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Renal Cell Carcinoma: Insights into Risk Factors, Diagnosis and Management

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Abstract In the last decade, there is an increasing incidence of renal cell carcinoma (RCC) worldwide. Most patients with RCC are diagnosed late with advanced stages of the disease which are often refractory to treatment and associated with poor prognosis. Management of RCC has changed greatly over the past years. Progress in the surgical management of the primary tumor and increased understanding of the molecular biology of the disease have led to the development of new therapeutic lines. This mini-review sheds light on the risk factors, the clinical presentation, methods of diagnosis and the up-to-date lines of management of RCC.

Keywords: *kidney, carcinoma, diagnosis, management*

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1. Introduction

Renal cell carcinoma (RCC), also known as renal cell adenocarcinoma, is the most common type of kidney cancer. About 90 % kidney cancers are RCC which may appear either as a single tumor within a kidney, two or more tumors in one kidney or tumors in both kidneys at the same time [1]. There are several subtypes of RCC, depending mainly on the histopathological picture of the tumor. Knowing the subtype of RCC can be a factor in deciding treatment and can also help doctors determine if cancer might be due to an inherited genetic syndrome [2].

Renal cell carcinoma (RCC) accounts for 2%–3% of all adult malignancies, representing the seventh most common cancer in men and the ninth most common cancer in women. The incidence of RCC has increased over the recent years [3]. Active and passive cigarette smoking is an established risk factor for RCC as well as hypertension. Obesity, end-stage renal failure, acquired renal cystic disease and tuberous sclerosis can be also considered as important risk factors. Approximately 2%–3% of RCC are hereditary and several autosomal dominant syndromes are described as predisposing factors for RCC, such as Von Hippel Lindau (VHL) disease [4]. The aim of this review article was to shed light on different types of RCC regarding to their risk factors, different methods of diagnosis and possible lines of management.

2. Types of RCC

The most common type of renal cell carcinoma is clear cell renal cell carcinoma. In this type, the cells that make up clear cell RCC look very pale or clear. The second most common subtype is papillary renal cell carcinoma. These cancers form little finger-like projections (called papillae) in some, if not most, of the tumor. These cancers are sometimes called chromophilic because the cells take in certain dyes and look pink under the microscope [5]. The chromophobe renal cell carcinoma subtype accounts for about 5% of cases of RCCs. The cells of these cancers are also pale, like the clear cells, but are much larger and have certain other features that can be recognized. In addition, there are rare types of RCC such as multilocular cystic RCC, collecting duct RCC, medullary carcinoma, mucinous tubular and spindle cell carcinoma and neuroblastoma-associated RCC [6].

3. Etiology and Risk Factors of RCC

3.1. Environmental Factors

The actual cause of RCC is not yet well understood. Findings of recent studies suggest that several environmental factors may contribute to the development of RCC. An international case-control study has provided insight into the causative role of environmental factors. Tobacco smoking was identified in numerous studies as the most important risk factor for the development of RCC [7]. Cigarette smoking has been estimated to contribute to as many as one third of all cases of RCC in the United States. The relative risk of developing RCC increases according to the number of cigarettes smoked per day and the number of years a person had smoked. Cessation of smoking affected risk. Persons who had not smoked for more than 15 years had 75% of the risk of current smokers.

There was an inverse relationship between the risk for RCC and the age at which a person started to smoke cigarettes. Persons who started smoking at an older age had about two thirds the risk of those who started smoking at a younger age [8].

3.2. Obesity

Studies have shown that obesity is also a risk factor, particularly in women. Study findings suggested that there was a linear relationship between increasing body weight and increased risk of RCC [9]. High body mass index was a risk factor for women and to a lesser extent for men. Risk of RCC was three times higher for women with a weight in the top 5% than for those with a weight in the lowest 25%. Physical exercise and height were unrelated to risk [7].

3.3. Hypertension and Antihypertensive Medications

Some studies have proposed that hypertension and use of antihypertensive medications increase the risk for developing RCC [10]. Results of the international study indicate that hypertension and use of diuretics and other antihypertensive medications had some effect on the risk for RCC [9]. Other scientists reported that analgesics such as acetaminophen, aspirin and phenacetin did not increase the risk for RCC, even though other findings suggest that these agents increase the risk for transitional cell carcinoma originating in the renal pelvis [11].

3.4. Other Factors

Additional factors associated with the development of RCC include use of unopposed estrogens, occupational exposure to petroleum products, heavy metals, and asbestos and a high-protein diet [12]. Investigators have also reported increased risk of developing RCC for patients with acquired cystic kidney disease associated with chronic renal insufficiency, tuberous sclerosis, or polycystic kidney disease [9].

4. Clinical Presentation of RCC

Initial signs and symptoms of RCC usually result from local effects of the primary tumor, distant metastases, or paraneoplastic syndromes. The most common presentations are hematuria, abdominal pain or a palpable flank or abdominal mass. Hematuria may be gross or microscopic and is painless unless partial clotting causes obstructive symptoms [13].

A broad range of paraneoplastic syndromes have been reported with RCC. Non-specific signs and symptoms include fever, anorexia, weight loss and anemia, which are present in about 30% of patients at diagnosis. More specific signs may be present in less than 5% of patients including erythrocytosis. hypercalcemia, hepatic dysfunction and amyloidosis. Recently, it was reported that paraneoplastic syndromes are associated with adverse prognosis among patients with renal cell carcinoma undergoing nephrectomy [14]. RCC can spread by direct extension or by metastasis via lymphatic or venous routes [1]. The structures that may be involved include the liver, colon, pancreas, bones, adrenal gland, pituitary gland and the subcutaneous tissues [15,16].

5. Diagnosis of RCC

RCC might be found because of the characteristic signs or symptoms a person is having, or it may be discovered because of lab tests or imaging tests a person is getting for another reason or accidently. The incidental diagnosis of RCC is becoming more common due to the frequent use of abdominal computed tomography (CT) and/or ultrasonography for evaluation of an unrelated problem [9]. If symptoms, signs, or findings suggestive of RCC, the patient must undergo imaging evaluation for the presence of a renal mass. Ultrasonography is less sensitive than abdominal computed tomography (CT) in detecting a renal mass. Actually, it is useful to distinguish a simple benign cyst from a more complex cyst or a solid tumor [17].

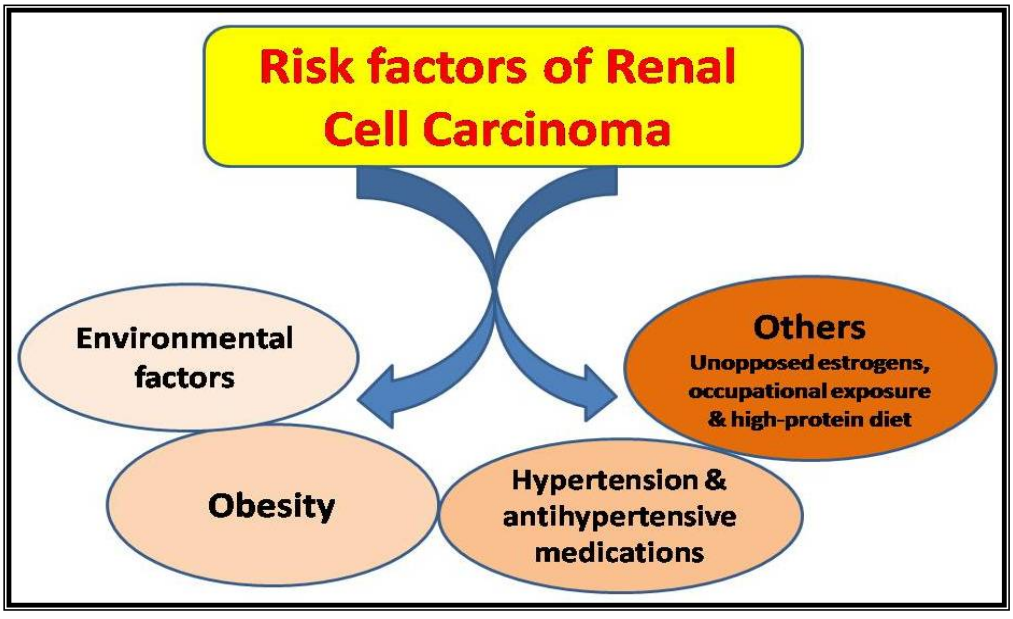

Figure 1. Risk Factors of Renal Cell Carcinoma

The major criteria that differentiate a simple cyst from a tumor or abscess on ultrasonography include that the cyst is rounded and sharply demarcated with smooth walls with no echoes within the cyst and the presence of a strong posterior wall echo indicating good transmission through a cyst. If all of these criteria are fulfilled, no further evaluation is necessary since the likelihood of a malignancy is extremely small. On CT, a simple cyst has a smooth appearance without a clearly delineated wall, has no enhancement with intravascular contrast and has the density of water. If the criteria for a simple cyst by ultrasonography are not satisfied, the patient should undergo CT scanning before and after injection of iodinated contrast [18].

Magnetic resonance imaging (MRI) may be useful when ultrasonography and CT are non diagnostic or when radiographic contrast cannot be administered because of allergy or poor renal function.Dynamic, contrast-enhanced MRI may also be useful in determining histology, with clear cell carcinoma showing greater signal intensity change in the corticomedullary and nephrographic phase than either papillary or chromophobe carcinomas [19].

Intravenous pyelogram (IVP) is a useful procedure in detecting the presence of abnormal renal mass in the urinary tract. This procedure involves the injection of a contrasting dye into the arm of the patient. The dye travels from the blood stream and into the kidneys which in time, passes into the kidneys and bladder. This test is not necessary if a CT or MRI scan has been conducted [20]. Renal angiography uses the same principle as IVP, as this type of X-ray also uses a contrasting dye. This radiologic test is important in diagnosing renal cell carcinoma as an aid for examining blood vessels in the kidneys. This diagnostic test relies on the contrasting agent which is injected in the renal artery to be absorbed by the cancerous cells. The contrasting dye provides a clearer outline of abnormally-oriented blood vessels believed to be involved with the tumor. This is imperative for surgeons as it allows the patient’s blood vessels to be mapped prior to operation [21].

Diagnosis of RCC may be established by taking a biopsy from the site of metastasis. After the presumptive diagnosis has been made based upon imaging studies, the patient must be evaluated for the extent of local involvement and the presence of metastatic disease before surgery. A biopsy can be used to confirm diagnosis of RCC in patients who are not surgical candidates prior to initiating appropriate medical treatment, although biopsy of a metastatic lesion is often preferable [22].

Persons at high risk for development of RCC should undergo periodic screening with abdominal ultrasonography, CT or MRI to detect early disease. RCC screening includes patients with inherited conditions associated with an increased incidence of RCC or other renal tumors, end-stage renal disease especially younger subjects without serious comorbid diseases who have been on dialysis for three to five years or more, a strong family history of RCC and Prior kidney irradiation [23].

6. Complications of RCC

Complications of RCC include secondary conditions, symptoms, or other disorders that are caused by RCC. In many cases, the distinction between symptoms of RCC and its complications is unclear. The most common complication are paraneoplastic syndrome, blood clots, congestive heart failure, peripheral neuropathy, distant metastasis and death [1,24].

7. Treatment of RCC

7.1. Treatment of Localized RCC

The most suitable treatment for most people with localized RCC is surgery to remove a part or all of the kidney, and if necessary, the nearby lymph nodes. The removed part depends upon cancer's size and site in the kidney, whether there are one or multiple tumors, and kidney functions. In case of multiple tumors, or the tumor is large or located centrally within the kidney, complete removal of the kidney may be necessary, especially if the other kidney works normally [25]. Radical nephrectomy is the medical term for a surgery that removes the entire kidney and surrounding tissues. Most people can live with only one kidney. In other instances, or if the kidneys do not work well, removing a part of the kidney may be a better option by nephron-sparing treatments [26]. Normally, the kidneys filter waste out of the blood with tiny structures, known as nephrons. Nephron-sparing treatments allow some of the nephrons to continue working. This treatment is generally preferred if it is feasible and especially if the kidneys do not work well, a situation in which preserving as many nephrons as possible is a priority. Nephron-sparing treatments include surgery to remove a part of the kidney (called partial nephrectomy) which is the more common treatment [25]. A treatment that destroys the cancer by burning it (called radiofrequency ablation) or freezing it (called cryoablation) may represent an alternative to partial nephrectomy [27]. For patients with localized RCC, further treatment is not usually provided after surgery. Further treatment has not been proven to decrease the chance of the cancer recurrence [28].

7.2. Treatment of Advanced Renal Cell Carcinoma

For people with advanced or metastatic RCC, medical treatment may be recommended instead of or along with surgery. Medical treatment may also be recommended if cancer recurs after surgery [29]. Surgery to remove the kidney or areas of metastasis outside the kidney may be done before medical treatment. For patients with advanced RCC, surgery can only reduce symptoms or delay systemic medical treatment. The most commonly used medical treatments for advanced RCC include immune therapy and targeted therapies [30].

Immune therapy (also called immunotherapy) usually refers to the drugs that affect the immune system to stop or slow the growth of cancer cells, including interleukin-2 (IL-2) and nivolumab [31]. Interleukin-2 acts by stimulating the immune system to attack the cancer cells. The treatment is given intravenously over five days while patients are hospitalized. The treatment is typically repeated in 15 to 22 days and may be repeated again 12 to

14 weeks after the first dose. IL-2 therapy can produce long-term cancer control in up to 10 percent of patients. Treatment with IL-2 may cause severe life-threatening side effects such as low blood pressure, fever, kidney failure, and an irregular cardiac rhythm. So, IL-2 is only recommended if the patients are healthy enough to tolerate the side effects and are being treated in a facility with experience in its administration [32].

Nivolumab is a type of drug called an "anti-PD-1 checkpoint inhibitor" that modulates the body's immune system so it can reject the kidney cancer [33]. Nivolumab is given once every two weeks by IV injection and is continued unless there is an evidence of disease progression, complete disappearance of the disease, or severe side effects. Treatment with nivolumab may decrease the extent of kidney cancer and help live longer. Nivolumab can cause the body to develop an immune reaction against its own tissues. This can result in a wide range of side effects that can be severe and even life-threatening [34].

Targeted therapies represent drugs that directly inhibit the growth of the tumor. They act by interfering with a step in the cancer's growth process. Targeted therapies cannot cure the cancer, but they may allow patients to live longer and have fewer symptoms [35]. These therapies represent an option for patients with advanced or metastatic RCC, either as an alternative to or after immunotherapy. One group of these agents targets the vascular endothelial growth factor (VEGF) pathway, which partly controls the growth of blood vessels. The blood vessels feeding RCC tumors are particularly dependent on VEGF. So, treatment with anti-VEGF therapies can damage tumor blood vessels, and this may slow or stop the tumor from growing for long periods of time. Drugs in this category include: Pazopanib, Sunitinib, Cabozantinib, Axitinib, Sorafenib and Bevacizumab [36]. Another group of drugs used for targeted therapy of RCC involves blocking a specific protein, called the mechanistic (or mammalian) target of rapamycin (mTOR). These include temsirolimus and Everolimus [37]. These medicines are given one at a time rather than in combination. The most common side effects for mTOR inhibitors include rashes and fatigue, and for VEGF targeted therapy, fatigue and high blood pressure [38].

8. Prognosis of RCC

The prognosis of RCC is affected by several factors, including tumor size, degree of invasion and metastasis, histologic type, and nuclear grade. Staging is the most important factor in the outcome of renal cell cancer [39]. If the disease is limited to the kidney, only 20–30% develop metastasis after nephrectomy. More specific subsets show a five-year survival rate of around 90–95% for tumors less than 4 cm. For larger tumors confined to the kidney without venous invasion, survival is still relatively good at 80–85%. 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 may affect the survival rates. For example, younger people have a better outcome despite having more symptoms at presentation, possibly due to lower rates spread of cancer to the lymph nodes [40].

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). Some people have the renal cell cancer detected before they have symptoms (incidentally) because of CT scan or ultrasound. Incidentally diagnosed renal cell cancer differs from those diagnosed after presenting symptoms of RCC or metastasis. The 5 year survival rate was higher for incidental than for symptomatic tumors: 85.3% versus 62.5%. Incidental lesions were significantly lower stage than those that cause symptoms, since 62.1% patients with incidental renal cell carcinoma were observed with stage I lesions, against 23% were found with symptomatic renal cell carcinoma. If it has metastasized to the lymph nodes, the 5-year survival is around 5% to 15% [41].

For metastatic RCC, factors which may present a poor prognosis include a low Karnofsky performance-status score, low hemoglobin level, high level of serum lactate dehydrogenase and high corrected level of serum calcium [42]. For non-metastatic cases, the Leibovich scoring algorithm may be used to predict post-operative disease progression [43]. Renal cell carcinoma is one of the cancers most strongly associated with paraneoplastic syndromes, most often due to ectopic hormone production by the tumor. The treatment for these complications of RCC is generally limited beyond treating the underlying cancer [1].

9. Conclusion

Renal cell carcinoma (RCC) has the highest mortality rate among various genitourinary cancers and its incidence rate is rising steadily. The etiology of RCC is still not fully understood but the environmental and genetic factors seem to play a major role. The clinical presentation ranges from asymptomatic cases to cases suffering from symptoms and signs of metastasis. The treatment strategies and the prognosis of RCC depend on the stage of the tumor and the presence or absence of distant metastasis. Further studies are needed to elucidate the biological basis of the disease and to discover the molecular markers for translational application to diagnosis and prognosis of cases of RCC.

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