, which has been validated and further developed by Heng et al, includes the ensuing prognostic criteria: [1] [16]

- Time from diagnosis to systemic treatment of less than 1 year
- Karnofsky performance status less than 80%
- Hemoglobin concentration below the lower limit of normal (LLN)
- Serum calcium (corrected for hypoalbuminemia) above the upper limit of normal (ULN)

- Platelet count above the ULN
- Neutrophil count above the ULN

Both systems categorize patients into the ensuing 3 risk stratification groups: [1]

- Favourable risk (no risk factors) - Median survival 20 months (MSKCC/Motzer); 2-year overall survival (2-years OS) 75% (IMDC)
- Intermediate risk (1 or 2 risk factors) - Median survival 10 months; 2-years OS 53%
- Poor/high risk group (3 or more risk factors) - Median survival 4 months; 2-years OS 7%

Furthermore, Albiges et al. identified obesity as a favourable prognostic factor in patients who are afflicted by metastatic renal cell carcinoma and who have been treated with targeted therapy. In a study of 1975 patients from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), the reported median overall survival was 25.6 months in patients with a body mass index (BMI) of 25 kg/m^2 or higher, compared with 17.1 months in patients with a BMI of less than 25 kg/m^2. The adjusted hazard ratio (HR) for obesity was 0.84. [1] [17]

Review of an external validation cohort of 4657 patients who had been treated for kidney cancer in clinical trials from 2003 to 2013 also revealed longer overall survival in obese patients, with median overall survival of 23.4 months versus 14.5 months for those with low BMI. [1] [17]

It was explained that the longer survival might be related to the fatty acid synthase (FASN) pathway. *FASN* acts as a metabolic oncogene and its overexpression has been noted to be associated with poor prognosis in renal cell carcinoma and other types of cancers. FASN was downregulated in overweight and obese patients in this reported study. [1] [17]

Education of patients [1]

The ensuing summations have been made about education of patients who have RCC: [1]

- Patients who are found to have a family history of genetic syndromes associated with increased risk for renal cell carcinoma should be educated about these syndromes, and genetic counselling

should be offered to the patients and their family members. For example, renal cell carcinoma develops in nearly 40% of patients with von Hippel-Lindau (VHL) disease and is a major cause of death in patients with that disorder.

- Patients at high risk for the development of RCC should be made aware of the early signs and symptoms of the disease, and the need for early intervention for possible cure should be stressed.
- With regard to patients who have early-stage RCC disease who have undergone treatment, education about possible recurrence of tumour should be provided.

History

The ensuing summations have been made about the history that tends to be associated with RCC: [1]

- ❖ Renal cell carcinoma (RCC) may remain clinically occult for most of its course.
- ❖ The classic triad of flank pain, haematuria, and flank mass is uncommon and tends to be reported in 10% of cases and it is indicative of advanced disease.
- ❖ Twenty-five to thirty percent of patients tend to be asymptomatic, and their renal cell carcinomas are found upon incidental radiology imaging studies for a different reason.
- ❖ The frequency of the individual components of the classic triad is as follows:
  - Haematuria – 40%
  - Flank pain – 40%
  - A palpable mass within the flank or abdomen – 25%
- ❖ Visible haematuria tends to be encountered less commonly than non-visible haematuria in renal cell carcinoma; when present, the appearance of blood throughout the urinary stream suggests an origin in the upper urinary tract.
- ❖ Visible haematuria with vermiform clots also indicates upper urinary tract bleeding, with clot formation in the ureters.

Other signs and symptoms of RCC include the ensuing: [1]

- Weight loss (33%)
- Fever (20%)
- Hypertension (20%)

- Hypercalcaemia presentations (5%)
- Night sweats
- Malaise
- Varicocele (2% of males) - Usually left sided, due to obstruction of the left testicular vein

❖ Renal cell carcinoma is stated to be a unique and challenging tumour because of the frequent occurrence of paraneoplastic syndromes, including: hypercalcemia, erythrocytosis, and non-metastatic hepatic dysfunction (for example, Stauffer syndrome).

❖ Poly-neuromyopathy, amyloidosis, anaemia, fever, cachexia, weight loss, dermatomyositis, increased erythrocyte sedimentation rate (ESR), and hypertension are also documented to be associated with renal cell carcinoma.

❖ Cytokine release by tumour (for example: interleukin (IL)-6, erythropoietin, nitric oxide) causes these paraneoplastic conditions.

❖ Resolution of symptoms or biochemical abnormalities may ensue successful treatment of the primary tumour or metastatic foci.

Clinical Examination Findings

The ensuing summations have been made regarding the physical examination findings in patients who are afflicted by RCC: [1]

About 30% of patients with renal carcinoma (RCC) manifest with metastatic disease. The clinical examination that is undertaken has been recommended to include a thorough evaluation for metastatic disease, particularly within the following organs with the documented percentage findings of metastatic lesions within the organs: [1]

- Lung (75%)
- Soft tissues (36%)
- Bone (20%)
- Liver (18%)
- Cutaneous sites (8%)
- Central nervous system (8%)

The advised findings during clinical examination of patients afflicted by RCC that should raise clinical suspicion for RCC include the following:

- In male patients, the presence of a varicocele and findings of paraneoplastic syndromes.

- Hypertension, supraclavicular adenopathy, and a flank or abdominal mass within.

Diagnostic Considerations

The ensuing summations have been made related to the diagnostic considerations for RCC: [1]

- Renal cell carcinoma (RCC) is a diagnostic consideration when a renal mass is found on a radiology imaging study. In 25% to 30% of cases, renal cell carcinomas are found incidentally in asymptomatic patients.
- A renal mass of indeterminate aetiology should be monitored periodically by the undertaking of radiology imaging studies such as intravenous pyelography (IVP), ultrasound scan, or computed tomography (CT) scanning. A cystic mass could be simply observed; nevertheless, patients with a solid mass should have a complete workup, including evaluation for metastatic disease and vascular extension of the primary tumour.
- Other documented diagnostic considerations in patients with a renal mass include the following: [1]
  - Abscess
  - Angiomyolipoma (benign neoplasm)
  - Metastasis from a distant primary lesion
  - Metastatic melanoma
  - Oncocytoma (benign neoplasm)
  - Renal adenoma (benign neoplasm)
  - Renal cyst
  - Renal infarction
  - Sarcoma
- It has been iterated that excruciating, sharp, bandlike back pain could be an early warning manifestation for spinal cord compression due to metastatic renal cell carcinoma and should not be ignored. It has been advised that urgent magnetic resonance imaging should be undertaken to exclude spinal cord compression, and high-dose dexamethasone therapy should be commenced.

It is worth pointing out that patients who have Bosniak 4 or Bosniak 5 lesions within their kidneys should undergo radiology image guided biopsy of their lesions due to the high possibility of the lesions containing a tumour. Also, patients who have Bosniak 3 cystic lesions within their

kidneys that has increased in size over a period of observation should also undergo radiology-image guided biopsy of their cystic lesions for pathology examination to exclude renal cell carcinoma.

Differential Diagnoses

Some of the iterated differential diagnoses of RCC include the ensuing conditions: [1]

- Acute pyelonephritis
- Urinary bladder cancer
- Chronic pyelonephritis
- Wilms Tumour
- Non-Hodgkin Lymphoma (NHL)

Approach Considerations

Summations related to the approach considerations of RCCs include the ensuing: [1]

- ❖ With the increasing use of radiology imaging studies, renal cell carcinoma (RCC) is increasingly detected incidentally, as a suspicious mass upon abdominal computed tomography (CT) or ultrasound scan. [1] [17] [18] Fewer patients manifest with symptomatic disease (for example: visible haematuria, flank mass, or pain).
- ❖ RCC is remarkable for the frequent occurrence of paraneoplastic syndromes, including: hypercalcemia, erythrocytosis, and nonmetastatic hepatic dysfunction (for example, Stauffer syndrome). Hence, laboratory studies in the assessment of RCC should include a workup for paraneoplastic syndromes.
- ❖ A number of radiology imaging options are utilised to assess and stage suspected renal cancer, including the ensuing:
  - CT scan of the abdomen, preferably with pelvic CT scan
  - Magnetic resonance imaging (MRI) scan, if venous involvement is suspected or the patient cannot tolerate contrast
  - Ultrasound scan
  - CT scan of thorax or chest x-ray
  - Excretory urography
  - Renal arteriography
  - Venography

- Bone scan if bone metastasis is suspected or alkaline phosphatase level is elevated
- Brain CT or MRI if patient has clinical presentations indicative of brain metastases

❖ It has been pointed out that the determination of whether a space-occupying renal mass is benign or malignant could be difficult as well as that radiology imaging studies should be tailored in order to enable further characterization of renal masses, so that non-malignant tumours could be distinguished from malignant tumours. [1]

❖ Contrast-enhanced CT scanning has become the radiology imaging procedure of choice for diagnosis and staging of renal cell cancer and has virtually replaced excretory urography and ultrasound scan of renal tract. [1]

❖ It has been pointed out that ultrasound scan examination could be useful in the assessment of questionable cystic renal lesions if CT scan imaging features of the renal lesion is inconclusive. It has been pointed out that large papillary renal tumours are frequently undetectable by ultrasound scan of the renal tract. [1]

❖ It has been iterated that excretory urography is not utilised frequently in the initial assessment of renal masses because of its low sensitivity and specificity. A small- to medium-sized tumour might be missed by excretory urography. [1]

❖ The undertaking of renal artery angiography is not utilised in the assessment of a suspected renal mass as frequently now as it was previously. [1]

❖ When inferior vena cava involvement by RCC is suspected, either inferior venacavography or magnetic resonance angiography (MRA) is utilised. MRA is currently the preferred imaging technique. [1]

❖ Knowledge of inferior vena cava involvement by RCC is important in planning the vascular aspect of the operative procedure. [1]

❖ Positron emission tomography (PET) imaging has remained controversial in kidney cancer. Currently, PET is not considered a standard part of the diagnosis of kidney cancer or in follow-up for evidence of relapse after nephrectomy.[1] [19]

❖ PET has a better sensitivity for the identification of metastatic lesions than for the identification of presence of cancer in the renal primary site. [1]

❖ When clinically indicated, bone scans are undertaken both in initial workup and follow-up. A bone scan is recommended for patients

who manifest with pain or an elevated alkaline phosphatase level. [1] [19]

Initial Laboratory Studies

The ensuing were stated to be the initial laboratory studies in the assessment of suspected renal cell carcinoma (RCC): [1]

- Urinalysis (UA) with urine cytology (if central lesion)
- Urine cytology (if central lesion is present, to evaluate for urothelial carcinoma)
- Full blood count (FBC) with differential
- CRP and serum urea and electrolytes
- Renal function tests
- Liver function tests (LFTs): Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
- Serum calcium
- Other tests as indicated by the patient's manifesting signs and symptoms.

Computed Tomography and Magnetic Resonance Imaging

The ensuing summations have been made about computed tomography and magnetic resonance imaging scan in RCCs: [1]

- ❖ It has been pointed out that Contrast-enhanced computed tomography (CT) scanning has become the radiology imaging procedure of choice for the identification and staging of renal cell cancer and has virtually replaced excretory urography and renal ultrasound scans.
- ❖ It has also been stated that in the majority of cases, CT imaging could differentiate cystic masses from solid masses and supply information about lymph node, renal vein, and inferior vena cava involvement.
- ❖ The 2017 American Urological Association (AUA) guideline for the management of the clinical T1 renal mass has recommended as a high-quality cross-sectional CT scan or MRI scan, first without and then with intravenous contrast if kidney function is adequate. The objectives are as follows: [1] [20]
  - To exclude angiomyolipoma radiographically if possible
  - To assess for locally invasive features

- To study the involved anatomy associated with the tumour and the kidney
- To ascertain the status of the uninvolved kidney and its vasculature

❖ The National Comprehensive Cancer Network (NCCN) guidelines for kidney cancer has recommended the ensuing as part of the initial workup: [1] [19]
- Abdominal/pelvic CT or abdominal MRI scan with or without contrast, depending on renal insufficiency
- Imaging of the thorax
- Brain MRI, if clinically indicated

❖ The NCCN guideline has recommended the abdominal MRI scan to assess suspected tumour involvement within the inferior vena cava, or as an alternative to CT for renal mass detection and staging in cases where utilisation of contrast is contraindicated because of allergy or renal insufficiency. [1] [19]

❖ A study by Sauk et al. concluded that multidetector CT imaging characteristics may aid in distinguishing differences at the cytogenic level among patients who have clear cell renal cell carcinomas. Imaging features which proved significant included degree of attenuation and presence of calcifications. [21]

Percutaneous Biopsy of the renal mass lesion

❖ It has been iterated that percutaneous cyst puncture and fluid analysis is utilised in the assessment of potentially malignant cystic renal lesions which have been detected by ultrasound scan or computed tomography imaging. [1]

❖ It has been documented that, based upon the AUA management guideline, a renal mass core biopsy through a percutaneous approach, with or without fine needle aspiration, is indicated in patients for whom the results might affect approach to treatment. [1]

❖ It has been pointed out that biopsy is especially appropriate in patients with clinical or radiographic evidence of lymphoma, abscess, or metastasis. [20]

Histology

❖ It has been iterated that renal cell carcinoma (RCC) has the following common sub-types, in addition to other rare sub-types: [1]

- Clear cell or conventional (75% of cases)
- Papillary (10-15%)
- Chromophobe (5%)
- Collecting duct (< 1%)
- Translocation associated
- Tubulocystic
- Unclassified

❖ It has been iterated that Clear cell carcinoma is characterized by unusually clear cells with a cytoplasm which is rich in lipids and glycogen, and it is most likely to demonstrate 3p deletion. [1]
❖ Papillary renal cell carcinomas are divided into type 1 and type 2. [1]
❖ Papillary tumours are more likely to be bilateral and multifocal and might have trisomy 7 and/or trisomy 17. [1]
❖ Chromophobe carcinoma is typified by large polygonal cells with pale reticular cytoplasm, and it does not exhibit 3p deletion. [1]
❖ Collecting duct carcinoma is an unusual variant that is characterized by a very aggressive clinical course. This disease tends to afflict younger patients and may manifest as local or widespread advanced disease. These cells could have three different types of growth patterns: acinar, sarcomatoid, and tubulopapillary. [1]
❖ Sarcomatoid de-differentiation might occur with several subtypes and tends to be associated with a poor prognosis. [1]

Procedures

The following may be undertaken to exclude urothelial carcinoma: [1]

- Cystoscopy and ureteroscopy of central lesions
- Biopsy of central mass lesions

Staging of Renal Cell Carcinoma [1]

The following are some of the staging systems that tend to be utilized for the staging of RCC:

- The Robson modification of the Flocks and Kadesky system
- The tumour, nodes, and metastases (TNM) classification
- The American Joint Committee on Cancer (AJCC) staging system

Robson staging system

The Robson modification of the Flocks and Kadesky system is said to be uncomplicated and is commonly utilised in clinical practice. This system was designed to correlate stage at manifestation with prognosis and is as follows: [1]

- Stage I – Tumour that is confined within the capsule of the kidney
- Stage II – Tumour invading perinephric fat but still contained within the Gerota fascia
- Stage III – Tumour invading the renal vein or inferior vena cava (A), regional lymph node involvement (B), or both (C)
- Stage IV – Tumour invading adjacent viscera (excluding ipsilateral adrenal) or distant metastases

TNM classification

The ensuing summations had been made about the TNM classification of renal tumours. [1]

- ❖ TNM classification is endorsed by the AJCC. The major advantage of this system is that it clearly differentiates individuals who have tumour thrombi from those with local nodal disease. In the Robson system, stage III disease includes both inferior vena cava involvement (stage IIIA) and local lymph node metastases (stage IIIB). Even though patients with Robson stage IIIB renal carcinoma have greatly decreased survival rates, the prognosis for patients with stage Robson IIIA renal carcinoma is not markedly different from that for patients with Robson stage I or II renal carcinoma. The TNM classification system is delineated below. [1]
- ❖ Primary tumours (T) are defined as the following:
  - TX – Primary tumour cannot be assessed
  - T0 – No evidence of primary tumour
  - T1 – Tumour 7 cm or smaller in greatest dimension, limited to the kidney: T1a, ≤4 cm; T1b, 4-7 cm
  - T2 – Tumour larger than 7 cm in greatest dimension, limited to the kidney: T2a, 7-10 cm; T2b, > 10 cm
  - T3 – Tumour extends into major veins or invades adrenal gland or perinephric tissues but not beyond the Gerota fascia: T3a, tumour invades adrenal gland or perinephric tissues but not beyond the Gerota fascia; T3b, tumour grossly extends into the renal vein(s) or vena cava below the diaphragm; T3c, tumour

grossly extends into the renal vein(s) or vena cava above the diaphragm
- T4 – Tumour invading beyond the Gerota fascia

❖ Regional lymph node (N) classification is not affected by laterality and is defined as follows: [1]
- NX – Regional lymph nodes cannot be assessed
- N0 – No regional lymph node metastasis
- N1 – Metastasis in regional lymph node(s)

❖ Distant metastasis (M) is defined as the following: [1]
- M0 – No distant metastasis
- M1 – Distant metastasis

AJCC staging system [1]

❖ The AJCC stages are as follows: [1]
- Stage I – T1, N0, M0
- Stage II – T2, N0, M0
- Stage III – T1-2, N1, M0 or T3a-c, N0-1, M0
- Stage IV – T4; or any T, N2, M0; or any T, any N, M1

❖ It has been iterated that the division of patients with renal cell carcinoma into low-, intermediate-, and high-risk groups with or without metastases may be useful in choosing appropriate therapy for these individuals. [1] [3] [22]

Approach Considerations [1]

❖ It has been iterated that the treatment approach to renal cell carcinoma (RCC) is guided by the probability of cure, which is related directly to the stage or degree of tumour dissemination. [1] [3] [4] [5]

❖ More than 50% of patients with early-stage RCC are documented to be cured, but the outcome for stage IV disease is poor.

❖ The American Urological Association guideline for management of clinically localized sporadic renal masses suspicious for RCC in adults has recommended reviewing all available treatment options and the associated benefits and risks with the patient. This review should entail oncologic issues, kidney function issues, and potential complications. [1] [20]

❖ The principal treatment options for RCC include the ensuing: [1]
- Surgery
- Thermal ablation
- Active surveillance
- Radiation therapy

- Immunotherapy
- Molecular-targeted therapy

❖ Therapy considerations should include the following: [1]
- Surgical resection remains the only known curative treatment for localized RCC, and it is also undertaken for palliation in metastatic disease.
- Radiofrequency ablation by an interventional radiologist could be considered as an alternative treatment for small lesions in carefully selected patients who are not candidates for the undertaking of surgery.
- Targeted therapy and immunomodulatory agents are considered standards of care in patients with metastatic disease.

❖ Options for chemotherapy and endocrine-based approaches are limited, and no hormonal or chemotherapeutic regimen has been accepted as a standard of care.

❖ Objective response rates with chemotherapy, either single-agent or combination, are usually lower than 15%. In view of this, various biologic treatment options have been evaluated. [1]

❖ RCC is an immunogenic tumour, and spontaneous regressions have been reported in the literature. Many immune modulators have been used successfully, including the following: [1]
- Interferon (IFN) and interleukin-2 (IL-2)
- The programmed cell death–1 (PD-1) protein receptor blocker nivolumab and similar immune checkpoint inhibitors
- Bacillus Calmette-Guérin (BCG) vaccination
- Autologous vaccines
- Lymphokine-activated killer (LAK) cells plus IL-2
- Tumour-infiltrating lymphocytes
- Nonmyeloablative allogeneic peripheral blood stem cell transplantation

❖ About 25% to 30% of patients manifest with metastatic disease at the time of their diagnosis, and fewer than 5% have a solitary metastasis. [1]

❖ The undertaking of surgical resection is recommended in selected patients with metastatic RCC. This procedure may not be curative in all patients but may lead to long-term survival in some cases. The possibility of disease-free survival tends to increase pursuant to resection of the primary tumour and excision of isolated metastasis. [1]

- The undertaking of surgical resection of a solitary metastasis is recommended in selected patients who have good performance status. [1]
- A large retrospective analysis from a single institution demonstrated an improved cancer-specific survival advantage, even with resection of more than one metastatic lesion. The study also revealed increased risk of death from RCC in patients who did not undergo surgical resection of metastasis. [23]
- A study by Alt and associates found that complete resection of multiple RCC metastases may be associated with long-term survival. [24]
- It has been iterated that active surveillance might be an acceptable approach to delay or avoid further intervention in the patient at high surgical risk. [1]
- It has been iterated that candidates for active surveillance include selected patients older than 70 years who have asymptomatic renal masses and slow growth documented on serial imaging. [1]
- A retrospective single-institution review of 51 patients demonstrated no metastatic spread with a median follow-up of almost 6 years; only 2 patients needed surgical intervention for local progression or symptoms. [25]
- The treatment of metastatic RCC has tended to be problematic, so it has been advised that whenever possible, patients should be directed to approved and controlled clinical trials. This applies as well in the adjuvant treatment of surgically resected RCC, for which no therapy has yet been found to offer survival benefit. [1]

Surgical Treatment

- It has been pointed out that surgical resection remains the only known effective treatment for localized renal cell carcinoma, and it is also undertaken for palliation in metastatic disease. [1]
- Partial or radical nephrectomy may be undertaken, depending upon the tumour and patient characteristics. Open, laparoscopic, or robotic surgical techniques may be utilised. [1]

Partial Nephrectomy

Some of the summations made related to the undertaking of partial nephrectomy in RCC include the ensuing: [1]

- For a T1a renal mass, the National Comprehensive Cancer Network (NCCN) has recommended partial nephrectomy, stating that radical nephrectomy should not be undertaken when nephron-sparing procedures are possible. [1]
- For T1b tumours, the NCCN guideline iterated that the standard of care is either radical nephrectomy or partial nephrectomy (when possible). [19]
- With regard to patients with a T1 renal mass, the AUA management guideline has recommended prioritizing partial nephrectomy, as it minimises the risk of chronic kidney disease (CKD) or CKD progression and is associated with favourable oncologic outcomes, including excellent local control. [20]
- Thermal ablation is a less invasive treatment option that might be preferable in the patient at high surgical risk, but it is associated with a higher risk of local tumour recurrence when compared with surgical excision. Biopsy is recommended for all patients undergoing thermal ablation. [1]
- The AUA guideline panel has cautioned that larger tumours (> 3.5 cm) and those with uneven shape or infiltrative appearance may be linked with increased risk of recurrence when managed with thermal ablation. [20] A study by Zagoria and associates found that in patients who are poor surgical candidates, radiofrequency ablation can emanate in durable oncologic control of renal cell carcinomas that are smaller than 4 cm. [26]

Radical Nephrectomy

The ensuing summations have been made regarding the undertaking of radical nephrectomy in renal cell carcinomas: [1]

- Radical nephrectomy, which remains the most commonly undertaken standard surgical procedure for the treatment of localized renal cell carcinoma, entails complete removal of the Gerota fascia and its contents, including a resection of kidney, perirenal fat, and the ipsilateral adrenal gland, with or without ipsilateral lymph node dissection. Radical nephrectomy provides a better surgical margin in comparison with simple removal of the kidney, because perinephric fat may be involved in some patients. About 20% to 30% of patients with clinically localized disease develop metastatic disease pursuant to undergoing nephrectomy. [1]
- AUA guidelines has recommended considering radical nephrectomy for patients who have a solid or Bosniak 3/4 complex cystic renal