Renal Cell Carcinoma: From a Pathologist’s Perspective

Sujatha Siddappa1* and Vilvapathy Senguttuvan Karthikeyan1

1Institute of Nephro Urology, India

*Corresponding author: Sujatha Siddappa, Department of Pathology, Institute of Nephro Urology, Bangalore, India, Email: sujathasiddappa@gmail.com

Published Date: April 30, 2016

INTRODUCTION

Investigation and management of Renal Cell Carcinoma (RCC) has undergone lot of change due to advances in genomics and biological discoveries. Recognition of mutations of the von Hippel-Lindau (vHL) gene and resultant stabilization of the hypoxia response pathway as a major driver of clear cell type RCC has gone a long way in targeting therapy [1-3]. Numerous new therapies are emerging [1].
EPIDEMIOLOGY AND ETIOLOGY

RCC is a common malignancy with an increasing incidence over the past decade, largely due to the increased incidental detection of Small Renal Masses (SRMs) on cross-sectional abdominal imaging [4-6]. Worldwide, RCC is the 9th commonest cancer with the highest incidence in developed countries [1]. RCC is a tumour with increased predilection to the male sex with a ratio of 2:1 peak incidence is between the ages of 40 and 69 years. The point to be noted is that a significant number of RCC are reported in patients less than 20 years of age and inherited variants have also been documented [7]. Though reason for this and in men is not clear, genomic, occupational, and other environmental exposures such as smoking have been implicated. With the increased use of abdominal imaging, more and more incidental renal masses and RCC are being discovered [8]. The exact cause for sporadic tumours is still unknown. Surrogate risk factors include smoking, obesity, systemic hypertension and phenacetin use. The lowest incidence is in countries of the Asian sub-continent and the end of the spectrum comprises of the European nations and South American region [7].

CLINICAL PRESENTATION

The classic triad of abdominal mass, hematuria, and flank pain accompanied by the various associated paraneoplastic syndromes (internist’s tumor) exists only in half of the patients. With widespread abdominal imaging, more than half of all renal tumors are incidentally discovered at a low stage and are increasingly amenable to treatment [4]. RCC predominantly presents as an incidental diagnosis and are almost always lower grade or stage of disease process and hence herald a better prognosis [7]. Thus in the modern era, RCC is being referred to as the “radiologist’s tumor” [4]. In addition, common findings include low haemoglobin, fever and elevated Erythrocyte Sedimentation Rate (ESR). The uncommon presentation is a non-functional liver and kidney (hepatorenal), increase in the number of red blood cells – polycythemia, increased calcium, inflammation of the blood vessels, emboli in the blood vessel - thromboembolism, nephritic syndrome and increased blood sugar levels due to glucagon secretion. Gonadotropin, renin and mineralocorticoid secretion or deficiency and prolactin secretion, alpha fetoprotein deficiency or systemic amyloidosis has been reported. In accordance to publication documentation the finding of microscopic hematuria is a salient finding [7].

CLASSIFICATION AND PATHOLOGY

We have come to know in the past decade that not all RCC are related and all cancers are independent entities [9]. RCC are adenocarcinomas, derived from renal tubular epithelial cells [10]. RCC are circumscribed by a pseudocapsule of compressed parenchyma and fibrous tissue and are not grossly infiltrative, except collecting duct RCC and sarcomatoid variants. Grossly RCC consist of yellow, tan, or brown tumor interspersed with fibrotic, necrotic, or hemorrhagic areas with cystic degeneration in 10-25% of RCC (Figure 1). Cystic degeneration is associated
with a better prognosis [11,12]. Calcification is found in 10-20% and can be stippled or plaque like. Nuclear features are graded based on nuclear size and shape and prominence of nucleoli by Fuhrman's system. It is an independent prognostic factor for Clear Cell RCC (CCRCC) and a significant predictor of outcome for PRCC (Figure 2) [11,13-15]. Invasion of renal capsule, sinus or collecting system is found in 20% and further spread is often precluded by the Gerota fascia. Most RCC are believed to originate from normal proximal tubular cells as suggested by their ultrastructure like microvilli and renal medullary carcinoma and collecting duct carcinoma which are more aggressive and arise from distal elements of the nephron [11,16-18]. Clear cell, papillary, chromophobe renal cell carcinomas, collecting duct carcinoma, renal medullary carcinoma, and urothelial carcinomas occur in the kidney along with benign lesions mimicking RCC or complicating its management [11]. Additionally sarcomatoid variants have been identified as forms of differentiation of each of the preceding five histological variants. We also have the unclassified type which shows hybrids of the recognised tumour, sarcomatoid type of malignancy without recognizable epithelial component and neoplasms which contain whose description is not listed in the preceding variants. This would continue to be a sub-category with fluidity. The conclusion is that of WHO classifies all the variants with no major exclusions [1,7]. The International Union against Cancer staging system for RCC defines Stage 1 renal mass as an organ-confined tumor up to 4 cm diameter (T1a) and between 4.1 and 7.0 cm in diameter (T1b). Stage 1 renal masses are amenable for Nephron-Sparing Surgery (NSS) and this is the preferred approach to the resectable SRM [4].

**Figure 1:** Mounted museum specimen of renal cell carcinoma - Classic RCC; Well circumscribed tumor with variegated appearance.
Salient Gross Features

Bilateral occurrence of RCC has been accounted for in 1-2% and they can be synchronous or metachronous [1,7]. In 7-19%, multiple lesions in the kidney occur and clinicians have mammoth task in finding the correct approach towards the tumour [7]. There is no single common feature for all the variants and each have their own unique presentation, therein lies the beauty of these tumours and inkling of what it could start from a thorough gross exam of the specimen itself.

Clear cell RCC (ccRCC)

They make up to around 70% of all renal cancers [1]. Histologically, they have clear cytoplasm, with nested clusters of cells surrounded by a dense endothelial network, hence the name [1]. Most sporadic RCC are unilateral and unifocal. Bilateral involvement (synchronous or asynchronous) is found in 2-4% of sporadic RCC, although it is considerably more common in patients with familial RCC, such as vHL disease. Multicentricity, found in 10-20% of cases, is more common in association with papillary histology and familial RCC [7,11,19-21]. Satellite lesions are often small and difficult to identify by preoperative imaging, intraoperative ultrasonography, or visual inspection; they appear to be the main factor contributing to local recurrence after partial nephrectomy [19]. Microsatellite analysis suggests a clone origin for most multifocal RCC within the same kidney, but tumor in the contralateral kidney is likely to be an independent growth if it is synchronous or a metastasis if it is asynchronous [22,23]. CCRCC accounts for 70-80% of all RCC [11,16]. They are highly vascular, containing a network of delicate vascular sinusoids interspersed between sheets or acini of tumour cells [7].

Gross

They are expansile circumscribed lesions in flush with adjacent renal parenchyma but are not infiltrating. The cut surface is predominantly golden yellow due to the lipid content of the tumour, haemorrhage and necrosis is a common finding, the higher the grade the lesion is prone to have
more tan-brown areas that are visible on serial sectioning. Hereditary tumours by rule of thumb are prone for multicentricity (Figure 3). The other point to be kept in mind is that haemorrhage necrosis will lead to reabsorption and all that is left is a small tumour which is viable and the rest is hemorrhagic. Calcification and osseous metaplasia is a common finding which amounts to 10% of the CCRCC [7,11].

![Figure 3: von Hippel Lindau (VHL) syndrome; Renal cell carcinoma: Large tumor with characteristic yellow appearance with small cysts in cortex and second tumor in lower pole.](image)

**Microscopy**

Clear cells are typically round or polygonal with abundant cytoplasm containing glycogen, cholesterol, cholesterol esters, and phospholipids [24]. Granular cells with eosinophilic cytoplasm and abundant mitochondria can predominate. CCRCC is more likely to exhibit venous tumor extension [25]. The cells are arranged in nests, acini, solid sheets and alveolar structures. The common finding is that no matter what the presentation is they are suspended in a delicate fibrovascular stroma (Figure 4). The other finding is a cyst due to haemorrhage and reabsorbing with very little viable tissue lining the cyst wall available for diagnosis. In addition intracytoplasmic pigment laden cell rhabdoid features and cells with intracytoplasmic hyaline globules are seen. Features of sarcomatoid features are also seen rarely. Nuclei are graded as per Fuhrman’s system. Immuno profiling of CCRCC is positive staining for EMA, low molecular weight cytokeratin, CAM 5.2 AE1/AE3, CK18, vimentin and CD10. RCC markers show brush border reactivity [7,13]. Prognosis is worse even after stratification for stage and grade [26,27]. Chromosome 3 alterations occur in more than 90% of CCRCC, leading to mutation or inactivation of the VHL, PBRM1, SETD2, or BAP1 genes. The familial form of CCRCC, the vHL syndrome has tumour suppressor gene inactivated. Genetic feature closely associated with this CCRCC is loss or germ line mutation of the VHL tumour suppressor gene and is identified in 60-90% of sporadic cases. Loss of this protein results in stabilization of the family of Hypoxia Inducible Factors (HIF) which are protein transcriptional activators of genes involved in mediating hypoxia response. This transactivates genes involved
in angiogenesis, cell migration, and metabolism. The most commonly inactivated genes include PBRM1, BAP1, and SETD2. Mutations occur in a variety of additional histone modifiers (KDM5a, ARID1a, and UTX) [7,11]. Recent evidence suggests an association between SETD2 mutations and changes in chromatin packaging [28-30]. Mutations in genes associated with mTOR pathway signalling (PIK3CA, PTEN, and MTOR) are also identified [1]. Genetic eccentricity and chromosomal addition and deletion are to be taken into consideration in cases of metastatic tumors since they play a prominent role in tumour progress and its associated risk factors towards progress of the tumour [7,11].

![Image](image.jpg)

**Figure 4:** A. VHL, renal carcinoma - Clear cells and cysts; B. Typical alveolar arrangement of cells (H&E; 40X).

**Multilocular Cystic RCC**

This basically an uncommon variant of RCC. This has been separated as an entity in the current WHO classification. This was primarily interpreted as cystic lymphangioma, synonymously known as Pearlman’s tumor with peak incidence between the 2nd and 8th decades [7].

**Gross**

They appear as multiloculated cysts surrounded by a fibrous capsule (Figure 5).

![Image](image2.jpg)

**Figure 5:** Multilocular cystic RCC.
Microscopy

They are seen as cystic cavity lined by clear cell carcinoma cells as in Fuhrman nuclear grade 1 (Figure 6). The differentiating feature between cystic nephroma and the present tumour is that the tumour cells are in the stroma which not seen in cystic nephroma. The conclusion is that multilocular cystic neoplasm of low malignant potential [7].

Figure 6: Multilocular cystic RCC; A. Septa contain epithelial cells (mistaken for lymphocytes); B. Epithelial cells in the septa of multilocular cystic RCC react with antibodies to epithelial markers - EMA expression.

Papillary RCC (PRCC)

PRCC is the second most common tumour and has two subtypes - types 1 and 2 [11]. The diagnosis is made based on features of papillary architecture on microscopy. Cells typically display a basophilic cytoplasm, and the foamy histiocytes are characteristic of PRCC [1]. The second most common histological subtype, represents 10-15% of all RCC [15]. Occurrence is common between 6th and 8th decades. Clinically they present as hematuria without mass per abdomen, hence they are identified incidentally most often [7,11].

Gross

They are white with spherical fairly well defined mass normally has a granular appearance and frequent haemorrhage, mimicking cystic components radiologically (Figure 7). Hemorrhage and necrosis is more prominent when the tumor is large. Bilaterality and multicentricity is seen in 40% and is more common in end-stage renal failure and acquired renal cystic disease [7,26]. The cytogenetic abnormalities associated with the more common type 1 PRCC are characteristic and include trisomy of chromosomes 7 and 17 and loss of the Y chromosome [31]. PRCC is more likely to be hypovascular, perhaps owing to the lack of VHL mutations that regulate VEGF, the primary proangiogenic molecule in RCC [32]. Mutations in the MET proto-oncogene predisposes
to multifocal T1 PRCC and mutations in the Fumarate Hydratase (FH) gene carries a risk for familial T2 PRCC [33,34]. Though sporadic tumours fall into the T1 or T2 PRCC, it is not clear about the mutations and if they are similar to hereditary PRCC [1].

Figure 7: Papillary renal cell carcinoma. A. Papillary appearance in friable tumour. B. Gross showing tumour haemorrhage and pseudoencapsulation. C. Yellow streaks reflecting foamy macrophages.

Microscopy

PRCC has basophilic or eosinophilic cells arranged in papillary or tubular configuration’s the nomenclature is based on the dominant histological presentation. They are sub-classified as types 1 and 2 based on their cytological features. Type 1 PRCC is characterised by papillary structures or tubules lined by epithelial cells that are small by minimal cytoplasm and hyperchromatic nuclei that are uniform in size and some of them exhibit features of grooving (Figure 8). Type 1 PRCC is more common with basophilic cells and scant cytoplasm and associated with HPRCC syndrome (Figure 9). Type 2 tumours comprise of comparatively larger cells with pleomorphic nuclei and prominent nucleoli in a pseudo-stratified manner (Figure 10). The point to be noted is that both the grades may show predominantly tubular forms or in the form of sheets, in the absence of papillary form calcification and psammoma bodies can be seen, hemorrhage and necrosis in this tumour does not portend bad prognosis. Foamy macrophages and pigment laden macrophages are common (Figure 11). Papillary variant has lymphnode metastasis, vascular invasion. Subsequent distant metastasis is not a common finding. IHC profile of PRCC includes positive staining with AE1/AE3, EMA, vimentin, CD10, RCC markers and acetyl CoA racemaseas with CCRCC CD10 will be present at least focally in most cases mucicarmine and PAS will exhibit focal positivity CK7 is positive for grade 1 carcinoma and negative for grade 2 [7,11,26].
Figure 8: PRCC; A. Foamy macrophages with papillae; B. Tubulopapillary pattern.

Figure 9: PRCC; A. Eosinophilic cytoplasm; B. Nuclear pseudostratification and eosinophilic cytoplasm.

Figure 10: Hereditary papillary renal cell carcinoma (HPRCC) A; Tumors with papillary or tubulo-papillary architecture, type 1. Macrophages seen in papillary cores; B. Hereditary PRCC showing diffuse positivity for antibody to cytokeratin 7.
Chromophobe RCC (CRCC)

Tumor cells in this histological type have a largely empty cytoplasm and typically have the characteristic perinuclear clearing, with a low mitotic rate and these have the lowest risk of developing metastases [1]. CRCC represents 5% of all RCC and appears to be derived from the cortical portion of the collecting duct [35]. Loss of chromosomes 1, 2, 6, 10, 13, 17, and 21, 24 mutations in PTEN (10q23), TP53 (17p13) and mutations in tumor suppressor genes have been identified in CRCC [1]. The familial syndrome is linked to Birt-Hogg-Dube (BHD) syndrome caused by germ line mutations in the folliculin gene, FLCN [36,37]. They usually present in the 5th to 7th decades and there no evidence of gender predominance. In most cases this is an incidental finding [7,11].

Gross

They are usually well-defined or well circumscribed tan coloured masses which range from 8-20 cm (Figure 12). The cut surface shows foci of hemorrhage and necrosis, in 90% of the cases the tumour is within the confines of the kidney [7,11].

Figure 11: Hereditary leiomyoma renal cell carcinoma (HLRCC); A. Papillary architecture, type 2 (H&E staining, x10); B. Thick papillae are covered by tall cells with abundant cytoplasm, large pseudostratified nuclei and prominent nucleoli.
Figure 12: Chromophobe RCC-typical homogenous tan colored tumor in lower pole.

Microscopy

The tumor cells typically exhibit a relatively transparent cytoplasm with a fine reticular pattern that has been described as a “plant cell” appearance. Most CRCC are resistant to the pigment used during typical hematoxylin and eosin staining, but eosinophilic variants constitute about 30% of cases [38,39]. In either case, a perinuclear clearing or “halo” is typically found and electron microscopic findings consist of numerous 150-300nm microvesicles, which are the single most distinctive and defining feature of chromophobe cell carcinoma and characteristically stain positive for Hale colloidal iron, indicating the presence of a mucopolysaccharide unique to CRCC (Figure 13-15) [11]. The point of interest is that the classical chromophobe tumour has two populations of cells -the larger pale chromophobe cells and smaller eosinophilic cells with nuclei with perinuclear halo. The larger cells are usually seen lining the vascular channels. The eosinophilic cells have nuclear features of resinoid, crenated or irregular shapes, but the tumour can present as exclusive cell population. Cell membranes are prominent almost plant like in appearance typically and binucleation is a common finding. Occasional sarcomatoid features are also seen. Microscopically typically solid brad columns with cores separated by delicate vascular stroma are seen [7].
Renal Cell Carcinoma

Immunohistochemistry

IHC reveals positive staining for pan-cytokeratin, epithelial membrane antigen, and parvalbumin and negative for vimentin and CD10 [35]. CRCC is commonly seen in the Birt-Hogg-Dubé syndrome, but most cases are sporadic (Figure 16) [40]. Most studies of the clinical behaviour of CRCC suggest a better prognosis for localized CRCC than for CCRCC but a poor outcome in the subset of patients with sarcomatoid features or metastatic disease [41,42].
Figure 16: Birt-Hogg-Dubé syndrome (BHD); A. Hybrid oncocytic tumour composed of a mixture of clear cells and cells with abundant eosinophilic cytoplasm. B. Small cluster of clear cells is surrounded by normal tubules, scattered through the renal parenchyma.

Collecting Duct Carcinoma

Carcinoma of the collecting ducts of Bellini accounts for <1% of all RCC, presents earlier with advanced stage and poor prognosis and are infiltrative into cortex [35,43-45]. They show a gender predilection for the males 70%. More than 50% of the patients are above 50 years. The other interesting finding is that 50% of patients show regional lymph node involvement or diagnosis [7,11].

Grossly

On cut section this tumor is found in the central part of the kidney. The tumor is not well-defined and is rather in flush with the surrounding tissue. Grey to tan coloured with its size ranging from 2-23 cm with an average diameter of 4-6 cm. Larger tumours may replace the entire renal tissue by tumor and in certain cases is also seen bulging into the pelvis (Figure 17) [7,11].

Figure 17: Collecting duct carcinoma of Bellini-Tumor in flush with renal parenchyma.
**Microscopy**

They consist of dilated tubules and papillary structures lined by a single layer of cuboidal cells, creating a cobblestone appearance. Cells usually show grade 3 morphology. Prominent desmoplastic response with acute inflammatory infiltrate accompanies the infiltrating neoplasm. The tumor is seen infiltrating the adjacent renal parenchyma. Collecting ducts adjacent to the tumour will show cytological atypia. IHC stains AE1/AE3, EMA, vimentin, cytokeratin34, BE12, peanut lectin and common inference is that these that these markers are equivocal. Hematoxylin eosin stains are preferred modality for interpretation (Figure 18,19) [11].

![Collecting duct carcinoma; A. Medullary location; B. Tubular type; C. High power-small papillary infoldings of tubular lamina (H&E; 40X).](image)

**Figure 18:** Collecting duct carcinoma; A. Medullary location; B. Tubular type; C. High power-small papillary infoldings of tubular lamina (H&E; 40X).

![Collecting duct carcinoma; A. Tubulopapillary type of growth; B,C- High grade cytological atypia.](image)

**Figure 19:** Collecting duct carcinoma; A. Tubulopapillary type of growth; B,C- High grade cytological atypia.
Differential Diagnosis

PRCC appears to have interconnected structures and lack infiltrative features. Tubules are discrete within a fibrous stroma, with infiltrative features. A point to be noted is that this tumour is basically a diagnosis by exclusion. Deletions on chromosome 1q and monosomy of chromosomes 6, 8, 11, 18, 21 and Y have been reported [46-48]. Positivity for E-cadherin and c-KIT help to distinguish this entity from aggressive PRCC [49].

Prognosis

These patients have an overall bad prognosis. Most of the patients succumb to the tumour metastasis or present as presenting complaints of metastasis, 80% of the patients die of tumour metastasis within 2 years of diagnosis. The 10 Year Survival (YS) in one of the studies is around 1.5% [7,11].

RENAL MEDULLARY CARCINOMA

Renal medullary carcinoma almost exclusively in patients with the sickle cell trait and is typically diagnosed in young African-Americans, predominantly in the male, in the third decade of life also known as seventh sickle cell nephropathy [50,51]. There have also been reported cases without sickle cell trait. This carries worst prognosis with most patients succumbing to their disease in a few months and they are metastatic at diagnosis with a mean survival of 15 weeks. Renal medullary carcinoma is thought to arise from the calyceal epithelium near the renal papillae but is often highly infiltrative. It is found exclusively in patients with a hemoglobinopathy and it is most commonly the sickle cell trait. It is characterized by loss of expression of the chromatin regulatory gene SNF5/INI-1 [1,11]. It is also designated as an aggressive lesion a variant of collecting duct carcinoma. The patients present with hematuria, flank and abdominal pain. Patients also come with metastasis as the initial presentation. In the clinical setting of a young patient with sickle cell trait, local invasion of the renal sinus on radiology strongly suggests renal medullary carcinoma [7,11].

Gross

The neoplasm is medullary in location. Cut surface shows a poorly defined tan coloured lesion sizes range from 4-12 cm, focal haemorrhage, necrosis, and invasion of the perirenal fat and renal capsule. The other interesting finding is the presence of satellite lesions in the renal cortex [1,7].

Microscopy

The tumour has two main findings that the tumour cells which are large and irregularly placed are in diffuse nests are more or less equal in proportion to the second element the desmoplastic stroma. The latter two are the main components in forming the tumour mass. The two main patterns are adenoid or cystic pattern. The infiltrative margin is rimmed by lymphocytes and tumour cells admixed with neutrophils. The tumor cells are large with abundant cytoplasm.
The nucleus is high grade with prominent nucleoli. The stromal elements would be intermixed with stromal, rhabdoid or spindle in appearance; sickle cells are a rare finding since the tumour is associated with a trait of sickle cell. IHC stains positive for AE1/AE3, EMA, CAM5.2, CEA and epithelial mucin [1,7,11].

**SARCOMATOID DIFFERENTIATION**

Sarcomatoid differentiation is seen in 1-5% of RCC represent poorly differentiated regions of other histology subtypes of RCC [52,53]. It is characterized by spindle cell histology, positive staining for vimentin, infiltrative growth pattern, aggressive local and metastatic behaviour and poor prognosis (Figure 20). It is currently stated to a dedifferentiation of any of the RCC [7].

![Figure 20: CRCC with sarcomatoid dedifferentiation.](image)

**VARIANTS**

The prognosis is dependent on the extent of sarcomatous content in the lesion. The tumour is known to be associated with clear cell, papillary variant, chromophobe and collecting duct variant. It is a challenge in identifying the primary tumour it is originally associated with a diagnosis by deletion when after multiple sections fail to detect. Sarcomas of kidney are rare when compared to sarcomatoid tumours of the kidney [7,11].

**UNCLASSIFIED RCC**

Unclassified RCC represents 1-5% of presumed RCC are poorly differentiated and are associated with a highly aggressive biologic behavior and a particularly poor prognosis [54,55]. Low-grade tumors such as hybrid oncocytic tumors are indeterminate between CRCC and oncocytoma, should not be placed into this category, which denotes poor prognosis. These tumor types individually contribute to <5% each of RCC cases and are thought to be derived from the
tubules, with regional variance in the site of origin. They can also arise from the cells and tissues that constituting the renal medulla and collecting system. These tumors namely the collecting duct carcinoma, renal medullary carcinoma, and urothelial carcinoma are highly distinct disease entities with no much resemblance to ccRCC [1,7,11]. Classification will change as we move on over the years and the classification will be an inclusive one with the addition of this entity. The entity called as unclassified tumours will prevent the act of pigeonholing the tumour to its name regardless of its criteria [7].

**RARE NOT SO COMMON VARIANTS**

**Lympho Epithelial Carcinoma of the Kidney**

First reported in 2002 identified by soft tumour experts Elsilver and his colleagues. It was first identified in a female patient in her late 60s and with nodal metastasis. She succumbed to death with 10 months of diagnosis which treated was with radical nephrectomy and chemotherapy. Lymphocytic infiltrate with carcinomatous cells was observed [1,7,11].

**RCC Following Neuroblastoma**

The hypothesis is based on the tumours due to genetic susceptibility. The role of therapy for the evolution of the tumour is to be borne in mind. The time of detection of tumor ranges from 3-35 years. Their gender distribution is equal and both unilateral and bilateral presentations are documented. About 25% of the tumours has behaved in an aggressive manner but prognosis is dependent on the TNM staging. These tumours by their nomenclature per se are unique by virtue of the fact that they do not fit into the Heidelberg classification [1,7,11].

**Microscopy**

We can see the tumour cells in the form of sheets papillae and reticular fashion. All the cells are large with abundant eosinophilic to clear cytoplasm associated with pleomorphic nuclei and occasional giant cell. IHC is positive for cytokeratins CK8, and CK18, EMA and vimentin. Genetic studies of 14q31 and 29q13. Diagnosis is by corroborating with all the above factors [1,7,11].

Low grade mucinous tubular and spindle cell carcinoma: First documented in 1997, it has a female gender predilection and peak incidence is 6th to 8th decades. It is usually incidentally diagnosed and occasionally patients present with hematuria [1,7,11].

**Gross**

It is a solid tan coloured mass whose size ranges from 2-17 cm.

**Microscopy**

Predominantly cells are tubular to spindle shaped with bland cytological appearance. IHC is positive for cytokeratin, vimentin, NSE, EMA, chromogranin and AMCR [1,7].
RCC Due To Translocation and TFEB Gene Fusion

This is a recent addition. They usually present in childhood and in young adults with their ages ranging from 9-33 years. Microscopically they present as solid cords of cells with patchy papillary formation and psammoma bodies. They also have an alveolar pattern lined by large eosinophilic cells with clear cytoplasm or granular to clear cytoplasm with round nucleus and prominent nucleoli. IHC is invariably positive for HMB-45 and Melanin-A and is negative for keratin. Specific binding to TFEB protein is present. TFE3 is specific for Xp11.2 tumours [1,7,11].

The conclusion of the different histological classification gives a more eloquent picture of the nature of each tumour for its aggressiveness. In summary multilocular cystic carcinoma is least aggressive. Chromophobe and PRCC are of intermediate aggressiveness, collecting duct and medullary are of the most aggressive of histological variant [11].

Premalignant and benign Lesions Arising in the Kidney

Benign lesions like angiomyolipomas share radiographic characteristics with RCC. Sarcomatous change can produce a large growth and spontaneous haemorrhage. Oncocytomas which have low malignant potential, share cytological and biological features with CRCC and can complicate the diagnosis on histopathology [1].

STAGING AND PROGNOSIS

The staging of RCC goes back to 50 years. The commonest staging system is the AJCC Tumor Node Metastasis (TNM) system and it was last revised in 2010. (1)Patients with stage I RCC have a five year disease specific survival (5YS) of 80-95%. Stage II RCC has 5YS of around 80% and tumor invasion of the urinary collecting system is associated with significantly worse prognosis in stages I and II with 5YS dropping drastically to 60% In stage III RCC, 5YS is 60% and during the cytokine era (1986-2006), stage IV RCC had a 5YS <10%, with median Overall Survival (OS) of 10-15 months. With the advent of targeted agents, the median OS in patients with stage IV is beyond two years now [56-60]. In addition to the above mentioned factors tumour staging has a direct inverse impact on patient morbidity and mortality [1].

Nuclear Grading

Grade Description

1- Small, round, uniform nuclei with inconspicuous or absent nucleoli
2- Larger nuclei with irregular outline and small nucleoli
3- Larger nuclei with irregular outline and prominent nucleoli
4- Grade 3 features with bizarre, multinucleated cells with or without spindle cells

The above grading when relevantly applied will not only validate the tumour grading system but also will sub classify each tumour within each tumour stage group [13].
TNM STAGING OF RENAL NEOPLASM (AJCC 7TH EDITION, 2010) [1,61]

TX-primary tumor cannot be assessed
T0-no evidence of primary tumor
T1-Tumor 7cm or less in diameter, limited to kidney
T1a-Tumor 4cms or less in diameter, limited to the kidney
T2-Tumor more than 7 cm in diameter limited to the kidney
T3-Tumor invades the major vein or invades adrenal gland or perinephric tissue but not beyond the Gerota fascia
T3a-Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia
T3b-Tumor grossly extends into the vena cava below the diaphragm
T3c-Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4-Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
Nx-Regional lymph nodes cannot be assessed
N0-No regional lymph node metastasis
N1-Metastasis in regional lymph node(s)
Mx-Distant metastasis cannot be assessed
M0No-distant metastasis
M1-Distant metastasis

ROLE OF PERCUTANEOUS NEEDLE BIOPSY FOR RENAL MASSES

Despite more small (T1) tumours being identified mortality from RCC remains the same. Earlier detection and treatment have not had dramatic effects on population outcomes, thus implying that not all SRM will be dangerous. Percutaneous Renal Mass Biopsy (RMB) provides a minimally invasive method for discriminating benign from malignant renal masses, and helps in stratifying malignant risk. With advances in image-guidance, RMB can be performed safely and effectively, with a low complication and a high diagnostic yield (> 90%) [62]. There is a resurgence in RMB in the past 10 years to stratify patient risk and to avoid unneeded surgical or ablative therapies [63-68]. This change is due to increasing incidence of SRM, RCC, smoking, obesity, hypertension
and increased imaging utilization (ultrasound, Computed Tomography [CT], Magnetic Resonance Imaging [MRI]) performing earlier and aggressive surgical or ablative therapy, to rule out benign lesions before treatment decisions and low risk of significant complications following percutaneous RMB [62,69-72]. The established indications for RMB in solid renal mass are: known extra renal primary malignancy to identify if renal lesion is benign, malignant or metastatic; in unresectable solid renal mass for tissue confirmation before systemic and/or radiation therapy as no nephrectomy specimen may be available; in presence of significant comorbidities with minimal physiologic reserve and not suited for elective surgery and to decide how aggressively to manage the renal mass and if renal mass is presumed secondary to infection [62,64]. Imaging characteristics which suggest RMB should be done include: small homogeneous hyperdense avidly enhancing renal mass on CT and minimal fat AML; intracellular lipid-containing T2-hypointense renal mass on MRI; avidly arterially enhancing T2-hypointense renal mass on MRI; rapidly developing ill-defined mass in a patient with risk factors for urinary tract infection and to rule out focal bacterial pyelonephritis; infiltrative renal mass to rule out urothelial carcinoma and lymphoma as management of these entities differs dramatically from both one another and that of traditional solid renal masses; multiple solid renal masses without macroscopic fat to rule out lymphoma and hereditary syndromes (BHD syndrome, hereditary leiomyomatosis, familial renal oncocyotma) [73,74]. PB of the largest and/or most suspicious-appearing renal mass can help determine the type and aggressiveness of management [62].

**Techniques**

Coaxial technique has been devised to improve the biopsy success rate and reduce procedure time. A larger gauge cannula (18G) is advanced to the renal mass, and then a smaller gauge (≤21G) needle is placed through it. Fine Needle Aspiration (FNA) specimens are read by the cytopathologist at the time of the procedure to ensure the adequacy of the sample and core needle biopsies are for histological analysis [62]. Automatic side-cutting needles produce 8-17mm core specimens and can be sent in formalin. Reported sensitivity of FNA for diagnosing malignancy ranges from 64-97% and is highly dependent on the competence of the cytopathologist. Core needle biopsy has sensitivities for malignancy ranging from 79-100% and false-negative rates of 0-21% [62]. Core biopsy specimens has the advantage of being amenable for IHC and genomic analysis. Minimum number of specimens needed to provide an adequate specimen has not been determined [75].

**Complications**

Complications reported include haemorrhage, needle track seeding, pseudoaneursyms and arteriovenous fistulae [76-80]. Clinically significant hematomas or bleeding is unusual though >90% patients have some bleed. Needle track seeding is a potential risk is seen in <0.01% patients. Recent series report no cases of tumor seeding probably attributable to improved practices such as the coaxial technique [62].
Diagnostic Accuracy

The probability of malignancy within a small solid renal mass has been found to be inversely related to renal tumor size, with up to 22% of such masses measuring 1 to 4 cm proving benign. In addition, malignancies found in these smaller masses tend to be lower grade and more indolent than those found in larger masses [62]. In a recent study, Halverson, et al. retrospectively evaluated 151 small renal masses that underwent both percutaneous renal mass biopsy and subsequent partial or radical nephrectomy. For diagnosing malignancy, there was complete concordance between the histology rendered from core biopsy and that rendered by surgery. Histologic concordance was 94% and Fuhrman nuclear grade concordance was 65%. Similar results have been reported by others with histologic subtyping accuracy ranging from 88-94%, and grading accuracy ranging from 64-70% [80,81]. Lack of concordance was largely attributed to tumor heterogeneity, which is undoubtedly present in many tumors. Image-guided percutaneous renal mass biopsy is a highly accurate procedure with minimal morbidity that can be used to detect benign disease, differentiate primary from secondary renal masses, and decrease the number of unnecessary extirpative therapies. Image-guided biopsy will likely continue to aid in the management of incidentally detected renal masses, in particular for patients undergoing active surveillance algorithms and/or minimally invasive therapy [82]. Advances in the understanding of the limited biological potential of many SMRs, expanding treatment and surveillance options for RCC, improved biopsy techniques, and the integration of molecular factors into prognostic and therapeutic algorithm shave renewed interest in RMB. Intratumoral heterogeneity, sampling error and inconsistent classification of RMB failures in published studies make a precise determination of RMB accuracy difficult. Uniform reporting of RMB safety and efficacy in the literature as well as further studies addressing tumor heterogeneity and sampling error are needed. Differentiation of oncocytoma from oncocytic neoplasms poses a diagnostic dilemma, but incorporation of more sophisticated molecular analyses into enhanced RMB has promising potential [62,82].

Despite these limitations, RMB has a definite and expanding role in the evaluation and treatment of renal masses, but remains significantly underutilized. While the ability to differentiate between high and low grade malignancies remains the chief limitation of RMB, we anticipate the further integration of percutaneous biopsy into clinical algorithms will guide patient counseling and inform personalized decision making. Future studies will focus on the role of repeat biopsy and the use of biomarkers and molecular fingerprinting in order to facilitate a more rational approach to the management of renal masses [62].

MANAGEMENT OF LOCALIZED DISEASE

Partial (PN) or Radical Nephrectomy (RN) remains the gold standard for the management of renal masses. The selection of tumors for PN has long been dictated by the anatomic location of the tumor, tumor stage, or other features that limit the potential for a complete tumor resection [1].
Nephrectomy (Partial v Radical) and Laparoscopy

Randomized clinical trials have examined the potential for nephron sparing approaches to preserve kidney function and reduce the long term morbidity associated with having a solitary kidney [83]. RN has a 10YS of 81.1% and NSS has 10YS of 75.7% and PN had preservation of renal function [84]. The recent guidelines recommend PN when anatomically feasible or RN when appropriate [85]. Laparoscopy has the advantages of improved postoperative recovery and greater surgical field visibility. Laparoscopic PN is associated with an increased rate of conversion to RN when compared with robotic techniques and a greater decrease in estimated glomerular filtration rate. There were no significant differences with respect to warm ischemia time, estimated blood loss, transfusion rate, or postoperative complication and cost comparison models currently favour the standard laparoscopy [86].

Nephron Sparing Surgery

NSS includes surgical PN and ablative therapies such as cryoablation and radiofrequency ablation are also successfully used to preserve renal tissue on an ipsilateral renal unit. NSS has been proven feasible decades ago for patients with imperative indications to preserve maximum kidney function. Chronic Kidney Disease (CKD) has been linked to cardiovascular disease, hospitalization, and death [87,88].

Nephron Sparing Surgery (NSS) is the standard of care for clinically localized T1a SRMs, however alternative minimally invasive and conservative treatment options are possible in select comorbid or elderly patients [1]. The optimal treatment modality is based on clinical assessment of patient comorbidities and tumor characteristics, but SRMs represent a heterogeneous group of benign and malignant histologic entities, with clinical and biologic behaviour unpredictable by conventional imaging [1,62].

Indications for PN

Absolute indications for NSS include conditions rendering the patient dialysis dependent with complete resection of a tumor-bearing kidney. These conditions include bilateral tumors or a tumor in a solitary functioning kidney. Relative indications for NSS include conditions that present any current or future risk to renal function. These risks include, but are not limited to, calculus disease, renal artery stenosis, chronic pyelonephritis, ureteric reflux, diabetes, and hypertension [4]. General guidelines suggest that peripheral tumors 7 cm and smaller are more amenable to NSS. Better outcomes are observed with solitary clinical stage T1 tumors. AUA and NCCN clinical guidelines prefer partial nephrectomy to RN for the feasibly resectable T1a renal mass. RN and NSS are equivalent treatment alternatives for the T1b renal mass. Partial nephrectomy has a higher local recurrence rate for tumors larger than 7 cm but is possible when imperative indications exist. With lower oncologic efficacy in T2 tumors, NSS should be used in limited situations [1,4].
Evaluation

After complete history and thorough clinical examination imaging in the form of chest X-ray or Computed Tomogram (CT) and abdominal CT or Magnetic Resonance Imaging (MRI) to exclude locally advanced or metastatic disease with three-dimensional reconstruction to accurately visualize vascular anatomy and the relation of tumor to normal renal parenchyma and regarding lymphadenopathy, or segmental or renal vein invasion. The approach to a SRM is based on tumor size, stage, and location. The RENAL Nephrometry and PADUA scores provide useful scoring systems to predict operative time, Warm Ischemic Time (WIT), change in glomerular filtration rate, and conversion to nephrectomy [1,4,11]. Higher body mass index and increased intraabdominal fat are also predictive for perioperative complications and/or surgical difficulty for patients with SRMs [62]. For completely endophytic tumors, a preoperative renal ultrasound is a useful adjunct; tumors that are isoechoic to kidney tissue on ultrasound may be very difficult to identify intraoperatively. Patient counseling involves a review of the alternatives including active surveillance, ablative therapies, option of Renal Mass Biopsy (RMB), NSS, and RN. Healthy, thin patients with RENAL Nephrometry scores of 8 or less are more straight forward with lower risks of complications from NSS. Patients with abundant perirenal fat or higher RENAL Nephrometry scores (9-12) are counseled about higher risks of complications and longer operative times [4,89-91]. Stronger considerations for either observation or RN are made in morbid patients with SRMs or T1b renal masses, respectively. Percutaneous RMB can be a useful adjunct with sensitivity, specificity, positive predictive value, and Negative Predictive Value (NPV) of 89, 60, 100, and 75% respectively. Patients with benign pathology on biopsy are preferably observed [1,4,11].

Technique for Nephron-Sparing Surgery

The goal of PN is complete excision of potentially malignant tissue without malignant cells at the border of the surgical specimen, with maximum preservation of nearby normal renal parenchyma. Most NSS requires renal vessel occlusion during the excision, and renal tubular tissue is particularly sensitive to ischemia; the WIT, therefore, should be minimized. Damage to renal tubular tissue is directly related to WIT. Although the upper limit of WIT is debatable and probably has other patient variables, a limit of 20 minutes is a generally accepted guideline. If the WIT is expected to be longer than 20 minutes, thought should be given to cooling the kidney tissue with ice slush, as lowering the renal parenchymal temperature allows for longer periods of excision. In addition, application of renal cooling should be strongly considered in patients with imperative indications for partial nephrectomy. There are techniques for limiting renal ischemia during partial nephrectomy that include selective clamping of segmental renal vessels or parenchymal compression that limits WIT to areas of polar excision. Intraoperative ultrasound with Doppler can be useful for not only illuminating the planes for planned excision but also to determine arterial inflow for the tumor. A process for a zero ischemia partial nephrectomy has been described that uses anesthetic permissive hypotension with meticulous dissection and clipping of the intrarenal vasculature. Renal autotransplantation with ex vivo tumor excision has
also been described in rare instances. It is worth noting that tumors of nearly all sizes and location shave been treated with NSS, including some with renal vein invasion [92,93]. The kidney can be approached with traditional open surgery or laparoscopically [4].

**Ablative Approaches**

Ablative therapies have seen an increase in use and acceptance for a variety of reasons. Renal masses can be managed with definitive radiofrequency ablation, microwave ablation, cryoablation and stereotactic radiation. The effect on the tumor is unclear because evidence of viable tumor cells has been found on post-ablation histological examination, even when radio graphically the tumor appears to be fully ablated. No randomized studies have compared ablative therapies with nephrectomy or directly compared the ablative options themselves. Owing to the limited invasiveness of ablative techniques, they have an important role in managing small renal masses in patients whose comorbidities or other factors preclude surgical intervention [1,11].

**RISK FACTORS FOR PROGRESSION**

Several clinical algorithms have been evaluated and validated for predicting the risk of developing recurrence after definitive local treatment. One of the first is the still widely used Leibovich prognostic score, which incorporates tumor size, stage, grade, histologic necrosis, and regional lymph node status in an algorithm designed to assess risk for developing metastatic disease [94]. Other models include the Mayo Clinic Stage, Size, Grade, And Necrosis (SSiGN) model; the University of California, Los Angeles Integrated Staging System (UISS), which quantifies stage, tumor grade, and performance status; and other preoperative clinical risk algorithms [95-100]. A recent review of algorithms compared these tools [101]. Although many biological and genetic features of RCC have recently been identified, none has yet been prospectively validated as risk factors. As our knowledge about these gene mutations, gene expression patterns, and protein expression patterns develops, it will be essential to integrate them into currently used clinical algorithms [1].

**Prognostic Algorithms for Patients with Metastatic Disease**

The Memorial Sloan Kettering Cancer Center (MSKCC) assessed 670 patients with metastatic RCC who received immunotherapy and devised a prognostic algorithm [102]. Five independent adverse features were ultimately included in the algorithm including the Karnofsky performance status (≤2), less than one year between diagnosis and first systemic treatment, hypercalcemia, anemia and lactate dehydrogenase >1.5 times the upper limit of normal. Patients with none of the five negative features had a median survival of 30 months, whereas those with three or more had a median survival of 4.8 months. With advent of molecularly targeted therapy, a six component algorithm was derived wherein instead of lactate dehydrogenase it included thrombocytosis and leucocytosis. This algorithm also separated patients into prognostically distinct categories [1,103].
MANAGEMENT OF METASTATIC DISEASE

The treatment of metastatic RCC has changed greatly over the past 15 years. Established practice is to perform cytoreductive nephrectomy before starting systemic drugs in most patients [104-106]. This is followed by treatment with a chosen combination of eight US Food and Drug Administration approved agents, which include immunotherapeutic drugs, antiangiogenic agents, and mTOR inhibitors. Data from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) program point to an increase in overall survival for patients with metastatic RCC who were diagnosed after 2005 [104]. Median survival among patients receiving cytoreductive nephrectomy increased with the introduction of targeted therapy (19 v 13 months), while median survival among patients not receiving cytoreductive nephrectomy increased only slightly (4 v 3 months) [104]. Nevertheless, even with treatment, in most people the disease progresses and is the cause of their death. Better treatments are clearly needed [1].

Cytoreductive Nephrectomy

In the US, about 17% of patients diagnosed with de novo RCC present with metastatic disease [4]. Survival advantage was observed in patients with metastatic RCC who underwent cytoreductive nephrectomy before treatment with interferonalfa [105,106]. There is a gradual rise in the proportion of patients who underwent cytoreductive nephrectomy from 29% in 1993 to 34% in 2010 [104].

Adjuvant Therapy

Unfortunately, no adjuvant therapies have been proved to have a significant benefit in RCC. Randomized trials of cytokine immunotherapies showed no benefit [107-109]. Preoperative therapy is currently used to shrink borderline or unresectable tumors when it is a safe option for patients with biopsy confirmed clear cell histology. Effects on the risk of recurrence or other outcomes are not known [1].

MOLECULAR BIOMARKERS

The availability of agents directly targeting tumorigenic and angiogenic pathways has significantly improved the outcomes of patients with advanced RCC in recent years. However, all patients eventually become resistant and a substantial percentage experience immediate disease progression with first-line targeted therapy. In addition, patients have variable clinical benefit and/or tolerance to different agents, including drugs within the same class. Thus, the choice of therapy for an individual patient remains empiric at present. Upon this landscape, several molecular biomarkers have been investigated with the purpose of guiding therapy [1].

Many potential prognostic and predictive molecular biomarkers have now been identified in RCC, although none has yet entered into clinical practice, and all require prospective validation in appropriately designed randomized studies. This includes prognostic biomarkers correlating with the outcome of patients independent of therapy, and predictive biomarkers of treatment
response, including circulating biomarkers (such as VEGF and VEGF-related proteins, cytokine and angiogenic factors, and lactate dehydrogenase), and tissue-based biomarkers (such as single-nucleotide polymorphisms). In the near future, however, validated biomarkers may become integral to management strategies in RCC, enabling tailored treatment for individual patients to improve clinical outcomes [110].

To date, the strongest biomarker evidence in mRCC is from independent prognostic markers or independent predictors of response in phase III studies, or pooled data from multiple studies. Baseline VEGF has been identified as an independent prognostic marker in two randomized phase III studies [111,112]. There is a large body of evidence investigating SNPs as potential biomarkers, although the research is still in its infancy and requires further investigation. In addition, data are emerging to suggest that specific CAFs or multi-CAF signatures may have predictive value as biomarkers of response to VEGF inhibitors, although large prospective studies are required to validate these preliminary findings. New biomarkers are also emerging. It has been shown that Programmed Death-1 (PD-1) receptor and Programmed Death Ligand-1 (PDL1)-positive renal cancers are associated with poorer prognoses than those that are PD-1/PD-L1 negative, and agents inhibiting various elements on the PD-1/PD-L1 pathway are currently in clinical development [113,114]. Whether tumor expression of PD-L1 is predictive of response to these agents in RCC is currently unknown but will be critical to explore as clinical development proceeds. MicroRNA and Circulating Tumor Cells (CTC) as biomarkers are other expanding fields that have not yet been well explored with advanced RCC treatments; preliminary studies indicate that circulating miR-1233 may be a potential biomarker for patients with RCC [115]. Moreover, detection of cytokeratin 8/18-expressing CTCs in peripheral blood correlated with poor OS [116]. Further studies are required to fully understand the potential of these markers as predictive and prognostic biomarkers in RCC. Progress in validating individual biomarker candidates is likely to be linked to the development of future immunotherapeutics or molecularly targeted agents. The combination of molecular or genetic biomarkers into a signature may also be valuable for differentiating patient groups in terms of response or potential for toxic effects. Targeted agents have significantly improved outcomes for patients with RCC, to the extent that advanced RCC may be considered a chronic treatable condition in some cases; however, there is a clear need to further incorporate molecular factors in clinical decisions. Although specific treatment guidelines will be required, the development of validated clinical and molecular biomarkers should facilitate patient management and further improve clinical outcomes by allowing more specific tailoring of treatment to the individual patient [110,117].

**CURRENTLY AVAILABLE SYSTEMIC DRUGS**

Three major categories of systemic drugs are currently being used to treat metastatic RCC: cytokines, drugs that target the VEGF pathway, and mTOR inhibitors [1].
Cytokines

High dose Interleukin 2 (IL-2) was approved by the FDA in 1992 [75]. Patients showed an overall response rate of 15% and a complete response rate of 5%. Most complete responses achieved with high dose IL-2 were durable, which provided the main impetus for FDA approval. Because of the rigors of receiving high dose IL-2, the patient population was highly selected—patients had excellent performance status, robust lung and cardiac function, and an age of less than 70 years. A higher response rate and complete response rate with high dose IL-2 but no difference in overall survival, probably because the trial was underpowered. Similarly the response rate was 23.2% for high dose IL-2 versus 9.9% for subcutaneous IL-2 plus interferon with no difference in overall survival was seen between arms [118]. Efforts to identify predictive biomarkers for response to high dose IL-2 have so far been unsuccessful. Interferon alpha was the mainstay of treatment for patients with metastatic RCC until the advent of targeted therapies with modest survival advantage when compared with placebo [119,120]. Interferon was clearly inferior to most of the newer agents in terms of Progression-Free Survival (PFS) measures and was poorly tolerated and thus has been phased out in metastatic RCC except in combination with bevacizumab [1].

Drugs that Target the VEGF Pathway

The discovery of VHL mutations in VHL disease and in most sporadic CCRCC, led to the development of agents that target circulating VEGF and VEGF receptors. Five agents have been approved by the FDA for the treatment of metastatic RCC, including the intravenous VEGF inactivating antibody bevacizumab, and the orally bioavailable small molecule VEGF receptor inhibitors sorafenib, sunitinib, pazopanib, and axitinib [1,121-127]. These agents vary in the number of addition tyrosine kinases that they target and the avidity with which they bind and inactivate the VEGF receptor [128]. These agents are thought to target the tumor endothelium and to have minimal effect on the tumor cells [129]. A striking finding in patients treated with these agents is the association between treatment emergent or antecedent hypertension and improved patient survival [130].

Sorafenib increased PFS to 5.5 months and was FDA approved in December 2005 but unfortunately, when tested in a phase II randomized study, PFS was 5.7 months for sorafenib compared with 5.6 months for interferon and has therefore been second line treatment for most patients. Sunitinib was FDA approved in January 2006 a PFS of 11 months when compared with IFN [125]. Sunitinib is currently a commonly used first line treatment. Pazopanib was FDA approved in October 2009 for the treatment of advanced RCC with PFS of 11.1 months in treatment naive subgroup [132]. Pazopanib was non-inferior to sunitinib with a median PFS was 8.4 months with pazopanib and 9.5 months with sunitinib, and 11/14 quality of life measures favoured pazopanib over sunitinib. Axitinib was FDA approved in January 2012 for treatment refractory RCC based on 723 previously treated patients with metastatic RCC to axitinib or sorafenib [127].
Overall PFS for axitinib was 6.7 months versus 4.7 months for sorafenib and PFS for patients who progressed on sunitinib was 4.8 months for axitinib treated patients and 3.4 months for sorafenib treated patients. Axitinib dose escalation improved the overall response rate but did not alter PFS [133]. Combination of bevacizumab plus interferon was FDA approved in 2009. No phase III studies to test the efficacy of bevacizumab monotherapy have been published [1].

**mTOR Inhibitors**

The second major class of molecularly targeted agents used to treat metastatic RCC targets mTOR, a serine-threonine protein kinase within the family of Phosphatidylinositol-3-Kinase (PI3K) related kinases. Mutations in the PI3K pathway upstream of mTOR and in mTOR itself occur in RCC, suggesting that this pathway is important for renal carcinogenesis. Both agents bind to the prolyl isomerase FKBP12, and this complex in turn inhibits mTOR activity. Temsirolimus was FDA approved in 2007 [134,135]. Almost 20% of patients had non-clear cell histology and only two thirds had undergone cytoreductive nephrectomy. OS was 10.9 months versus 7.3 months for the interferon monotherapy arm. Temsirolimus is currently used mainly in poor risk patients as a first line drug. No significant difference was seen for PFS or overall response rate between temsirolimus and sorafenib and surprisingly OS was significantly longer with sorafenib. Though unclear why, this result dampened enthusiasm for temsirolimus as a treatment for patients who do not respond to VEGF receptor inhibitors. Everolimus was FDA approved in 2009 for the treatment of patients who progressed on sorafenib, sunitinib, or both. Everolimus is commonly used as a second line or third line drug. Currently, no data support the use of everolimus as a first line drug [1].

**EMERGING TREATMENTS AND CONCEPTS IN RCC**

**Immune Checkpoint Blocking Agents**

Recently, monoclonal antibodies against immune checkpoint blockade molecules including CTLA-4 (cytotoxic T lymphocyte antigen 4) and PD-1 (programmed cell death 1) have been shown to have clinical activity against several cancers, including RCC. For T cells to be activated for tumor cell killing, two sets of stimulating signals must be present. The first activating signal is provided by interaction between the T cell receptor and antigen bound to the Major Histocompatibility Complex (MHC). The second signal is mediated by interaction between a T cell costimulatory molecule CD28 and its ligands, the B7 proteins [136]. CTLA-4 is expressed by activated CD4 and CD8 T cells. It is a homolog of the T cell costimulator CD28 but has a higher binding affinity for CD28 ligands. Upon T cell activation, signaling pathways lead to production of CTLA-4, which is then mobilized from intracellular vesicles to the cell surface, where it out competes CD28 for binding to B7 proteins. Binding of CTLA-4 to B7 proteins interrupts CD28 costimulatory signals and thereby limits T cell responses [136,137]. Owing to the negative regulatory effects of CTLA-4 on T cell responses, it was hypothesized that blockade of CTLA-4 signaling would potentiate immune responses against tumor cells. The first antibody to block CTLA-4 (ipilimumab) was
tested for the treatment of metastatic RCC in the phase II clinical trial MDX010-11 but showed only modest activity [138]. Similar to CTLA-4, PD-1 also negatively regulates T cells. It exerts this effect by binding to two ligands, PD-L1 and PD-L2, which are expressed on several cells, including antigen presenting cells and tumor cells. A recent phase I clinical trial with an anti-PD1 antibody showed an 18-28% objective response rate. Among patients with metastatic RCC in this trial, there was a 27% clinical response rate, with most responses lasting more than a year [139].

Another almost concurrent phase I trial with an anti-PDL1 antibody found an objective response rate of 6-17% in patients with advanced non-small cell lung cancer, melanoma, and RCC [140]. Among patients with metastatic RCC in this trial, there was a 12% response rate, and 41% of patients whose disease stabilized remained stable for at least six months. A phase III clinical trial of anti-PD1 in patients with metastatic RCC is ongoing. Combinations of anti-CTLA-4 and agents that target the VEGF pathway are also being investigated. However, despite their promising efficacy, immune check point blocking agents have associated toxicities, known as immune related adverse events, including colitis, hepatitis, and hypopituitarism. Understanding the mechanisms and management of these adverse events will be an important aspect of effective use of these agents [1].

Other Targeted Agents

Newer agents that target the VEGF pathway, PI3K pathway, and mTOR pathway are in development. Recently, the FDA rejected a newer VEGF receptor inhibitor, tivozanib, as there was no significantly improved median OS, although it did significantly prolong median PFS, when compared with sorafenib in patients with advanced RCC [111]. Cabozantinib, a tyrosine kinase inhibitor of VEGF, the cellular receptor KIT, and MET, was tested in a phase II trial and showed a 28% overall response rate and 52% stable disease rate, with a median PFS of 14.7 months. A phase III clinical trial of dovitinib, an inhibitor of fibroblast growth factor, in addition to a VEGF receptor inhibitor, failed to show a superiority of this combination versus sorafenib in terms of PFS [141].

GENOMIC HETEROGENEITY AND IMPACT ON TREATMENT

Owing to its prevalence, CCRCC is the most genetically well studied subtype of RCC. A recent analysis of data from the Cancer Genome Atlas (TCGA)-which included comprehensive integrated analyses of somatic alterations as well as analysis of DNA methylation profiles, RNA expression profiles, and protein expression profiles-has illustrated the genomic heterogeneity of CCRCC [1]. Firstly, these analyses confirmed previously identified major genetic changes that underlie CCRCC, including mutations in genes that control cellular oxygen sensing (such as VHL) and the maintenance of chromatin states (such as PBRM1, BAP1, and SETD2), as well as genes in them TOR pathway (PIK3CA and MTOR) [105]. In addition, hypermethylation of promoter DNA was associated with higher stages and grades of CCRCC. Furthermore, CCRCC can be separated into different prognostic groups on the basis of gene expression, DNA methylation, and protein
expression profiles. Aggressive cancers with worse survival show gene expression changes that favor a metabolic shift toward fatty acid synthesis (Warburg-like phenotype). For example, reduced expression of the Krebs cycle gene AMP Activated Kinase (AMPK) and increased expression of the pentose phosphate pathway gene Acetyl-Coa Carboxylase (ACC) is associated with worse survival. In addition, decreased methylation of the MIR21 gene promoter correlated with increased expression of the micro R-21 gene, which down regulates the tumor suppressor gene PTEN, and is associated with worse survival. By contrast, better survival is associated with decreased methylation of the tumor suppressor gene GRB10 (growth factor receptor bound protein 10) gene promoter and increased expression of the GRB10 protein, which is a negative regulator of PI3K. Collectively, these data suggest that key genes involved in DNA methylation, chromatin structure, and cellular metabolism may serve not only as potential prognostic markers but also as potential therapeutic targets for CCRCC. In addition, these observations define a great deal of genomic variety across tumors. A recent study that examined the intra tumoral heterogeneity of CCRCC identified substantial differences in mutations from different sites within a single primary tumor, as well as a distinct mutational profile for metastatic lesions. The mutations identified also showed evidence of convergent evolution [142]. Further studies will be needed to translate these findings into clinical settings [1].

CONCLUSION

RCC is an important and increasing public health threat in the developed world. Substantial progress has been made in the management of localized disease, with nephron sparing approaches emerging in the past 15 years. For patients with metastatic disease, cytoreductive nephrectomy is still considered a reasonable approach in those who subsequently receive contemporary systemic drugs. The most commonly used agents to treat metastatic RCC are drugs that inhibit VEGF receptors, such as sunitinib and pazopanib, and those that inhibit mTOR, such as everolimus and temsirolimus. Unfortunately, most patients ultimately progress on treatment and die of their disease. The new class of checkpoint blocking antibodies that target the PD-1 and the CTLA-4 receptors may provide profound and durable responses in a subset of patients. Ongoing work will help define the utility of these agents in the treatment of RCC, and will enable us to identify those most likely to benefit. Similar efforts are under way to identify the determinants of response and resistance to antiangiogenic drugs, and to design the next generation of agents, which will target factors that engender resistance to established agents.

References


87. Lane BR, Novick AC. Nephron-sparing surgery. BJU Int. 2007; 99: 1245-1250.


