Renal Cell Carcinoma

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Renal Cell Carcinoma(RCC) is a kidney cancer that originates in the lining of the proximal convoluted tubule. This is responsible for 90-95 percent of cases of RCC.[1]. The body is remarkably good at hiding the symptoms and as a result people with RCC have advanced disease by the time it is diagnosed.[2], The symptoms of RCC include a classic triad of Haematuria (40%), flank pain (40%), Mass in abdomen or flank (25%). Other symptoms include weight loss (33%), loss of appetite, recurrent fever (20%), malaise, night sweats, chronic fatigue, sleep disturbance, and Varicocele on left side in males, when the tumor advances into left renal vein, blocking the left testicular vein. The RCC is associated with a number of paraneoplastic syndromes, caused by hormones produced by either the tumour or body defence system in 20% cases. These affect the tissue not invaded by RCC. These include Hypertension due to increased production of renin, Hypercalcaemia, Anaemia or Polycythemia due to decreased or increased production of erythropoietin respectively, thrombocytosis and secondary Amyloidosis. [3]

The most common causes of RCC include, Hypertension, Smoking, Obesity, which are responsible in 50 percent cases of RCC, and long term use of NSAIDs. Hysterectomised women are at double risk of developing RCC [4]. Patients with cystic disease of kidneys requiring dialysis are 30 times more likely than general population to develop RCC.[5] The Immediate relatives have a 2-4 fold increased risk of developing RCC. Other genitically linked conditions which increase the risk of developing RCC, includes, Heriditary papillary renal carcinoma, hereditary liomyomatosis, Brit-Hogg-Dube syndrome, Hyperparathyroidism-jaw tumor syndrome, Familial papillary thyroid carcinoma, Von Hippel -Lindau disease and Sickle Cell disease.[6]

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The tumor arises from the cells of proximal renal tubular epithelium. The two subtypes are sporadic and Heriditary. Both sporadic and hereditary are associated with mutations in the short arm of chromosome 3, with the implicated genes being either tumor suppressor genes VHL and TSC or oncogenes like c-met.

The WHO has classified RCC in 2004 , Since then several novel subtypes have been added[7]. These include the following:

- Clear cell papillary renal cell carcinoma and Clear cell renal cell carcinoma with smooth muscle stroma
- Mucinous tubular and spindle cell carcinoma (MTSCC)]
- Multilocular cystic clear cell renal cell carcinoma
- Tubulocystic renal cell carcinoma
- Thyroid-like follicular renal cell carcinoma
- Acquired cystic kidney disease-associated renal cell carcinoma
- Renal cell carcinoma with t(6;11) translocation (TFEB)
- Hybrid oncocytoma/chromophobe renal cell carcinoma
- Hereditary leiomyomatosis and renal cell carcinoma(HLRCC)

Diagnosis

Diagnosis is made on consideration of signs and symptoms and a medical history. Tests include, complete Blood count, urine analysis, Serum Electrolytes, Renal function tests, Blood clotting system, Serum Calcium. Radiological investigations are Ultrasound scan, CT scan, MRI scan, IVU, CXR and Angiography.

Staging

The staging of renal cell carcinoma is the most important factor in predicting its prognosis [8]. Staging can follow the TNM staging system, where the size and extent of the tumour (T), involvement of lymph nodes (N) and metastases (M) are classified separately. Also, it can use overall stage grouping into stage IIV, with the 1997 revision of AJCC (Table No 1)

Grading:
Histological grade is related to the aggressiveness of the cancer, and it is classified in 4 grades, with 1 having the best prognosis (5 year survival over 89%), and 4 with the worst prognosis (46% of 5 year survival).

The recommended histologic grading scheme for RCC is the Fuhrman system (1982), which is an assessment based on the microscopic morphology of a neoplasm with haematoxylin and eosin (H&E staining). This system categorises renal cell carcinoma with grades 1, 2, 3, 4 based on nuclear characteristics. The details of the Fuhrman grading system for RCC[9] are shown (Table No. 2)

Management
The initial treatment is most commonly either complete or partial nephrectomy, where the cancer has not metastatised or confined to the kidney.[10] The five year survival is 65-90%, but this is lower in case of metastasis.[11]

Management depends on the stage of RCC, type of RCC, pre existing co morbid factors and the overall health of the person. If the tumor that has spread outside the kidney, to the lymph nodes, lungs or main veins of kidney, then multiple therapies are used including surgery and medications. The tumor is resistant to chemo and radiotherapy. RCC responds to immunotherapy with IL-2 or Inf-alpha, biologic or targeted therapy, Cryotherapy, Radiofrequency Ablation and Surgery. In elderly patients with co morbidities and poor surgical candidates, active surveillance is useful.

Surgery in the form of partial nephrectomy (nephron sparing) is advocated in case of tumor ?4 cm, patients with diabetes, hypertension and non/ poor functioning other kidney. Total nephrectomy is radical which include all kidney, draining lymph nodes, gerota fascia and adrenal gland. This form of surgery has complications during and after surgery. Tumor spread to renal vein, IVC and RT atrium can also be removed, so as metastasis if few and small. Some surgeons also do it laparoscopically.

Percutaneous ablative therapy include the insertion or image guided probe passed through the skin into the tumor and the heat (radio frequency ablation) or cold (cryo ablation) is applied. This destroys tumor cells. Here one can't be sure about the complete destruction of tumor and will need long term active surveillance.

Table No. 1. Staging of Renal Cell Carcinoma

Stage I	Tumour of a diameter of 7 cm (approx. 2 3⁄4 inches) or smaller, and limited to the kidney. No lymph node involvement or metastases to distant organs.
Stage II	Tumour larger than 7.0 cm but still limited to the kidney. No lymph node involvement or metastases to distant organs.
Stage III any of the following	Tumor of any size with involvement of a nearby lymph node but no metastases to distant organs. Tumour of this stage may be with or without spread to fatty tissue around the kidney, with or without spread into the large veins leading from the kidney to the heart.
	Tumour with spread to fatty tissue around the kidney and/or spread into the large veins leading from the kidney to the heart, but without spread to any lymph nodes or other organs.
Stage IV any of the following	Tumour that has spread directly through the fatty tissue and the fascia ligament-like tissue that surrounds the kidney.
	Involvement of more than one lymph node near the kidney
	Involvement of any lymph node not near the kidney
	Distant metastases, such as in the lungs, bone, or brain.

Table No. 2: Grading of Renal Cell Carcinoma

Grade Level	Nuclear Characteristics
Grade I	Nuclei appear round and uniform, 10 μm; nucleoli are inconspicuous or absent.
Grade II	Nuclei have an irregular appearance with signs of lobe formation, 15 μm; nucleoli are evident.
Grade III	Nuclei appear very irregular, 20 μm; nucleoli are large and prominent.
Grade IV	Nuclei appear bizarre and multilobated, 20 μm or more; nucleoli are prominent.

Targeted drugs are used as immunotherapy which boost host immune system, interleukin-2 or interferon alpha. Ten commonly used drugs are, Nivolumab, Cabozantinib, Lenvatinib, Sunitinib, Temsirolimus, Bevacizumab, Sorafenib, Everolimus, Pazopanib and Axitinib. More medications are expected to become available in the near future as several clinical trials are currently being conducted for new targeted treatments, including: atezolizumab, varlilumab, durvalumab, avelumab, LAG525, MBG453, TRC105, and savolitinib. They have a list of side effects which limits its use.

- Gastrointestinal effects nausea, vomiting, diarrhea, anorexia
- Respiratory effects coughing, dyspnea (difficulty breathing)
- Cardiovascular effects hypertension(high blood pressure)
- Neurological effects intracranial hemorrhage (bleeding into the brain), thrombosis (blood clots) in the brain
- Effects on the skin and mucus membranes rashes, hand-foot syndrome, stomatitis
- Bone marrow suppression resulting in reduced white blood cells, increasing the risk of infections plus anemia and reduced platelets
- Renal effects impaired kidney function
- Fatigue.

Metastasis

When RCC metastatise, it commonly spreads to lymph nodes, lungs, liver, adrenal glands, brain or bones. [3]. Immunotherapy and targeted therapy have improved the outlook for metastatic RCC. [12,13]

Prognosis

Prognosis depends on the extent of disease at the time of presentation and aggression of tumor. The 5 year survival is 90-95% for tumors less than 4cm confined to kidney, 81% for larger tumor confined to kidney, 74% if renal capsule and Gerota fascia is invaded, 53% if renal vein and lymph nodes are involved and is 8% if it is locally invasive or has distant metastasis. The tumor is graded I-IV, Grade I has a 5 year survival of 89% and Grade IV has 46%. If nephrectomy has been done for early disease, the 20-30% will develop metastasis.

The prognosis is influenced by several factors, including tumour size, degree of invasion and metastasis, histologic type, and nuclear grade. Staging is the most important factor in the outcome of renal cell cancer. The following numbers are based on patients first diagnosed in 2001 and 2002 by the National Cancer Data Base is in (Table No. 3)

Taken as a whole, if the disease is limited to the kidney, only 2030% develop metastatic disease after nephrectomy.[14] More specific subsets show a five-year survival rate of around 9095% for tumors less than 4 cm. For larger tumors confined to the kidney without venous invasion, survival is still relatively good at 8085%. For tumors that extend through the renal capsule and out of the local fascial investments, the survivability reduces to near 60%. Factors as general health and fitness or the severity of their symptoms impact the survival rates. For instance, younger people (among 2040 years old) have a better outcome despite having more symptoms at presentation, possibly due to lower rates spread of cancer to the lymph nodes (stage III).

Table No 3: Prognosis

Stage	Description	5 Year Survival Rate
I	Confined to the kidney	81%
II	Extend through the renal capsule, confined to Gerota's Fascia	74%
III	Include the renal vein, or the hilar lymph nodes	53%
IV	Includes tumors that are invasive to adjacent organs (except the adrenal glands), or distant metastases	8%

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