Renal cell carcinoma: an overview of the epidemiology, diagnosis, and treatment

In Depth Review

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ABSTRACT

Renal cell carcinoma (RCC) is the most common type of urogenital cancer. It has a mortality rate of 30-40% and is more commonly seen in men than women. In addition to gender, other risk factors of RCC include obesity, hypertension, smoking, and chronic kidney disease. Following the improvements in diagnostic tests, such as CT and MRI imaging, the incidence of patients diagnosed with RCC has rapidly increased over the past decades. The most common type of RCC, based on histological and molecular subtypes, is clear cell carcinoma which occurs frequently due to mutations in the *VHL* gene. Nephron-sparing surgery is a selective technique to maintain kidneys in patients while radical nephrectomy and partial nephrectomy are used to remove small tumors. In addition to surgical approaches, adjuvant therapy and targeted therapy are applied in patients with metastatic RCC. In this review, we give an overview of the most recent research on RCC which would help physicians to better manage patients with RCC.

KEYWORDS: renal cell carcinoma, kidney cancer, genetics

Introduction

Kidney cancer is the cause of 5% of malignancies and is the sixth most common cancer in men. It is also the cause of 3% of malignancies and the tenth most common cancer in women [1]. Renal cancer occurs mostly in European and North American populations. However, the occurrence rate of renal cancer is lower in Asia. According to the Global Cancer Statistics in 2020, the incidence and mortality of kidney cancer were 431,288 and 179,368, respectively. Renal cell carcinoma (RCC) rises from renal tubular epithelial cells and accounts for more than 90% of kidney cancers [2]. The death rate of RCC has been reported to be approximately 2% of all cancers in 2016 [3]. Furthermore, the incidence of RCC has increased in recent years [4] as a result of improved cross-section abdominal imaging [5]. Although RCC is the most common urogenital malignancy, most cases of RCC are diagnosed accidentally.

Diagnosis of RCC at early stages is critical in treating patients and reducing death rates. However, optimal screening modalities and approaches have not been established yet [6]. Choosing the best therapeutic approach is necessary for improving the outcome of patients with RCC. Therefore, this article aimed to present the recent advances in the diagnosis, treatment, and molecular characterization of RCC which could help to identify the best modality to diagnose and treat RCC patients.

Epidemiology

RCC is a complex and heterogeneous disease with different clinical features. In 2013, RCC was recognized as the seventh cause of cancer with over 140,000 deaths per year. RCC constitutes 2% to 3% of all cancers. It is the most lethal urogenital cancer with a mortality rate of 30-40% compared to bladder and prostate cancers which have a mortality rate of about 20%. Its incidence, which increases continuously, varies throughout the world and is higher in developed countries compared to developing countries. In addition, the incidence of RCC is higher in men than women (male to female ratio is 1.5:1) and the mortality rate is higher in men compared to women. Furthermore, RCC mostly occurs at the age range of 60 to 70 years and declines after 70 years of age. This could be due to less use of aggressive diagnostic testing within this age range [7]. The most important cause of such an increase in the incidence of RCC is the improvement in diagnostic procedures and public consciousness of the importance of periodic health screening [4]. Therefore, the number of patients being diagnosed in the early stages is also increasing. Despite the increase in the total incidence over the past three decades, especially in developed countries, due to early diagnosis and therapy, the mortality rate of RCC has decreased rapidly [8]. However, despite the progress in disease control and survival, locally advanced disease and distant metastases still occur in many patients [9]. Approximately, 20-30% of the patients are metastatic at the early stage of diagnosis, 30-50% of patients progress to metastasis with local disease, and nearly 40% of patients with localized RCC have distant metastases even after surgery[10]. The usual symptoms of RCC include hematuria, flank pain, and palpable abdominal mass which only occur in 4-17% of the cases [10]. The most common distant metastasis involves the lungs, bones, and brain but the adrenal glands, the opposite kidney, and liver may also be involved [11].

Although the metastasis of RCC to the small intestine and pancreas is rare, gastrointestinal bleeding can be seen in patients which may be the first manifestation of the involvement of these organs [12]. In addition, approximately 40% of patients diagnosed with RCC expire [13].

Risk factors

The strongest risk factors of RCC are age and gender [7]. Other potential risk factors include location, ethnicity [14], history of smoking [15], history of using tobacco products [16], hypertension (HTN) [17], and obesity [18]. However, recent studies have suggested that overweight patients with RCC have a better prognosis which is contrary to the role of obesity as a risk factor for RCC and requires further investigation. Some minor risk factors which may be associated with RCC include chronic kidney disease (CKD), acquired renal cystic disease, end-stage renal disease (ESRD), chronic use of palliatives, exposure to cadmium and trichloroethylene, consumption of red and processed meat, viral hepatitis, vitamin D level, type-2 diabetes, increased triglycerides, decreased physical activity, and genetic syndromes [19].

Pathophysiology

RCC is heterogeneous cancer that may originate from different cells throughout the nephrons. Many studies have revealed that the histological subtype classification of RCC has an essential impact on the prognosis and treatment choice. The World Health Organization (WHO) classifies RCC into different subtypes based on its morphologic, molecular, and genetic features. Based on the histological features, clear cell, papillary RCC (type I and II), and chromophore are the most common solid RCC subtypes which constitute 70-90%, 10-15%, 3-5% of kidney malignancies, respectively. Both clear cell carcinoma and papillary RCC originate from the proximal tubule traits while chromophore RCC is raised from the distal connecting tubules (DCT) and collecting duct system, particularly intercalated cells [20]. Most clear cell carcinomas are sporadic (95%) and only 5% of this type of cancer is associated with hereditary syndromes such as von Hippel-Lindau disease and tuberous sclerosis.

This type of cancer has a high growth pattern and tends to metastasize to the liver, lungs, bones, and, especially, the lymph nodes (up to 15%). Clear cell carcinoma has the least favorable prognosis compared to papillary RCC and chromophobe RCC. Papillary RCC is a less-growing mass that is divided into type I and type II based on its histological and genetic differences. These types cannot be differentiated by routine imaging procedures. Both types of papillary RCCs have sporadic and hereditary forms. Papillary type I can be detected at an early stage compared to type II; therefore, it has a better prognosis. Chromophobe RCC is more common in the sixth decade of life.

This type of RCC is less aggressive than clear cell RCC and has the best prognosis among all RCCs [7]. According to the WHO, in 2004, the other less common histological types of RCC included hereditary cancer syndromes, multilocular *cystic* RCC, collecting duct carcinoma, medullary carcinoma, mucinous tubular, spindle cell carcinoma, neuroblastoma-associated RCC, Xp11.2 translocations–TFE3 carcinoma, and unclassified lesion (Table1). In 2016, the WHO declared a new classification for RCCs based on the Vancouver consensus conference of the International Society of Urological Pathology (ISUP).

This new classification was based on the advances in electron microscopic, immunohistochemistry, cytogenetically, and molecular diagnostics techniques.

This RCC classification is classified based on different features such as cytoplasmic features, architectural features, anatomic location of the tumors, pathognomonic, and other features. In addition, RCC is divided into 16 subtypes [21]. The recent RCC classification by the WHO is shown in Table 1.

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

Table 1: The WHO classification of renal cell carcinoma (RCC) (2016) [20].

Genetics

RCC is a type of cancer that has various genetic and epigenetic alterations [13]{Khandia, 2018 #48}. The first classification of RCC based on molecular genetics was performed by Heidelberg in 1997. This type of classification then entered the WHO tumor classification of 2004, 2012 Vancouver ISUP [22], and the recent classification of the WHO (2016) [21]. Approximately 3% of RCC cases have a familial background with an autosomal predominant pattern. Therefore, RCC can be divided into sporadic or hereditary (uncommon) types. The subtypes of RCC have different mutations and epigenetic alterations in the genes that cause RCC. Most of the genes that play an important role in hereditary RCC include *VHL*, *MET*, *FH*, *BHD*, and *HRPT2*. The most common mutation occurs in the *VHL* gene which causes the hereditary clear cell RCC [23].

Clear cell RCC has various genomics alterations. The first and most frequent among these (around 90%) is loss of the short arm of chromosome 3 codes the *VHL* gene. VHL is a tumor suppressor that is seen in patients with susceptibility to von Hippel–Lindau inherited syndrome. However, this type of genetic alteration has the best prognosis among patients with clear cell RCC [24]. Other loci on chromosome 3 which might be responsible for the initiation, progression, or inactivation of tumor suppressor genes include 3p25-26, 3p12,3p14.2, 3p21.1, 3p21.3, 3p22, and 3p26.2. Some chromosomal aberrations indicate a poor prognosis of clear cell RCCs such as 4p, 14q, and 9p, while gaining 5q31 is associated with prolonged survival in high-grade clear cell RCC. Deletions of the Y chromosome are commonly associated with clear cell RCC and distant metastasis. In addition, trisomy of chromosome 7 is a frequent aberration in clear cell RCC. Furthermore, gaining chromosome 8q, which codes the c-Myc oncogene, is associated with metastatic disease and the risk of cancer-specific death. Other genes associated with clear cell RCC are *PBRM1* (approximately 40–50%), *SETD2* (12%), *BAP1* (10%), and *KDM5C* (5%). These genes are involved in chromatin remodeling and histone methylation. *PBRM1*, a gene involved in tumor growth and metastasis, is a potential marker for predicting the prognosis of clear cell RCC [25].

Although on the morphological basis papillary RCC type I and type II are similar to each other, they have cytological distinctions which are characterized by different gene alterations in each type. Recently, the National Institute of Health (NIH) subdivided papillary RCC type II into at least three subtypes based on its molecular and phenotype features. Papillary RCC type I is an autosomal dominant disease that is recognized by the overexpression of the *MET* gene with different genetic alterations. The *MET* gene is an oncogene on chromosome 7q31. This type of papillary RCC is

associated with an indolent clinical course, is bilateral, and is multifocal in some patients while in other patients it has solitary lesions which progress to an aggressive course [26]. However, papillary RCC type I has a low-grade tendency and better prognosis than papillary RCC type II [27]. In comparison to papillary RCC type I, papillary RCC type II is less associated with mutation of the *MET* gene [28]. Most gene alterations in this type of cancer include silencing of CDKN2A and CPG islands, fusions of TFE3, mutations in genes *SETD2*, *BAP1*, *PBRM1*, *TERT*, *NF2*, *FH*, and increased expression of the NRF2-antioxidant response element (ARE) pathway. Papillary RCC type I is commonly associated with trisomy of chromosomes 3q, 7, 8, 12, 16, 17, 20, and loss of chromosome Y in men. Gaining an 8q chromosome and losing 1p and 9p chromosomes are common in RCC papillary type II [29].

Chromophobe RCC is a rare type of kidney cancer that originates from the distal region of nephrons. This type of cancer has a low malignancy rate (5-6%). Chromophobe RCC has two types of cellular elements; type 1, which consists of small with moderately granular cytoplasm, and type 2, which contains abundant eosinophilic cytoplasm that is denser at the periphery of the cell. Most chromophobe RCC cases are sporadic [30]. Moreover, a mutation in the *PTEN* gene in the germline causes a higher risk of developing chromophobe-like or oncocytoma-like neoplasms which are characterized as Cowden syndrome. In addition, chromophobe RCC represents chromosome abnormities such as losing chromosomes 1, 2, 6, 10, 13, 17, and 21 [23]. The chromosome abnormalities in chromosomes 1, 2, 6, 10, 13, and 17 are more common in the classical type of chromophobe RCC than the eosinophilic type which indicates that this type has more chromosome instability [31]. In addition to losing these chromosomes, gaining copies of chromosomes 4, 7, 11, 12, 14q, and 18q are also observed in chromophobe RCC [32]. Moreover, a mutation in the short arm of chromosome 7 is associated with loss of the *mTOR* gene, a tumor suppressor and activator of the c-kit. Although germline mutations of the *PTEN* gene are the most common gene alteration in chromophobe RCC, a low incidence of somatic mutation of TP53 has been observed in this type of renal cancer. Other genes which are frequently mutated in chromophobe RCC are *FAAH2*, *PDHB*, *PDXD1*, *ZNF 765*, *PRKAG2*, *ARID1A*, and *ABHD3* [33].

The most common genetic alterations of RCCs are summarized in Table 2.

Type of RCC	Chromosomal abnormalities	Gene mutations
Clear cell RCC	· Loss of chromosome -3p21 and chromosome Y · Gaining 5q31, 8q, 4p, 14q, 9p · Trisomy of chromosome 7	VHL, PBRM1, SETD2, BAP1, KDM5C, c-MYC
Papillary RCC (Type I)	· 7q31 · Trisomy of chromosomes 3q, 7, 8, 12, 16, 17, 20 · Loss of chromosome Y	MET
Papillary RCC (Type II)	· Gaining of chromosome 8q · Loss of chromosome 1p and 9p	CDKN2A, SETD2, BAP1, PBRM1, CpG island methylation, NRF2-ARE, TFE3, TERT, NF2, FH
Chromophobe	· Loss of chromosome 1, 2, 6, 7, 10, and 17 · Gaining of 4, 7, 11, 12, 14q, and 18q	PTEN, TP53, mTOR, c-kit, FAAH2, PDHB, PDXD1, ZNF 765, PRKAG2, ARID1A, ABHD3

Table 2: A summary of the most common gene alterations of renal cell carcinomas (RCCs) [23–37].

Clinical diagnosis and staging

Signs and symptoms

More than 50% of RCCs are accidentally discovered. Random detection of renal masses has increased significantly following routine imaging for various medical disorders [38]. A renal mass may be a simple kidney cyst that may not require any treatment or follow-up. However, some

masses are benign renal lesions (such as oncocytoma or angiomyolipoma) or malignant RCCs that require interventions. Only 30% of patients with RCC are diagnosed based on the symptoms. Small masses usually do not cause symptoms. Therefore, many patients remain asymptomatic for a long period and up to 20-30% of the patients have metastasis at the time of diagnosis. The *classic triad* of flank *pain*, hematuria, and abdominal mass are not common presentations of RCC and are seen in 4-17% of the cases. In addition, the patients may have abdominal pain, fever, hematuria, weight loss, anemia-induced fatigue, or secondary symptoms that are caused by metastatic spread such as bone pain and cough. At all stages, RCC may produce biologically active pseudo-hormonal or pseudo-cytokine products leading to clinical paraneoplastic syndromes such as hypertension, anemia, cachexia, weight loss, fever, polycythemia, hypoglycemia, hypercalcemia, liver function disorders, and neuropathy without any association to metastasis [39]. Although physical examination has a limited role in the diagnosis of RCC, some signs may be important such as abdominal mass, peripheral lymphadenopathy (LAP), lower limb edema, and varicocele caused by renal thrombosis or inferior vena cava (IVC) [40].

Laboratory investigation

Evaluation of the kidney function in a patient with RCC is important because the treatment usually involves a complete or partial loss of a kidney. In addition, multifocal tumors may have bilateral nephrectomy. Therefore, kidney function should be monitored at diagnosis and follow-up visits [41]. In addition, the evaluation of RCC's systemic effects requires the evaluation of complete blood cell count (CBC), liver function tests (LFT), and urinary analysis, lactate dehydrogenase (LDH), calcium, and alkaline phosphatase (ALKP) are also important [42]. Thyroid function tests (TFTs) should be performed especially in those patients who would be treated with tyrosine kinase inhibitors (TKIs) [43].

Diagnosis

Imaging modalities can detect renal masses with acceptable accuracy. For example, RCC is commonly detected by abdominal ultrasound and clinical benign cystic kidney lesions are easily diagnosed with ultrasound without the need for further imaging evaluation [44]. In recent years, contrast-enhanced ultrasound (CEUS) has been used as an accurate and inexpensive imaging method for evaluating indeterminate renal lesions. It lacks nephrotoxicity and ionizing radiation, and has the ability to rapidly evaluate the enhancement pattern of renal lesions. However, studies have reported that CEUS cannot effectively discriminate between benign and malignant solid renal masses. In suspected malignant cases, computed tomography (CT) scan or magnetic resonance imaging (MRI) should be performed [45]. If possible, CT and MRI should be carried out by contrast since contrast absorption is an important factor in detecting malignant lesions [46]. Other determinants of malignancy include the size, growth rate, fat content, contrast absorption pattern, and hyper attenuation of the mass in the CT scan [47]. MRI is preferred in cases of renal insufficiency, allergy to contrast material containing iodine, young patients, and pregnant women to avoid radiation. Furthermore, MRI should be performed for small lesions with a diameter of 1 to 2 cm in which the attenuation measurement may not be precise [48]. Currently, according to the Bosniak classification, MRI is more useful than CT scan due to the higher enhancement in definitive cysts [49]. The main purpose of imaging is to examine the characteristics of the mass, identify possible abdominal metastases, mass expansion, and venous involvement for staging. Additional imaging (for example, CT scan of the thoracic and brain, bone scan of the entire body, or whole-body MRI) can be considered in symptomatic patients, cases of abdominal bulky disease, or metastatic RCCs. Although positron emission tomography (PET) scan may be useful in the diagnosis and follow-up of RCC, it is still not part of the standard strategy. Therefore, routine use of PET/CT is recommended [50]. Other new imaging technologies (such as advanced MRI techniques or the combination use of

iodine PET and CT to isolate antibodies that attach to carbonic anhydrase IX) may be used to evaluate and detect renal masses [43]. Although benign lesions can be observed with imaging, histopathologic proofing is required in suspected malignant lesions. Due to the standard treatment of solid kidney masses and their early removal, biopsy has limited effect on the decision-making of treatment. Since nephrectomy is a treatment approach in both primary and metastatic lesions, a nephrectomy without the need for percutaneous needle biopsy may result in histopathologic evidence [51]. For histopathologic confirmation, percutaneous biopsy should be performed in patients who are treated without intervention, patients undergoing percutaneous ablation, and patients with locally advanced masses or metastasis who are not candidates for nephrectomy [52]. Kidney biopsy has a low morbidity rate with a total rate of developing complications (especially bleeding, infection, and arteriovenous fistula) of about 3.5-3.5%. However, seeding of tumors through the biopsy pathway is not risky because of the advanced biopsy techniques [53]. Although kidney biopsy plays a decisive role in the evaluation and treatment of renal masses, it is not used commonly due to concerns about accuracy and safety [54].

A summary of the diagnostic approach to RCCs is shown in Figure 1.

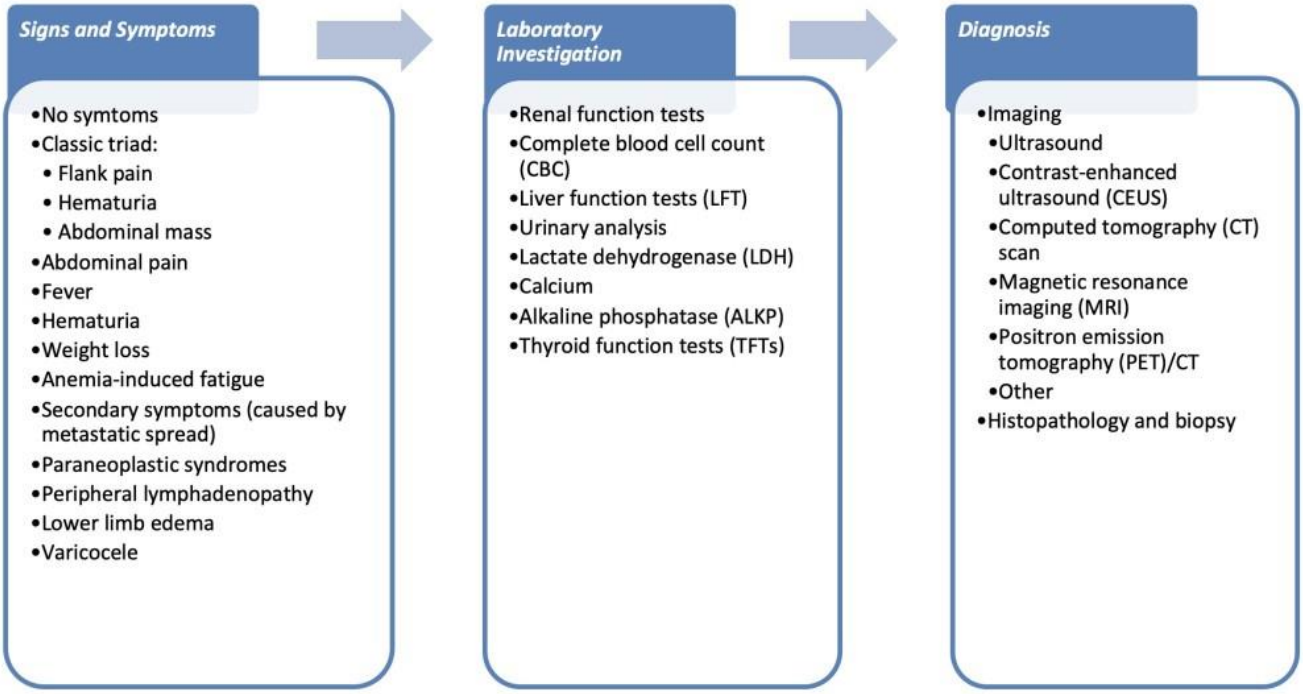

Figure 1: Diagnostic approach to renal cell carcinomas (RCCs).

Management

Despite the advances in RCC biology, surgical treatment is still crucial. Although historicallyRE nephrectomy has been the standard of care for managing kidney tumors, the diagnosis of small renal lesions and the continuing evidence of the fact that chronic surgery-induced kidney disease can increase the morbidity of the patients have led to more conservative approaches.

Active surveillance of nephron surgery and minimally invasive techniques have been introduced in daily clinical practices. These approaches have limited the invasion and destruction of iatrogenic renal function and have added to the treatment options [55].

Active surveillance

Approximately 20% of the small kidney masses ultimately have a benign pathology and their average growth rate is usually slow (2-3 mm/ year) [56]. Because of the causes of mortality, especially in elderly patients, and to avoid short and long-term complications of the surgery, the use of active surveillance (AS) is important. Small tumors (less than or equal to 4 cm) in elderly patients, patients with severe comorbidities, or those with a short life expectancy can be monitored [57]. Active surveillance is also recommended for large tumors to determine the rate of the tumor's growth, especially if the patient is at high risk and has a short-term life expectancy. The definitive threshold for tumor size and growth rate that goes toward AS is not well specified. A biopsy may be useful before the initiation of AS. In different protocols, imaging is recommended for AS in the first three and six months, and later, every 6 months at 2-3 years, and then, annually. However, the risk of cumulative radiation and the high costs should also be considered [56].

Minimal invasive techniques

Since surgery is still a standard treatment for RCC, the use of minimally invasive techniques for treating small randomly found tumors has significantly increased. Cryotherapy (CRYO) and radiofrequency ablations (RFA) were first only recommended for patients with one kidney or for those who could not undergo major procedures. The clinical indications for these treatments have increased since primary reports have shown acceptable cancer control [51]. Thermal or CRYO treatment may occur in T1 tumors where surgery cannot be performed. Survival results are similar to surgery but the local recurrence is more. The temperature degradation property which is used in RFA is both cold or hot for apoptosis in cancer cells treated with renal ablation. This thermal damage of RFA is induced by frictional heating (50-120℃) which occurs by ionic oscillation through high-frequency alternating (375-500KHZ). CRYO causes cell death directly through the degradation of the cell membrane, and indirectly, by inducing vascular problems through small vessels leading to tissue coagulation necrosis. Complications after RFA and CRYO include renal bleeding or abscess formation, or extra effects in the intestine, pleura, spleen, pancreas, and vessels [58].

Surgery

Nephron preservation surgery

Nephron sparing radiation nephrectomy is the removal of the entire kidney. However, only the tumor is removed in the nephron-sparing surgery technique and the normal kidney parenchyma is preserved and the negative margins of surgery are sufficient. Currently, nephron-sparing surgery is a selective treatment when it is possible to maintain a part of the kidney [59]. Since the time of its presentation, surgery for nephron-sparing has been increasingly documented to have the same oncological control as well as the additional benefit of maintaining the kidney and less risk of postoperative cardiovascular occurrences compared to radical nephrectomy [60]. Partial nephrectomy should be performed for T1 tumors (less than 7 cm), except for those that are not technically possible to be removed due to their location. RCC stage T2 may also be selected for partial nephrectomy depending on its location [61]. The standard indications for nephron-sparing surgery by the guideline of the European Association of Urology (EAU) 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 a 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 [51]. Nephron sparing surgery is also recommended for locally advanced and metastatic diseases [62].

Nephron preservation surgery should be the preferred approach, except for disorders that can reduce the positive effects of conservative approaches such as short-term life expectancy, or other

risk factors like low experiment surgeries or low volume surgical operation, prolonged ischemic time, the use of non-conservative homeostasis techniques, large or complex anatomical kidney mass with a low percentage of nephrons that can be maintained. Conservative surgical techniques require experience and may be associated with a risk of bleeding (3%) and urinary leakage (4%) [63]. As a result, nephron preservation surgery for patients with RCC is less common, especially in non-academic hospitals. The tumor manifestations that allow nephron-sparing surgery instead of radical nephrectomy include diameter, location, depth, and proximity to the hilar vessels and urinary collecting system. The four best scores used for pre-surgical evaluation aimed at improving patient selection, surgical management, research report, and outcome prediction include C-index, RENAL, PADUA, and DAP. While RENAL has the best correlation with surgery outcome [64]. The selection of surgical approach in nephron-sparing surgery, (open, laparoscopic, or robotic) depends on the tumor characteristics and the experience of the surgeon. The approaches are similar in terms of surveillance and neither is superior. In hospitals with a robotic surgery system, the nephron-sparing treatment is 16-35% more used than hospitals without such technology [65].

In laparoscopic partial nephrectomy (LPN), the surgery is longer, there is a higher risk of kidney ischemia, and complications are higher. Therefore, open partial nephrectomy should be preferred. Laparoscopic nephron-sparing surgery is usually limited to simpler cases or cases when the surgeons are more experienced. Open nephron-sparing surgery, which until 2000 was the standard treatment, is currently used only in cases of anatomical difficulties (such as large tumors or urinary tract infections) or for those with low invasive techniques [66]. Radical nephrectomy and partial nephrectomy should be performed with smaller tumors. Radical nephrectomy is suitable for T2 and larger tumors. Nowadays, radical laparoscopic nephrectomy is the standard option in T2 tumors. Compared to open radical nephrectomy it has shorter hospitalization, less loss of blood during the surgery, less need for painkillers, and shorter recovery. However, they have similar outcomes. Open radical nephrectomy is a standard surgical procedure for T3 and T4 tumors. Radiation nephrectomy with the help of a robot increases the costs without improving the morbidity compared to laparoscopic procedures [67]. The R.E.N.A.L.-Nephrometry Score has been introduced to help in the decision-making of surgical treatment of renal masses by objectifying the salient anatomic features. It has been suggested that Nephrometry Scores may also aid in the prediction of functional, perioperative, and pathologic outcomes. Furthermore, older age, male gender, high body mass index (BMI), high preoperative glomerular filtration rate (GFR), and small RCC size have been reported to be independent risk factors for developing acute kidney injury (AKI) following radical nephrectomy. Radical nephrectomy has also been reported to be a risk factor for CKD. For example, Cho et al. reported a 4.24-fold higher risk of developing new-onset CKD after radical nephrectomy in patients that had post-operative AKI. As a result, preoperative evaluation and preservation of renal function are essential in the management of renal masses [68].

Other surgical options

Adrenalectomy has been an inevitable component of radical surgery. However, in recent years, adrenalectomy has become optional if there is no adrenal inversion based on preoperative imaging or observation during the operation. Regardless of the T stage, RCC patients with LN (PN1) have poor survival outcomes (20-30% within three years after operations). The value of LND in RCC is controversial and lymphadenectomy has no long-term survival, except in the presence of large clinical or radiological LNs that should be removed during surgery in addition to hilar lymph dissection [69]. In addition, SLN (Sentinel LND) is currently not an option for RCC. Approximately 10% of patients with RCC have tumor vein thrombosis in the renal vein, IVC, or the expansion to the right atrium. However, the prognosis in such cases is poor. Surgery is challenging and is associated with increased complications, but survival is better with surgery compared to non-surgical management

[70]. *Cytoreductive nephrectomy* (CN) may be preferred in patients with a good performance status of Eastern Cooperative Oncology Group (ECOG) <2 and good prognostic features. Studies in this field were carried out in areas where cytokines were used and it was not determined whether CN had the same benefits as treatment with TKIs. Nonetheless, non-randomized retrospective studies have suggested that CN may be beneficial in metastatic RCCs treated with TKIs. Primary tumor resection may also be performed in moderate cases and patients with poor risks. Well-conditioned patients with a low risk of surgery are the right candidates for removal of a significant proportion of the tumor bulk with CN. Historically, patients with metastasis were not candidates for CN and were excluded from randomized trials. However, a recent International MRCC Database Consortium study that was conducted on 1658 patients with synchronous RCC metastasis, indicated the advantages of CN in patients with metastatic brain disease. Surgical metastasectomy is recommended in patients with isolated resistive metastases and can be done at the same session of removing the primary tumor or at another time. Metastasectomy may have survival benefits in patients who respond to systemic therapy, have metachronous pulmonary metastases, or have a metastatic span of two or more years. Therefore, the metastasectomy option should be evaluated in all appropriate patients [71].

Adjuvant therapy

Although treatment with surgery is possible in RCC, 20% to 30% of patients with distant metastases and 2% to 5% of patients are involved with local recurrence. Therefore, adjuvant treatment after surgery is important. However, almost all studies in this field, except for a small number of conveying reports, were negative resulting in observation to be the standard approach after surgery outside of clinical trials. Adjuvant approaches include hormone therapy, radiotherapy, immunotherapy, vaccine, and target agents. However, no benefits were found in patient survival. In addition, none of the studies have shown any results indicating the effectiveness and benefits of interleukin-2 (IL-2) and interferon α (INFα) in metastatic disease as adjuvant treatments [72].

Metastatic disease at diagnosis

Immunotherapy for the treatment of metastatic disease

Historically, patients with metastatic clear cell RCC were treated with systemic therapy based on immunosuppressive agents, especially INFα and IL2. However, the outcome would only slightly improve. Immunotherapy with a longer high IL-2 dose causes a complete response in less than 10% of patients and is associated with severe toxic effects with treatment

Aldesleukin and INFα (along with Bevacizumab) are the only safe modulating drugs that are approved in selected metastatic RCC. INFα is used in doses, schedules, and various formulas with a response rate of 10-15%. The average response time is four months. There is no relationship between the dose and the response. A dose of 5-10 million units per body surface area (unit/m^2) is used three times a week. Patients who benefit from INF treatment have usually undergone nephrectomy. They have a good performance status (PS) and have isolated pulmonary metastases. Although INFα has some efficacy in the treatment of metastatic RCC, it is not recommended in treating metastatic RCC as a single drug. IL2 causes tumor regression in RCC by activating the immune system. In 1990, treatment with a high-dose IL2 became a commonly used modality for patients with good PS and organ function. Regardless of its activity, high-dose IL2 has severe toxicity. Severe hypotension, fluid retention, vascular leak syndrome, multiple organ failure, *axotomy*, oliguria, cardiac arrhythmia, fever, metabolic acidosis, dyspnea, and skin complications are common side effects. Patients usually need severe care, and the mortality associated with the treatment is 2-4%. Due to the toxicity of high-dose IL2, studies have considered other prescribing methods. IL2 was found to be not effective in moderate to low doses in contrast to high doses. High-dose IL2 in

selected patients causes long full-term implantation but its morbidity and mortality rate is also important. Therefore, it remains an option in the experimental centers that can manage its toxicity risk. High-dose IL2 may be recommended for young patients in very good conditions with low tumor volume as well as in patients with isolated pulmonary metastases in experienced centers [73].

Target factors in the treatment of metastatic disease

After decades, the main advancement in the treatment of metastatic RCC has been the advancement of treatments that primarily target biological pathways. Factors that target the VEGF/PDGFR/MTOR route are principles of treatment. TKIs are effective factors in the treatment of advanced RCC, both as the first line and the second line treatment options. Five types of TKIs have been approved internationally for the treatment of advanced RCC. Cabozantinib, axitinib, pazopanib, sorafenib, sunitinib are protein inhibitors. MTOR includes another group of target agents. Temsirolimus and everolimus are MTOR inhibitors that have been approved. Bevacizumab is an antibody monoclonal anti-VEGF that is approved when combined with INF. Finally, immunotherapy with nivolumab, an anti-PD-1 immune checkpoint inhibitor, has become became a promising strategy. The important factors in the choice of treatment, the histology of the tumor, and the classification of patients are based on the risk. TKI therapy may be indicated in the clear cell RCC subclass. There is no standard treatment in histology except for clear cells, and studies that use targeted agents are in progress [2]. Table 3 shows a summary of some of the available medications for target treatment.

Drug	Explanation
Sunitinib [74, 75]	· Recommended as the first category of the first-line treatment. · Recommended as the first category of the second-line treatment followed by cytokines and as category 2A of the second-line treatment following TKI.
Pazopanib [76]	· Recommended as the first category of the first-line treatment in metastatic clear cell RCC. · As an adjunct to category 1 as the second-line treatment in treating patients previously treated with cytokine. · There is no data on using pazopanib as the second-line treatment after the failure of TKI.
Temsirolimus [77]	· Indicated as the first category of the first-line treatment in patients with metastatic clear cell RCC that indicate poor prognosis.
Sorafenib [77]	· Recommended as the first category followed by treatment with cytokines and as the second category to treat anti-VECF. · Used as category 2A of the first-line treatment of metastatic RCC. · Effectiveness as the first-line is less than the previous ones and is not preferred.
Everolimus [78]	· As the first category of treatment after a failure of one or two lines of TKI.
Axitinib [77]	· As the second category of the second-line treatment in patients previously treated with TKI or cytokine.
Cabozantinib [78]	· A small molecule of TKI that targets RET, MET, VEG FR-2.
Nivolumab [79]	· Anti-PD-1 immune checkpoint inhibitor; Anti-body against the death of cell (PD-1). · Recently approved to be used as the second-line treatment of metastatic RCC. · A new standard of the second-line treatment of metastatic clear cell RCC.

Table 3: A summary of some of the available medications for target treatment [2].

The most common side effects of treatment with targeted drugs in metastatic RCC include fatigue, HTN, nausea, diarrhea, and dysphonia [2]. Although sorafenib is better in terms of overall survival (OS), the TKI-TKI sequence seems to be better than TKI-mTOR. In the available studies, any of the two TKI-TKI-MTOR and MTOR-TKI-TKI sequences are clinically acceptable. Complications of Grade 3 and 4 are seen in one-third of patients that have improved with new targeted therapies (pazopanib) which is the preferred factor compared to everolimus in the second line treatment of metastatic RCC (MRCC) that failed treatment with VEGF TKI. The INTOR ECT study compared the effectiveness of the TKI-TKI sequence against temsirolimus, TKI-mTOR inhibition with sorafenib following sunitinib treatment. METEOR Trial of Phase 3 showed that cabozantinib is preferred to everolimus in the second line treatment of MRCC in patients who have undergone previous treatment with VECF TKI[80].

Other treatment options in metastatic disease

Considering the use of radiotherapy (RT) as part of a multimodality approach, RCC seems to be a radio-resistance tumor because of its poor results with low-dose RT. Although this was challenged by the discovery of evidence that RT stereotactic with high-tech fraction dose affects primary tumors and oligomentasase disease. The most common clinical information regarding the prediction of prospects for patients with metastatic RCC is treatment with targeted therapies including Ca, corrected HB serum, KPS, the time of onset of the disease to the onset of treatment, absolute neutrophil count, and platelet count [80].

Conclusion

RCC is the most common type of urogenital cancer and has a mortality rate of 30%-40%. However, most cases of RCC are diagnosed accidentally. Following the improvements in diagnostic tests, the incidence of patients diagnosed with RCC has rapidly increased over the past decades. Although the diagnosis of RCC at early stages is critical in treating patients and reducing death rates, optimal screening modalities and approaches have not been established yet. In addition, choosing the best therapeutic approach is necessary to improve the outcome of RCC. Therefore, knowledge of the recent advances in the diagnosis and management of RCC could help the physicians, especially the nephrologists, to better diagnose and treat RCC.

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