Renal Cell Carcinoma: Epidemiology, risk factors, genetics, and treatment.

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Abstract

Renal Cell Carcinoma (RCC) is the most common type of kidney cancer. It has affected the world with a mortality rate of 30 to 40%, which is more commonly seen in men than women (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). With improvements in diagnostic tests, such as CT and MRI imaging, a drastic amount of diagnosed patients has grown rapidly in RCC. There are many risk factors which include obesity, hypertension, smoking, and chronic kidney disease. The most common type of RCC is clear cell carcinoma that frequently occurs due to mutations in the *VHL* gene. The most selective technique to maintain kidneys in patients is Nephron Sparing surgery, but surgeries to remove small tumors include radical nephrectomy and partial nephrectomy. Patients with metastatic RCC are treated with surgical approaches, adjuvant therapy, and targeted therapy. This article covers RCC including its epidemiology, risk factors, pathophysiology, genetics, and treatments.

Introduction:

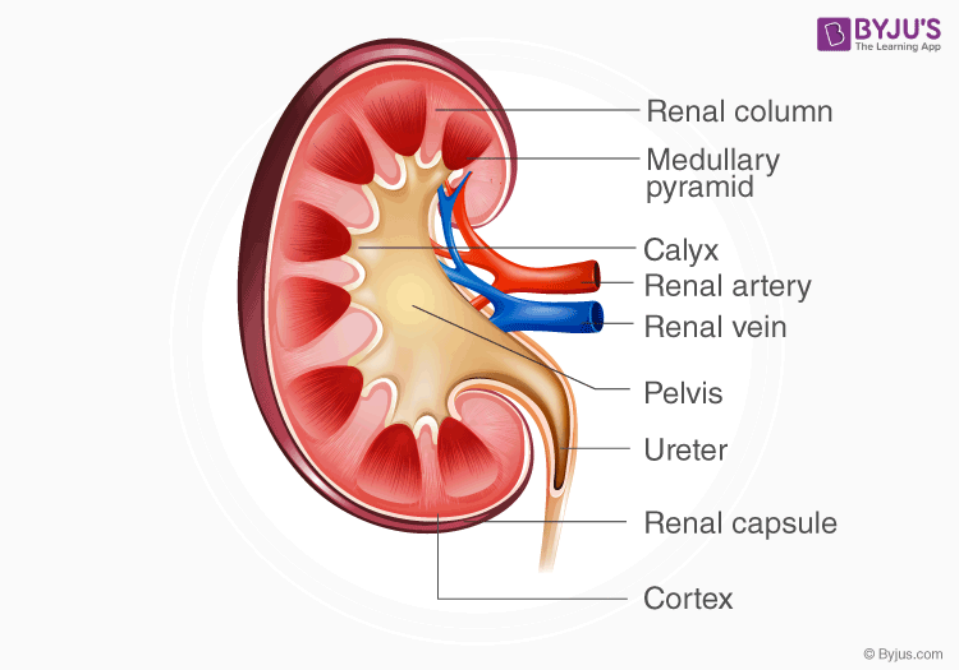


Image above shows a healthy kidney with the basic parts.

Kidney cancer starts in the kidney, which are two bean-shaped organs. They are located behind the abdominal organs with one kidney on each side of the spine. The kidney's purpose is to expel excess water, salt, and waste products from your body and turn those substances into urine. Kidneys are made up of cellular tissue, but sometimes those tissues behave irregularly. When there are changes in a kidney's DNA, they start to grow in an abnormal way and form tumors, which is how kidney cancer develops. RCC forms in the tubules, which are tiny tubes inside a kidney. The tubules' purpose is to directly move substances a person's body needs. For example, water and nutrients go to a person's bloodstream while filtering waste through your urine. The kidney's symptoms include: pain, blood in urine, hematuria, and palpable abdominal mass that occurs in 4-17% of cases.

Renal Cell Carcinoma is the most common kidney cancer there is. It has affected the world greatly with the cause of 3% of malignancies in women, and the tenth most common cancer in women (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). In men, RCC is the sixth most common kidney cancer, and it is the cause of 5% of malignancies (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). Malignancies are when abnormal cells divide without control and can invade nearby tissues. Additionally, the most common kidney cancer for adults is Renal Cell Carcinoma (RCC). It mainly occurs in Europe and North American populations, but according to the Global Cancer Statistics in 2020, the amount of RCC-related deaths were 179,368 and 431,288 people were diagnosed with RCC (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). The death rate of RCC in 2016 has concluded to approximately 2% of all cancers (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). The diagnoses have been significantly growing, leading to improved cross-section abdominal imaging. Even though RCC is the most common urogenital malignancy, it is commonly misdiagnosed. Optimal screening modalities have not been established yet, which is critical in reducing the amount of deaths in RCC. Therefore, having patients diagnosed in early stages is crucial in treating patients and reducing the amount of deaths.

Epidemiology

RCC is a very complex and heterogeneous disease with several clinical features. For example, RCC was recognized as the seventh most cause of cancer with over 140,000 deaths in 2013 (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). RCC is considered 2-3% of all cancers (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). RCC diagnoses are continuously increasing today, which varies across the world and is higher in developed countries than developing countries. RCC mainly occurs at the ages of 60 to 70 years old, but declines after 70 years old, which is due to less use of aggressive diagnostic testing within the

age range (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). The increase in the diagnosis of RCC is the improvement of diagnostic procedures and public consciousness of the importance of periodic health screenings. As a result, the amount of patients with RCC being diagnosed at early stages has drastically increased. Furthermore, due to early diagnosis and therapy, the mortality rate has dropped, but metastasis, the process where cancer cells spread to other parts of the body, still occurs in many patients. However, the change has still contributed to improvements, with 20-30% of patients being metastatic at an early stage of diagnosis (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). Secondly, 30-50% of patients are progressing to metastasis. Lastly, 40% of patients with localized RCC have distant metastases after surgery (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). The lungs, bones, opposite kidney, and liver are all common distant metastases.

Risk Factor

In RCC, the main major risk factors are age and gender. Other risk factors include location, ethnicity, history of smoking, history of using tobacco products, obesity, and hypertension. Multiple risk factors which may have an association with RCC include chronic kidney disease, acquired renal cystic disease, end stage renal disease, chronic use of palliatives, exposure to cadmium and trichloroethylene, consumption of red and processed meat, coral hepatitis, vitamin D level, type-2 diabetes, increased triglycerides, decreased physical activity, and genetic syndrome.

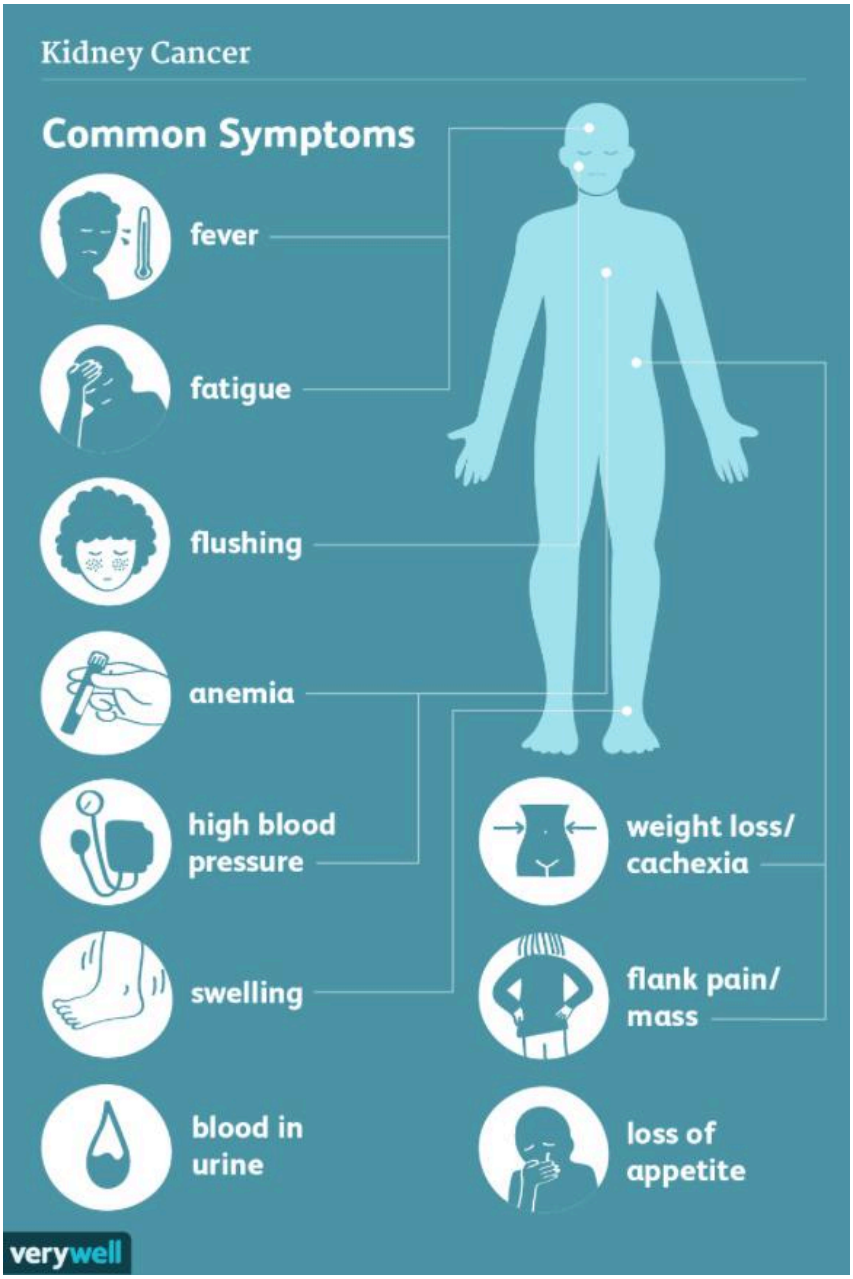
Genetics

WHO classification of renal cell carcinoma (2016)
Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of low malignant potential
Papillary renal cell carcinoma
Hereditary leionyomatosis and renal carcinoma-associated renal cell carcinoma
Chromophobe renal cell carcinoma
Collecting duct carcinoma
Renal medullary carcinoma
MiT family translocation renal cell carcinomas
Succinate dehydrogenase-deficient renal carcinoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Clear cell papillary renal cell carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Oncocytoma

The image above shows the WHO classification by Heidelberg (2016).

RCC is a type of cancer that has many genetic and epigenetic alterations. The first classification of RCC was by Heidelberg in 1997. She performed the classification on molecular genetics, which was entered as the WHO tumor classification in 2004, 2012 Vancouver ISUP, and the classification of the WHO in 2016 (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). About 3% of the RCC cases have a similar background with an autosomal predominant pattern, which showed that RCC can be divided into heredity types (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). This is uncommon. Subtypes of RCC have multiple different mutations and epigenetic alterations in the genes that cause RCC. The important genes that play an important role are the *VHL, MET, FH, BHD,* and *HRPT2* (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). The mutation which is most common is the gene *VHL* which causes the heredity of clear cell RCC. In clear cell RCC, *VHL* is the tumor suppressor which is seen in patients with susceptibility to von HippelLindau inherited syndrome. But this type of genetic alteration has the best prognosis among patients with clear cell RCC. 3p25-26, 3p12,3p14.2, 3p21.1, 3p21.3, 3p22, and 3p26.2 all are tumor suppressor genes, which could be responsible for the initiation progression or inactivation of those genes in chromosome 3 (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). The gene *PBRM1*, which involves tumor growth and metastasis, is a potential gateway for predicting the prognosis of clear cell RCC.

Signs and symptoms



The image above shows the different symptoms of RCC

Random detection of renal masses has significantly increased in following routine imagery for various medical disorders. So, more than 50% of patients with RCC are being diagnosed accidently. A renal mass could just be a simple kidney cyst that could have no treatment involved, but in some cases it isn't (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). Some benign renal lesions or malignant RCC require interventions. About 30% of patients with RCC are diagnosed with symptoms, but

small masses usually do not cause any symptoms (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). This leads to an increase in growth and build up over time, resulting in metastatic RCC at the time of diagnosis. The symptoms include having abdominal pain, fever, hematuria, weight loss, anemia-induced fatigue, or secondary symptoms caused by metastasis spread such as bone pain and cough. When all stages are completed, RCC may produce biological pseudo-hormonal or pseudo cytokine products, leading to clinical paraneoplastic syndromes. This includes: hypertension, anemia, cachexia, weight loss, fever, polycythemia, hypoglycemia, hypercalcemia, liver function disorders, and neuropathy. Some signs in physical examination may have a limited role in diagnosing RCC, but some signs may be important such as abdominal mass, peripheral lymphadenopathy, and lower limb edema.

Treatment

Nephron-sparing surgery

One treatment is surgery, specifically nephron preservation surgery. Nephron sparing radiation nephrectomy is the removal of the entire kidney, but when using the nephron-sparing surgery technique, only the tumor is removed. Moreover, during the technique the normal kidney parenchyma is preserved but the negative margins of surgery are sufficient. When it is possible to maintain part of the kidney, using the nephron-sparing treatment is very selective for the job. The treatment is very efficient with the same oncological control and the additional benefit for maintaining the kidney. It is also less risk of postoperative cardiovascular occurrences compared to radical nephrectomy. For T1 tumors, partial nephrectomy should be used, but if the tumor is in a location that is not possible to be removed, partial nephrectomy won't be an option. For T2 tumors, partial nephrectomy is also an option, but it depends on the location as well. By the guidelines of European Association of Urology, the standard indications for nephron-sparing surgery include: 1) Absolute: Applied for patients with an anatomical kidney or a functional kidney. 2) Relative: Applied for patients with functional kidney, a disorder that may damage the kidney function in the future or hereditary form of RCC that has a high risk of developing tumors in the kidney. 3) Elective: Applied for patients with one lateral localized RCC with a healthy kidney. Nephron sparing surgery is mainly used for metastasis and locally advanced diseases.

Nephron sparing surgery is not commonly used for RCC since the techniques require experience and may be associated with a risk of bleeding and urinary leakage. When using nephron sparing surgery instead of radical nephrectomy, it depends on the diameter, location, depth, and proximity to the hilar vessels and urinary collecting system. There are four best scores which are used to evaluate if a patient should have surgery or not. The scores are aimed at improving patient selection, surgical management, research report, and outcome prediction including C-index, RENAL, surgical approach in nephron-sparing surgery. This depends on the

experience of the surgeon and the tumor's characteristics. The approaches are similar to the terms of surveillance. There are 16-35% of hospitals that utilize robotic surgery systems for nephron-sparing treatment (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022).

Laparoscopic partial nephrectomy

A second type of surgery for RCC is laparoscopic partial nephrectomy, which takes longer than nephron sparing surgery. In laparoscopic partial nephrectomy, there is a higher risk of kidney ischemia and complications are higher, which is why partial nephrectomy is preferred. Laparoscopic nephron-sparing surgery is only used if the surgeon has more experience. In the 2000s, open nephron-sparing surgery was the standard treatment, but now it is only used for cases of anatomical difficulties like large tumors or urinary tract infections, or for patients with low invasive techniques (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). Radical nephrectomy and partial nephrectomy should be used for smaller tumors. Radical nephrectomy is useful for T2 tumors and larger tumors. Adding on to that, radical laparoscopic nephrectomy is the standard treatment for T2 tumors for patients. Compared to open radical nephrectomy, there is less blood during surgery, less need of painkillers, and a shorter recovery. Radical open nephrectomy has upsides too though. It is a standard surgical procedure for T3 and T4 tumors.

Adjuvant therapies

Although surgery is used mostly for RCC, 20-30% of patients have distant metastasis and 2-5% of patients have local recurrence (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). Due to this, adjuvant therapy is important after surgery. The approaches are hormone therapy, radiotherapy, immunotherapy, vaccine, and target agents.

Immunotherapy treatment for metastasis disease

Immunotherapy for metastasis RCC only does a complete response in less than 10% of patients and the side effects are severe with toxic effects in the body (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). The only treatments that are safe include modulating drugs that are approved are Aldesleuki, INFa, and Bevacizumab. INFa is used in schedules, doses, and multiple formulas with a response rate of 10-15% (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). The average response rate is four months and there is no relationship between the dose and the response (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). Three times a week equals a dose of

5-10 million units per body surface area (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). Even though INF has good performance status, it is not recommended to be treated as a single drug because IL2 causes tumor regression by activating the immune system in RCC. During the 1990s, treatments with a high dose of IL2 were commonly used for patients with good PS and organ function. IL2 has various severe toxicity: severe hypertension, fluid retention, vascular leak syndrome, multiple organ failure, *axotomy,* oliguria, cardiac arrhythmia, fever, metabolic acidosis, dyspnea, and skin complications are all common side effects (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). Patients need severe care with a mortality rate of 2-4%, and due to the toxins in high doses of IL2, studies are encouraging other doses and methods (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). The morbidity and mortality rate is important in high dose IL2 selected patients causing long full-term implantation. High dose IL2 is still an option for young patients in very good conditions and low tumor volume, including patients with isolated pulmonary metastases in experienced centers.

Other treatment options for metastasis disease

The most common options for patients with metastasis RCC is with the targeted therapies including Ca, corrected HB serum, KPS, neutrophil count, and platelet count (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). It seems through the use of radiotherapy, part of a multimodality approach, RCC tends to be radio-resistence tumor. This is because of its poor results with low-dose RT.

Conclusion

Renal Cell Carcinoma is the most common type of kidney cancer with a mortality rate of 30%-40% (Bahadoram, S., Davoodi, M., Hassanzadeh, S., Bahadoram, M., Barahman, M., & Mafakher, L. 2022). In most cases, RCC is diagnosed accidentally. The diagnoses of patients with RCC has drastically increased due to the improvements in diagnostic tests. Having patients with RCC diagnosed at early stages is critical in treating patients and reducing death rates. Therefore, optimal screening modalities and approaches have not been established yet. Having knowledge of the recent advances in diagnosis and management of RCC could help physicians and nephrologists to better treat and diagnose Renal Cell Carcinoma.

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