Guidelines

Chinese guidelines for diagnosis and treatment of renal cell carcinoma 2018 (English version)

National Health Commission of the People's Republic of China

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1. Overview

Renal cell carcinoma (RCC), originating from the renal tubular epithelium, is a malignant tumor accounting for 80%–90% of renal malignancies. The most common histopathological type of RCC is clear cell carcinoma, followed by papillary RCC and chromophobe RCC, and then the rare type such as collecting ductal carcinoma. In China, the incidence of renal cancer is second next to bladder cancer in the urinary system.

With the development of medical imaging, early detection of RCC is gradually increasing. Radical nephrectomy or nephron-sparing surgery (NSS) can achieve satisfactory outcomes for localized renal cancer. According to statistics, the number of patients with advanced diseases at the time of diagnosis has dropped from 30% a few years ago to 17% currently. With the development of targeted therapy and new immunotherapeutic drugs, the efficacy for advanced renal cancer has been gradually improved.

2. Epidemiology and etiology

2.1 Epidemiology

The incidence of renal cancer accounts for approximately 3% of adult malignancies worldwide, and its distribution has obvious regional differences. Western countries such as North America and Western Europe have the highest incidence rates, while developing countries such as Africa and Asia have the lowest ones. The global incidence of renal cancer is currently ranked 9th in male malignancies (214,000 new patients) and 14th in females (124,000 new patients). The incidence rate of males and females is about 2:1, and the peak incidence is between 60 and 70 years old. According to GLOBOCAN's 2012 World Congress of Malignant Tumor Epidemiology, the global incidence of renal cancer ranks 14th among malignant tumors and the mortality rate ranks 16th. In the last decades, the incidence of RCC has continued to rise in most countries and regions, including North America, parts of Europe, Asia, Oceania and parts of Latin America, but renal-cancer related mortality has stabilized or declined in developed countries. According to China Cancer Registration Annual Report, the incidence of RCC has increased from 1988 to 2014 in China, the increased incidence is probably related to aging population, western lifestyles and early disease screening. The incidence of RCC in China was 3.96/100,000, 4.44/100,000, 4.64/100,000, 5.08/100,000, and 4.5/100,000 respectively from 2005 to 2009. On February 2018, the National Cancer Center of China released the latest cancer data from 339 cancer registration sites, covering a total of 280 million people in China. The data show that the incidence of renal cancer was 4.99/100,000 in 2014, of which 6.09/100,000 for males, and 3.84/100,000 for females.

2.2 Etiology

The etiology of renal cancer is still unclear, and the etiological factors include heredity, smoking, obesity, hypertension and antihypertensive drugs. Smoking and obesity are considered definite risk factors for RCC.

2.2.1 Genetic factors

Most RCC are sporadic, and 2%–4% of RCC is hereditary. Most of them are autosomal dominant inheritance in families caused by different genetic variations, including tumor suppressor gene and oncogene. Hereditary RCC includes von Hippel-Lindau (VHL) disease (bilateral multiple RCC and renal cyst), *MET* gene-related papillary RCC (type I), hereditary leiomyomatosis caused by abnormal fumarate hydrase gene and RCC (non-type I papillary RCC), Birt-Hogg-Dube (BHD) syndrome (multiple chromophobe RCC, heterozygous eosinophilic variants of chromophobe RCC, papillary RCC) and *HRPT2* gene-related hyperparathyroidism-jaw tumor syndrome (mixed epithelial and stromal tumor, papillary RCC) (*Table 1*). In general, the following population may be potential patients for hereditary renal cancer: 1) renal cancer patients ≤45 years old; 2) bilateral/multiple renal tumors; 3) family history of kidney cancer (RCC in at least one first-degree relative, or two second-degree relatives); 4) renal cancer combined with other tumor history (pheochromocytoma, interstitialoma, hemangioblastoma of nervous system, pancreatic neuroendocrine tumor, etc.), or combined with other lesions such as pulmonary cysts and spontaneous pneumothorax; 5) combined with rare skin lesions (leiomyosarcoma, angiofibroma, etc.); and 6) individuals or families have history of renal cancer-related syndrome. For these patients and their families, genetic mutation screening is recommended.

2.2.2 Smoking

Smoking is one of the pathogenic factors of renal cancer. A number of prospective studies on relationship between

Table 1 Common hereditary RCC and its clinical manifestations

Syndrome abbreviation	Mutation point	Pathology type	Clinical manifestations
VHL	VHL	ccRCC	ccRCC, pheochromocytoma, pancreatic and renal cysts, retinal hemangioblastoma of nervous system, paraganglioma, pancreatic endocrine tumor, lymphatic cystic tumor, adenoma of epididymis
HPRC	MET	pRCC I	pRCC
BHD	FLCN	Multi-RCC	Chromophobe tumor, mixed eosinophilic tumors, fibrofoliculom, cutaneous tag, pulmonary cyst, pneumothorax,
HLRCC	FH	pRCC II	pRCC, cutaneous uterine leiomyoma, uterus leiomyosarcoma
SDH RCC	SDHB, SDHD, SDHC	ccRCC, chromophobe RCC	ccRCC, chromophobe, eosinophilic pheochromocytoma, paraganglioma
cowden syndrome	PTEN	ccRCC	ccRCC, breast cancer, follicular thyroid cancer, endometrial cancer
MITF related tumor	MITF	RCC	Melanoma, PECOMA
HPT-JT hyperparathyroidism-jaw tumors	HRPT2	Wilms tumor	Multi-RCC, wilm's tumor, hyperparathyroidism, cancerous goiter
BAP1 related tumor	BAP1	ccRCC	ccRCC, uveal melanoma, melanoma, mesothelioma
Translocation [t (3;8), t (2;6)] related tumors	FHIT/FRA3B on chr3, RNF139 on chr8	ccRCC	ccRCC, thyroid papillary carcinoma

RCC, renal cell cancer; VHL, von Hipple-Lindau syndrome; ccRCC, clear cell renal cell carcinoma; HPRC, hereditary papillary renal carcinoma; pRCC, papillary renal cell carcinoma; BHD, Birt-Hogg-Dube' syndrome; HLRCC, hereditary leiomyomatosis and RCC.

renal cancer and smoking concluded that smoking is a moderate risk factor. The relative risk factor of renal cancer in people who had a history of smoking was 1.3 and 1.6 for people who are currently smoking. Smoking is the only recognized environmental risk factor for renal cancer.

2.2.3 Obesity

The degree of obesity is expressed by the body mass index (BMI). The increase of renal cancer is correlated with the increase of BMI. The specific mechanism by which obesity increases the risk of renal cancer is unclear. It may be related to increased androgen and estrogen release due to obesity, or some cytokines released by fat cells.

2.2.4 Hypertension and antihypertensive agents

Some population-based studies have shown that hypertension and its related medicines may be one of the factors in the pathogenesis of renal cancer. People with hypertension, those who use diuretics, especially thiazide diuretics and other antihypertensive agents, have a 1.4- to 2-fold increase in the risk of renal cancer. It is difficult to distinguish high blood pressure itself from antihypertensive agents, as both are often present in all studies. However, if blood pressure is better controlled, the risk of renal cancer would decrease, so antihypertensive agents may not be one of the risk factors.

2.2.5 Acquired cystic renal disease (ACRD) associated with long-term dialysis of end-stage renal disease

The incidence of renal cancer in patients with end-stage renal disease is higher than that in ordinary people. Patients with long-term dialysis are prone to acquire renal cystic disease, which may be the result of abnormal proliferation of cells within the renal tissue. There is a difference between renal cancer with ACRD and traditional renal cancer in ordinary patients, the onset age for ACRD patients with RCC is younger and the ratio of men to women is higher. The tumor with ACRD is usually bilateral, multiple and histopathologically papillary. Therefore, patients with end-stage renal disease should take regular B-ultrasound or enhanced magnetic resonance imaging (MRI) screening. For dialysis patients, radical nephrectomy is preferred even the renal cancer is less than 4 cm.

2.2.6 Others

Alcohol, occupational exposure to substances such as trichloroethylene, asbestos and polycyclic aromatic hydrocarbons, and high estrogens may increase the risk of renal cancer. In general, it is currently unable to find a

carcinogen with a clear relationship with renal cancer, and further research is necessary to identify the potential impact between genetic factors and environmental exposure.

3. Histopathology

3.1 Gross pathology

A vast majority of renal cancers occur in one kidney, and bilateral renal cancer (heterochronous or simultaneous) accounts for only 2%–4% of sporadic renal cancer. Renal cancer is often a single tumor, of which 10%–20% has multiple lesions. Multiple lesions are common in patients with hereditary and papillary renal cancer. Tumors vary greatly in size, and are often separated from the surrounding renal tissue by pseudo-envelope.

3.2 Classification of RCC

In 1981, 1997, 2004 and 2016, WHO launched four versions of the classification criteria for renal tumors. WHO Fourth Edition published in 2016 is currently used for classification of renal tumors (*Table 2*), and it follows the framework of 2004 version, which only updates in-depth understanding of the disease: such as multilocular cystic RCCs were renamed as multilocular cystic renal neoplasm, and Xp11.2 translocation/TFE3 fusion gene-related RCCs were classified into MiT transpositional cancer family. The latter includes RCCs with translocated *TFEB* gene. In addition, some new pathological subtypes have been added. As mentioned earlier, renal cancer is divided into hereditary renal cancer and sporadic renal cancer according to the relationship with genetic syndrome. It is unable to distinguish between hereditary and sporadic renal cancer through pathological morphology.

Table 2 2016 WHO classification for renal tumor histopathology

Renal cell tumors
Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of low malignant potential
Papillary renal cell carcinoma
Hereditary leiomyomatosis and renal cell carcinoma
(HLRCC)-associated renal cell carcinoma
Chromophobe renal cell carcinoma
Collecting duct carcinoma
Renal medullary carcinoma
MiT Family translocation carcinomas
Succinate dehydrogenase (SDH)-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

3.3 Pathological grading of RCC and papillary RCC

Pathological grading is an important prognostic factor that is only applicable to clear cell carcinoma and papillary RCC. In the previous WHO classifications, Fuhrman four-level grading system is the most commonly used grading system. In 1997, WHO recommended that the grade I and II in Fuhrman grading system be combined into level I, that is highly differentiated, grade III, moderately differentiated, and grade IV, poorly differentiated or undifferentiated. The 2016 version of the pathological grading system was further adjusted on basis of original Fuhrman four-level grading system, adding objective evaluation criteria, and the WHO/ISUP pathological grading system (*Table 3*) making it easier in operability and reproducible in practice.

3.4 Clinical staging of RCC

The most widely used renal cancer staging system is TNM staging system developed by the American Joint Committee on Cancer Staging (AJCC), which is currently upgraded in the 8th edition in 2017 (*Table 4*, *5*).

4. Diagnosis

4.1 Clinical manifestations

The clinical manifestations of RCC are complex and vary widely, which are caused directly by the renal tumor itself, hormones secreted by renal cancer cells or metastases. Due to increasing popularity of health checkups, most renal cancer patients are often unintentionally discovered in early stage by imaging examinations.

Early renal cancer often lacks clinical signs. When classic renal cancer "triple syndrome": hematuria, low back pain

Table 3 WHO/ISUP urological pathology grading system for RCC and papillary RCC

Grade	Definition
I	Nucleoli are absent or inconspicuous and basophilic at ×400 magnification
II	Nucleoli are inconspicuous and eosinophilic at ×400 magnification and visible but not prominent at ×100 magnification
III	Nucleoli are conspicuous and eosinophilic at ×100 magnification
IV	There is extreme nuclear pleophorphism, multinucleate giant cells, and/or rhabdoid and/or sarcomatoid differentiation.

Table 4 2017 8th version TNM classification

Category	Definition
T — Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor <7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor <4 cm or less
T1b	Tumor >4 cm but <7 cm
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but <10 cm
T2b	Tumors >10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below 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's fascia (including contiguous extension into the ipsilateral adrenal gland)
N — Regional lymph node	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
M — Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

Table 5 Clinical stage grouping for prognosis of RCC

Stage grouping	Status		
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

and abdominal mass appear, approximately 60% of these patients have reached T3. When left varicocele appears, it might suggest that left renal vein venous thrombus would already form. Therefore, early diagnosis of RCC is of great significance in clinical practice.

Paraneoplastic syndrome: The clinical manifestations are not caused directly by the location of the primary tumor or metastases, rather by abnormal immune response through products secreted by the tumor or other unexplained endocrinological secretion, or/and pathological lesions in nerves, digestion, hematopoiesis, bones and joints, kidney, skin and other systems. These lesions may cause corresponding clinical manifestations. All these manifestations are known as paraneoplastic syndrome. The incidence of paraneoplastic syndrome in patients with RCC is about 30%. It is manifested mainly as hypertension, increased erythrocyte sedimentation rate, polycythemia, abnormal

liver function, hypercalcemia, hyperglycemia, neuromuscular disease, amyloidosis, galactorrhea, coagulation mechanism abnormalities, etc. Patients with paraneoplastic syndrome have a worse prognosis.

Symptoms caused by metastatic lesions: part of RCC patients are diagnosed by metastatic manifestations as the first symptom, such as bone pain, fracture, cough and hemoptysis; or as cervical lymphadenopathy, secondary varicocele and edema of both lower extremities revealed by physical examination, and the latter suggests the tumor had invaded the renal vein and inferior vena cava. In patients with metastatic RCC, the common metastatic organs are: lung metastasis (48.4%), bone metastasis (23.2%), liver metastasis (12.9%), adrenal metastasis (5.2%), skin metastasis (1.9%), brain metastasis (1.3%) and other locations (7.1%).

4.2 Laboratory test

The goal of routine laboratory tests for patients with renal cancer are to understand the general condition and whether further treatments are appropriate. These tests include urinalysis, complete cell blood count, erythrocyte sedimentation rate, blood glucose, blood calcium, renal function (blood urea nitrogen, serum creatinine and Glomerular filtration rate), liver function, lactate dehydrogenase, alkaline phosphatase and other items. If an invasive or surgical treatment is required, then coagulation function test should be performed. Patients with RCC may be found to have hematuria, erythrocytosis and low hemoglobin, increased erythrocyte sedimentation rate, hyperglycemia, hypercalcemia, renal dysfunction and abnormal liver function. Urine cytology is required for patient with renal tumor that adjacent or involving renal pelvis. Tumors in solitary kidney, bilateral renal tumors, abnormal renal function indicators, and diseases in which renal function is impaired (such as diabetes, chronic pyelonephritis, polycystic kidney disease and contralateral kidney stones) require radionuclide renal scan to determine the separate renal functions and to assess the grade of renal insufficiency in each kidney. At present, there is no recognized serum tumor marker for early diagnosis of RCC.

4.3 Imaging examination

More than 50% of renal cancers are incidentally found with non-specific symptoms of the abdomen or other diseases currently. Imaging examination plays an important role in diagnosis and treatment at different stages of renal cancer, and it could find, locate, characterize and even determine the stage of the lesion of primary tumor. It can assist in positioning tumor during surgery and is also an important follow-up measure after surgery or for patients with non-surgical disease. Different imaging examinations have different values for diagnosis and treatment of renal cancer at various stages, therefore, specific selection should be based on advantages and disadvantages of each method and clinical needs.

4.3.1 Chest X-ray

Patients with RCC should take anteroposterior and lateral chest X-ray. Chest computerized tomography (CT) should be considered if patient is suspicious of nodules on the X-ray or clinical stage ≥III.

4.3.2 Ultrasonography

The easiest and most common method for finding renal tumors is abdominal ultrasonography. Renal contrast-enhanced ultrasonography is helpful in identifying the benign and malignant renal tumors. It would be a diagnostic approach for patients with chronic renal failure or allergic to contrast agents, and it is also a proper differential diagnosis method for patients with complicated renal cysts.

(1) Diagnosis of primary renal cancer with ultrasound

1) Gray-scale and Doppler ultrasound

Ultrasound examination with high popularity rate, is economical, simple and non-radioactive, therefore it is the first choice for diagnosis of renal tumors. Clinically, asymptomatic renal cancer is often found by ultrasound. Grey-scale ultrasound will show tumor size, location, and relationship to surrounding tissues. Color Doppler flow imaging (CDFI) will provide information about blood supply for tumor, and it is a preliminary evaluation for the formation of venous tumor thrombus. Grey-scale ultrasound and CDFI examination have a higher sensitivity for the identification of solid renal tumors.

2) Contrast-enhanced ultrasound

Enhanced imaging is the most important measure to distinguish benign solid renal mass from malignant one. Real-time grey-scale contrast-enhanced ultrasound (CEUS) has high sensitivity and accuracy for blood flow, and thus it could provide more information on early artery flow and microcirculation of tumor. It has high sensitivity

and specificity for detection of RCC.

(2) Preoperative staging of renal cancer

The scope of ultrasound examination is limited, and quality of imaging is affected by its resolution, patient's own conditions and operator's experience. The accuracy of tumor staging is not as good as CT, therefore it is not recommended for preoperative clinical stage evaluation.

(3) Intraoperative evaluation of renal cancer

Beside routine image-guided tumor biopsy, ultrasound is often used for intraoperative exploration to determine the scope of surgery due to its non-radioactive and flexible features. It can clearly display renal tumor and make definitive judgment for the relationship between tumor and renal pelvis as well as the scope of tumor thrombus within renal vein, inferior vena cava and right atrium in operation.

4.3.3 CT

Abdominal CT is most commonly used for preoperative diagnosis and postoperative follow-up of renal cancer. A full CT scan includes CT plain scan and contrast-enhanced CT. With high sensitivity and specificity, it could make qualitative diagnosis for most renal tumors. Once the RCC diagnosis is made with CT, preoperative needle core biopsy is usually not necessary. On CT scan with contrast agent, typical imaging manifestation is usually quick and high enhancement in RCC mass; the other characteristics of images for plain scan are uneven low-enhancement in the mass with round and elliptical shape; and enhanced scan shows medium to high enhancement in normal cortex and medulla, and the density of RCC mass is usually lower than that of normal tissues in the renal parenchyma. Necrosis and hemorrhage are common in RCC. However, CT examination is difficult to differentiate some rare types of renal cancer from benign tumors such as oncocytoma and angiomyolipoma with minimal fat.

In addition to qualitative diagnosis, CT examination can provide more diagnostic information for preoperative patients including: the extent of tumor invasion, whether the venous system is invaded (T stage), metastasis of regional lymph node (N stage), whether there is adjacent organ metastasis in scanning range (M stage), whether there is blood vessel variant (CTA) and a rough assessment of the morphology and function of both kidneys.

Bosniak *et al.* developed a classification system primarily based on CT imaging criteria that divides renal cystic lesions into four categories (*Table 6*).

4.4 MRI

Abdominal MRI is used for preoperative diagnosis and postoperative follow-up for renal cancer. It is indicated in patients who are allergic to intravenous CT contrast medium, and in pregnancy or patient who is unsuitable for CT scan. The sensitivity and specificity of MRI are equal to or slightly higher than that of CT for diagnosis of renal cancer. MRI is more accurate in evaluation of tumor thrombus within renal vein and inferior vena cava than CT.

4.5 Positron emission tomography (PET)

At present, ^{18}F-fluorodeoxyglucose (^{18}FDG) is a widely used imaging tracer for PET-CT. Approximately 50% of the agent is directly excreted by kidneys without metabolism, and thus it could affect the display of renal

Table 6 Bosniak classification of renal cystic masses

Bosniak category	CT features	Work-up
I	Simple benign cyst with a hairline-thin wall without septa, calcification, or solid components. Same density as water and does not enhance with contrast medium.	Benign
II	Benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions <3 cm in size, with sharp margins without enhancement.	Benign
IIF	These may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall. Minimal thickening of the septa or wall. The cyst may contain calcification, which may be nodular and thick, with no contrast enhancement. No enhancing soft-tissue elements. This category also includes totally intrarenal, non-enhancing, high attenuation renal lesions >3 cm. Generally well-marginated.	Follow-up, up to five years. Some are malignant
III	These are indeterminate cystic masses with thickened irregular walls or septa with enhancement.	Surgery or active Surveillance. Over 50% are malignant.
IV	Clearly malignant containing enhancing soft-tissue components.	Surgery. Most are malignant.

lesions. Besides, the low expression of GLUT-1 in grade I–II renal clear cell carcinoma membrane and the high level of 6-PO4-deoxyglucose (FDG-6-PO4) hydrolytic enzyme in RCC result in only half of primary renal cancer showing an increased FDG metabolism, and the other half show no difference compared with normal kidney. Therefore, ^{18}FDG PET-CT imaging has limited diagnostic value for primary RCC and is not recommended for routine use in evaluation of RCC. Other new tracing agents are ^{18}F or ^{11}C labeled acetate, which has a good imaging effect on well-differentiated, low-degree malignant renal cancer. These new tracing agents could remedy the imaging flaws of ^{18}FDG, but they are still under investigation and not used as a routine examination currently. The 2018 European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) Renal Cancer Guidelines also clarify that PET is not recommended for diagnosis and follow-up of patients with renal cancer. However, several studies have shown that PET-CT imaging is superior to conventional imaging methods in evaluation of lymph node and distant metastasis of RCC, especially for bone or skeletal muscle metastasis. Through metabolic change of glucose, early monitoring of therapeutic efficacy and evaluation of the prognosis of patients can be achieved. In 2017 Chinese Society of Clinical Oncology (CSCO) Renal Cancer Treatment Guidelines, PET/PET-CT is proposed to evaluate whether there are distant metastases or to evaluate the efficacy of systemic therapy on RCC patients.

4.6 Radionuclide bone scan

Radionuclide bone scan is used to detect the bone metastases and evaluate the efficacy of treatment for bone metastases. RCC patient with bone-related symptoms such as bone pain, elevated serum alkaline phosphatase or clinical stage ≥III should be examined by bone scan to determine whether there is bone metastasis. Whole body radionuclide scan can find metastasis 3–6 months earlier than X-ray. If bone metastasis is suspicious, further local tomographic fusion imaging of suspicious sites or MRI and CT should be considered.

4.7 Dynamic renal scan

Dynamic radionuclide renal scan can accurately evaluate the dual- and single-function of kidney in RCC patients before surgery, which is helpful in making proper surgical plan.

4.8 Needle core biopsy of renal tumor

Percutaneous biopsy includes needle core biopsy and fine needle aspiration (FNA). It would provide pathological and histological evidence for renal tumors that might not be diagnosed by imaging. The accuracy of needle core biopsy is higher than that of FNA for diagnosing malignant tumors, but the combination of two could improve the diagnostic accuracy. Needle core biopsy is preferred for solid renal tumors. If the initial biopsy has no results while imaging is suspected of malignancy, renal mass biopsy or surgery exploration should be considered. Although the risk of needle biopsy itself or chance of spreading to surrounding tissues is low, it cannot be ignored. Percutaneous renal biopsy is not indicated for critically ill patients. For patients who are scheduled for surgery, since the accuracy of abdominal contrast-enhanced imaging is very high, percutaneous renal biopsy is not recommended. For patients who are not indicated for surgery due to aging or surgical contraindications, or patients with advanced RCC who cannot receive surgery, since biopsy can make pathological diagnosis (including pathological type), it will help choose medications before systemic therapy. RCC patients who plan for ablation therapy should also receive tumor biopsy for pathological diagnosis.

5. Prognostic assessment of advanced/metastatic RCC

Prognostic risk models contribute to risk stratification and treatment options for advanced RCC. Currently, the standards commonly used include the standard from Memorial Sloan Kettering Cancer Center (MSKCC) and the standard from International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) (*Table 7*).

6. Treatment of RCC

Appropriate treatment should be selected according to the staging and patient's tolerance. Staging of RCC (clinical stage grouping and cTNM) is based on imaging findings. Patient's tolerance to treatment will be assessed by routine auxiliary examinations. According to results of pathological examination, postoperative treatment and follow-up were chosen according to the pathological stage grouping (pTNM).

Table 7 Prognosis of metastatic renal cancer

Risk factors	MSKCC risk model		IMDC risk model	
1	Time from diagnosis to treatment	<12 months	Time from diagnosis to treatment	<12 months
2	Karnofsky performance status	<80%	Karnofsky performance status	<80%
3	Corrected serum calcium	>10.0 mg/dL (2.4 mmol/L)	Corrected serum calcium	>10.0 mg/dL (2.4 mmol/L)
4	Hemoglobin	<Lower limit of laboratory reference range	Hemoglobin	<Lower limit of laboratory reference range
5	Elevated lactate dehydrogenase	>1.5 times ULN	Absolute neutrophil count (neutrophilia)	>ULN
6			Platelets (thrombocytosis)	>ULN
Risk grouping				
Low-risk	0 factor		0 factor	
Intermediate-risk	1–2 factors		1–2 factors	
High-risk	3–5 factors		3–6 factors	

MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ULN, upper limit of normal.

6.1 Surgery

For patients with localized and locally advanced RCC, radical nephrectomy remains the preferred treatment that may lead to cure for patients. For advanced renal cancer, cytoreductive nephrectomy + solitary metastasectomy or cytoreductive nephrectomy + medical therapy is recommended if the patient can tolerate surgery. If patient is intolerant of any kind of surgery, medical therapy is recommended.

6.1.1 Radical nephrectomy

In 1963, Robson *et al.* established the basic principle of radical nephrectomy and established it as the "gold standard" for surgical treatment of localized RCC. The scope of classic radical nephrectomy includes kidney, perirenal fascia, perirenal fat, ipsilateral adrenal gland, lymph nodes from the crus of diaphragm to aortic bifurcation, and the ureter above the bifurcation of iliac vessels. With the change of concept recently, routine adrenalectomy and regional lymph node dissection are not recommended.

(1) Indications for radical nephrectomy include: 1) localized RCC with no definite metastasis; 2) tumor thrombus in renal vein, inferior vena cava without distant metastasis; 3) tumor invasion to adjacent organs without distant metastasis, complete resection of tumor can be made with preoperative assessment; and 4) renal cancer with local lung metastasis, primary or metastatic lesions can be removed completely.

(2) Contraindications for radical nephrectomy include: 1) advanced RCC with distant metastasis; 2) tumor invasion to adjacent organs, local tumors are not removable; 3) patients with severe bleeding disorders; and 4) serious disease in heart, brain, liver, lung and circulatory system. Patient's condition is too poor to tolerate anesthesia and surgery.

(3) Management of complications after radical nephrectomy: Approximately 20% of patients will have complications after radical nephrectomy, and the mortality rate of radical nephrectomy is about 2%. Complications of radical nephrectomy may happen postoperatively which include myocardial infarction, cerebrovascular injury, congestive heart failure, pulmonary embolism, atelectasis, pneumonia and thrombophlebitis. However, adequate preoperative preparation, control of intraoperative hypotension, supplement of blood and body fluids, postoperative respiratory training, early activities, etc. may relieve the occurrence of these complications. Much attention should be paid to adjacent organs during operation and damage should be repaired in time once it occurs.

6.1.2 NSS for RCC

Radical nephrectomy resulting in one kidney left may lead to decreased renal function and increased chance of chronic renal insufficiency and dialysis. Chronic renal insufficiency increases the risk of cardiovascular disorders as well as

overall mortality. If feasible, NSS is recommended for T1a or even T1b and T2. To some extent, an indication of NSS also depends on the surgeon's experience and skills.

(1) Indication of NSS

Indications for NSS include: 1) absolute indications: congenital solitary kidney, contralateral renal insufficiency or impaired total renal function, and bilateral renal cancer, renal insufficiency or uremia caused by radical nephrectomy; 2) relative indications: renal cancer with benign disease in the contralateral kidney, such as kidney stones, chronic pyelonephritis and other diseases that may lead to deterioration of renal function (hypertension, diabetes, renal artery stenosis, etc.) after radical nephrectomy; and 3) optional indications: clinical stage T1a (tumor ≤4 cm) or T1b (tumor ≤7 cm), the tumor which is located in the periphery cortex of the kidney, asymptomatic solitary lesion of renal cancer with normal contralateral renal function can also receive NSS.

(2) Complications and management for NSS for RCC

1) Intraoperative bleeding: Clinically significant bleeding during surgery may be caused by incomplete renal artery occlusion, unblocked ectopic renal artery, or opening of renal vein. Therefore, preoperative vascular imaging to determine renal artery branches and ectopic renal blood vessels is usually important. Complete occlusion of kidney arteries should be done or blockade of the renal arteries and veins at the same time is necessary for some cases. All approaches above can reduce intraoperative bleeding. When patients are receiving minimally invasive surgery with laparoscopy or robotic-assistant laparoscopy, intraoperative bleeding may be blocked by increasing pneumoperitoneum pressure, adding addition clips near the blocked artery, and blocking ectopic arteries, or artery and vein at the same time. If necessary, open surgery or radical nephrectomy should be considered. The main cause of postoperative bleeding is the opening of intraoperative collection system and uncomplete suture of the segmental renal artery, and all these would result in bleeding into the collecting system or around the kidney. Postoperative bleeding may be limited to peritoneum or cause gross hematuria. Patients with early postoperative bleeding should be bed resting, continuous observing hemoglobin and hematocrit, monitoring vital signs, and blood transfusion if necessary. Angiography helps to determine the active bleeding arteries and bleeding can be controlled through intravascular embolization. Severe refractory bleeding may require secondary surgery.

2) Urine leakage: The drainage tube drains urine after partial nephrectomy, and urine leakage often disappears after renal collecting system heals. Persistent drainage of urine indicates the formation of urinary fistula. Causes of urinary fistula are opening of intraoperative collection system, incomplete closure during suture, or obstruction of collection system due to too deep suture and blood clot in collection system. Detecting the level of creatinine in the drainage fluid or the staining in the drainage fluid after intravenous injecting indigo carmine will help the diagnosis. Most urinary fistulas can heal if there is no obvious obstruction in urinary collection system. Ureteral stent might be required if hydronephrosis or persistent leakage of urine is significant. Most urinary fistulas are self-healing within a few weeks through appropriate conservative and interventional treatments. Few require secondary surgery to close the fistula or remove the kidney.

3) Renal insufficiency after NSS: Partial nephrectomy of functional or anatomical solitary kidney in patients is prone to various degrees of renal insufficiency. The cause of renal insufficiency may be intraoperative renal ischemia, as well as removal of too much normal renal tissues around the lesion. The renal insufficiency is generally mild and self-recovery if proper water and electrolyte balance are maintained. In most cases, compensatory hyperplasia of residual renal tissues can improve renal function. Severe renal insufficiency requires temporary or long-term hemodialysis. All patients who plan to receive NSS should be informed of the risk of renal insufficiency after surgery.

6.1.3 Other surgery related issues

(1) Open surgery/laparoscopic surgery/robot-assisted technology

Compared with traditional open surgery, the advantages of laparoscopic surgery are minimal invasion with small incision, less damage, less bleeding, faster postoperative recovery, fewer complications, shorter hospital stay, and same tumor control rate in short-term. The disadvantages are expensive equipment, complicated technology, long learning curve and longer operation time for beginners. With improvement of techniques, the operation time will be significantly shortened, and the thoroughness of resection will be as same as open surgery. The advent of robot-assisted surgery simplifies laparoscopic reconstruction techniques which could be the most difficult surgical procedure for laparoscopic surgery. The improvement has made several key surgical steps easier and the learning curve is shorter in robot-assisted laparoscopic partial nephrectomy. Currently, open surgery, laparoscopic

surgery or robot-assisted techniques can be applied to RCC patients. Options on these procedures largely depend on the size and location of the tumor and the surgeon's experience.

(2) Ipsilateral adrenalectomy

The extent of resection for classic radical nephrectomy includes the ipsilateral adrenal gland. However, the risk of ipsilateral adrenal gland involvement is very low in small tumor. Clinically, only patients with large renal tumor or a tumor located in the suprarenal pole would simultaneously remove ipsilateral adrenal gland during radical nephrectomy. Although it is still debating on whether ipsilateral adrenal gland should be preserved, ipsilateral adrenalectomy, in the absence of clinical evident of adrenal involvement during radical nephrectomy or partial nephrectomy, has no survival advantage.

In following conditions, ipsilateral adrenal gland should be preserved during radical nephrectomy: 1) clinical stage is I or II; 2) tumor <8 cm; 3) tumor located in the middle and lower part of the kidney; and 4) the adrenal gland is normal on preoperative CT scan. The ipsilateral adrenal should be removed if adrenal gland abnormalities were found during surgery.

(3) Regional lymph node dissection

Retroperitoneal regional lymph node dissection during radical nephrectomy is a debating issue for many years. No evidence showed that patients with RCC can benefit from retroperitoneal regional lymph node dissection currently. In a 20-year randomized phase III clinical study from European Organization for Research and Treatment of Cancer (EORTC), comparative analyses of lymph node dissection on resectable localized renal carcinoma (N0M0) were studied. The results showed no significant difference in disease-free survival, disease progression-free survival and overall survival. Therefore, regional or extensive lymph node dissection is generally not routinely performed with radical nephrectomy. If preoperative imaging shows regional lymphadenopathy or palpable nodes detected intraoperatively, retroperitoneal regional lymph node dissection would be performed to confirm pathological staging.

(4) Management of positive surgical margins after NSS

Recurrence of RCC is the most concerned issue for patients with partial nephrectomy. The recurrence rate of ipsilateral renal tumor after partial nephrectomy is 1%–6%, due to mostly multifocal or positive surgical margins. It remains controversial whether positive surgical margins after NSS would increase the risk of tumor recurrence or impact the patient's prognosis. Mid-term follow-up studies have shown that there is no increase in tumor recurrence even surgical margin is positive after partial nephrectomy. Some studies have shown that tumor residual is not found in most patients who underwent immediate salvage nephrectomy. The literature reports that 3%–8% of NSS will have postoperative positive surgical margin, but only those with higher pathological grades (grade III–IV) have an increased risk of recurrence.

(5) Treatment of venous tumor thrombus

Approximately 10% of RCC have concurrent tumor thrombus in renal vein or inferior vena cava. The classification of renal tumors with venous tumor thrombus is often based on the five-level classification from Mayo Clinic in the United States (*Table 8*). Because surgical treatment of venous tumor thrombus would have greater risk of complications, a comprehensive assessment is required before surgery, a detailed therapeutic plan should be developed, and an experienced team is required for surgery.

(6) Management of T4 RCC

Renal cancer which invades the Gerota's fascia and adjacent organs is classified as T4. And it may involve ascending colon, duodenum, descending colon, pancreas, diaphragm, liver, spleen, adrenal gland, ureter, etc. Early studies have shown that radical nephrectomy for T4 RCC had poor outcome, thus it is not recommended. However, some subsequent studies have shown that patients might benefit from surgery in recent years. According to MDACC, no positive surgical margins were found in 30 cT4NxM0

Table 8 Mayo Clinic tumor thrombus classification

Level of tumor thrombus	Description
Level 0	Thrombus limited to the renal vein, detected clinically or during assessment of the pathological specimen
Level I	Tumor thrombus extends into the IVC, <2 cm above the renal vein
Level II	Tumor thrombus extends into the IVC, >2 cm above the renal vein but below the hepatic veins
Level III	Tumor thrombus extends above the hepatic veins but below the diaphragm
Level IV	Tumor thrombus extends above the diaphragm.

patients after the tumor and invaded adjacent organs are removed. And 60% of patients had a decline in stage, among them, two were T2. A multivariate regression analysis showed that pT4 and lymph node metastasis were independent predictors of survival. The 3-year overall survival for patients with node-negative disease was 66%, and 12% if there is lymph node metastasis. This study shows that preoperative and intraoperative staging is not completely accurate, and a significant portion of patients were overestimated. Therefore, for cT4 patients with no distant metastases, if perioperative risk is in control with fairly physical conditions, surgical treatment may be considered.

6.2 Interventional therapy for RCC

6.2.1 Artery embolization treatment for RCC

(1) Artery embolization for RCC

Embolization of the renal artery can be used for palliative treatment to relieve clinical symptoms and improve quality of life for renal cancer patients.

1) Indications of embolization: (A) pain caused by renal tumor; (B) renal tumor-related hemorrhage, such as rupture of renal tumor and hematuria; and (C) preoperative embolization for some huge renal tumors with rich blood supply: the benefits of prolonged survival time, reducing intraoperative bleeding and postoperative complications are not clear, and thus it is not recommended for routine use.

2) Contraindications of embolization: (A) uncorrectable coagulation disorders; (B) severe infection; (C) significantly reduced peripheral blood leukocytes and platelets (it is not absolute contraindications, such as hypersplenism): white blood cells $<3.0\times10^9$/L, platelets $<50\times10^9$/L; and (D) severe renal dysfunction.

3) Postoperative complications: Post-embolic syndrome is the most common adverse event after renal artery embolization which is characterized by fever, pain, nausea and vomiting. The main cause is that embolization of renal artery will result in ischemia and necrosis of local tissue. Such adverse events can last for 5−7 days, and most patients can recover completely after treatment.

(2) Embolization of lung metastases

The lung is the most common metastatic site of renal tumors, and some patients have hemoptysis as the first symptom. Bronchial artery embolization is used to treat lung metastases, prevent complications associated with lung metastases, and improve quality of life.

1) Indications: (A) pain caused by lung metastases, such as pleural metastasis; (B) dyspnea caused by lung metastases, such as airway compression stenosis; and (C) lung metastases related hemorrhagic events, such as hemoptysis and hemothorax.

2) Contraindications: (A) uncorrectable coagulation disorders; (B) severe infection; (C) significantly reduced peripheral blood leukocytes and platelets (it is not an absolute contraindications, such as hypersplenism): white blood cells $<3.0\times10^9$/L, platelets $<50\times10^9$/L; and (D) severe renal dysfunction.

3) Postoperative complications: Post-embolic syndrome is the most common adverse event after bronchial artery embolization. It is characterized by fever, pain, cough, hemoptysis, etc. It is caused by ischemia and necrosis of local tissue due to bronchial artery embolism. It usually lasts for 5−7 days after interventional therapy, and most patients recovered completely after symptomatic treatment.

(3) Embolization of liver metastatic lesions

Liver is also one of the common metastatic sites for renal tumors. Selective hepatic artery embolization can be used to treat liver metastases, prevent deterioration of liver function, and improve the quality of life.

1) Contraindications: (A) uncorrectable coagulation disorders; (B) severe infection; (C) significantly reduced peripheral blood leukocytes and platelets (it is not an absolute contraindications, such as hypersplenism): white blood cells $<3.0\times10^9$/L, platelets $<50\times10^9$/L; (D) severe renal dysfunction; and (E) severe liver dysfunction (Child-Pugh C grade) which includes jaundice, hepatic encephalopathy, refractory ascites or hepatorenal syndrome.

2) Postoperative complications: Post-embolic syndrome is the most common adverse event after hepatic artery embolization surgery. It is characterized by fever, pain, nausea, vomit, transient abnormal live function, etc. It is caused by ischemia and necrosis of local tissues due to hepatic artery embolism. It usually lasts for 5−7 days after interventional therapy, and most patients recovered completely after symptomatic treatment.

6.2.2 Ablation therapy

In recent years, the widely used ablation treatments have the characteristics of less trauma and definite curative effect, so some liver cancer patients who do not accept or cannot undergo surgical resection will also get a chance of cure.

Ablation is a therapeutic approach, with imaging guidance to target, applying physical or chemical methods

to kill cancer tissues. Ablation for renal tumor and oligo-metastasis includes radiofrequency ablation and cryo-ablation. Ablation with ultrasound guidance, which is convenient, real-time and efficient, is the most commonly used method. CT and MRI combined with multimodal imaging systems can observe lesions which are not detected by ultrasound. Ablation under CT and MRI guidance can also be applied to metastatic lesions of lung, liver, adrenal gland and bone.

(1) Radiofrequency ablation

Radiofrequency ablation is performed percutaneously or laparoscopically. Complication rate, recurrence rate and tumor-specific survival rate are similar in both procedures for T1a renal tumor. When comparing with partial nephrectomy, there is no difference in the overall survival either. The complication and blood transfusion rate of radiofrequency ablation is lower than that of partial nephrectomy. And local recurrence rate is higher than that of partial nephrectomy, but distant metastasis is similar.

(2) Cryoablation

Cryoablation is performed percutaneously or laparoscopically. The overall survival, tumor-specific survival, recurrence-free survival, and complication rate are similar while compared with partial nephrectomy. Percutaneous ablation has shorter hospital stay than laparoscopic ablation. Compared with partial nephrectomy, some studies have shown that the overall survival rate, tumor-specific survival rate, recurrence-free survival rate, disease-free survival rate, local recurrence rate and distant metastasis rate are similar. Some other studies have shown that partial nephrectomy is superior to cryoablation in the above clinical ending points.

There is no difference in total survival, tumor-specific survival, recurrence-free survival and complication rate between radiofrequency ablation and cryoablation.

1) Indications for ablation therapy: (A) T1a patients with advanced stage or accompanied with other disease complications; (B) stage IV unresectable primary lesion with possible oligo-metastasis; (C) recurrent or stage IV unresectable primary lesion, patients may receive oligo-metastasis ablation on the basis of combined first-line treatment; (D) unwilling or intolerance of the surgery; (E) trying to preserve the nephronnephron nephron as much as possible; (F) renal dysfunction; and (G) contraindications to general anesthesia.

2) Contraindications for ablation: (A) uncorrectable coagulation problem; (B) severe infection; and (C) significantly lowed peripheral blood leukocytes and platelets (not absolute contraindications, such as hypersplenism): white blood cells $<3.0\times10^9$/L, platelets $<50\times10^9$/L.

3) Postoperative complications: fever, pain, bleeding, infection, etc., most are mild, and patients can recover completely after symptomatic treatment.

6.2.3 Other ablation technologies for renal cancer

Other ablative technologies include: microwave ablation, high-intensity focused US ablation, irreversible electroporation, and high-low temperature combined ablation. Above methods have been gradually applied in the ablation treatment for renal cancer.

6.3 Active surveillance

Active surveillance is defined as the initial monitoring of tumor size by serial abdominal imaging with delayed radical intervention reserved for tumors showing clinical progression during follow-up. Watchful waiting is different from active surveillance, and it is reserved for patients whose comorbidities prohibit any active treatment unless deterioration of clinical symptoms and the need of symptomatic treatment (usually palliative treatment), and patients do not need routine follow-up imaging.

The results of the prospective multicenter Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry study comparing primary intervention group and active surveillance group showed that overall survival for primary intervention group and active surveillance group was 98% and 96% at 2 year, and 92% and 75% at 5 year, respectively (log rank, P=0.06). At 5 year, CSS was 99% and 100% for primary intervention group and active surveillance group, respectively (P=0.3). Active surveillance was not predictive of overall survival or CSS in regression modeling with relatively short follow-up. However, tumor-specific survival on active surveillance and active intervention at 5 year (99% *vs.* 100%, P=0.3) and at 7 year (99% *vs.* 100%, P=0.5) showed similar results. In active surveillance group, patients were older, and had a worse Eastern Cooperative Oncology Group (ECOG) score and more severe concurrent complications, and they had smaller tumors and higher chance of multiple and bilateral renal cancer.

Among most old patients with concurrent complications and small renal masses (SRMs, maximum diameter ≤4 cm), surgical anesthesia and other comorbidities often have higher risks than the tumor itself. Prospective studies

showed that patients with SRMs in the active surveillance group had a 5-year overall survival of 53%–90%, tumor-specific mortality of 0.2%–1.9%, and progression-free survival of 97%–99%. Thus, active surveillance is a feasible choice for elderly or frail patients with SRMs. In 2009, the American Urological Association (AUA) published a guideline for the diagnosis and treatment for T1 renal tumors which suggests that active surveillance can be used as therapeutic options in small renal tumor patients with high-risk comorbidities. In 2017, American Society of Clinical Oncology (ASCO) recommended active surveillance as first-line therapy for small renal tumor patients with high risk and poor life expectancy. It clearly defined the indications: absolute indications referred to those with high-risk anesthesia or life expectancy <5 years; and relative indications referred to the treatment might have the risk of end-stage renal diseases, SRM<1 cm or life expectancy <10 years. However, long-term active surveillance is not recommended for young SRMs patients with no other diseases.

6.4 Drug treatment

Since the approval of sorafenib in 2005, the treatment of metastatic RCC has entered the era of targeted therapy. To date, the US Food and Drug Administration (FDA) approved more than ten medicines and protocols for metastatic renal cancer. The mechanism of these medicines includes: (A) anti-vascular endothelial growth factor/-vascular endothelial growth factor receptor (anti-VEGF/VEGFR) pathways: including sunitinib, pazopanib, sorafenib, axitinib, cabozantinib, lenvatinib, bevacizumab, etc.; (B) anti-mTOR pathway: including everolimus and temsirolimus; (C) immune checkpoint blockade: including nivolumab and ipilimumab; and (D) others: including cytokines (interleukin-2 and IFN-α) and chemotherapy (gemcitabine and doxorubicin). Chemotherapy offers therapy for RCC patients with sarcomatoid differentiation.

The combination therapy includes bevacizumab + IFN-α, nivolumab + ipilimumab (for medium-, high-risk late-stage clear cell RCC), lenvatinib + everolimus (for second-line therapy on advanced clear cell RCC), bevacizumab + erlotinib (for partially advanced papillary RCC, including patients with HLRCC), bevacizumab + everolimus (for partially advanced papillary RCC, including patients with HLRCC), and lenvatinib + everolimus (for advanced non-transparent cell RCC)

Currently, pazopanib, sunitinib, axitinib, sorafenib, everolimus, interleukin-2, IFN-α etc. have been approved for advanced renal cancer therapy in China.

6.5 Traditional Chinese medicine treatment

Traditional Chinese medicine is conducive to the recovery of body function, and it can not only reduce the adverse effects caused by immunotherapy and targeted therapy, but also alleviate patients' symptoms and improve their life's quality, which can be administered independently or combined with other anti-tumor agents as one of the RCC treatments.

6.6 Radiotherapy

Renal cancer is not sensitive to conventional radiotherapy. Previous clinical studies on postoperative radiotherapy for high-risk RCC showed no survival benefit. Therefore, adjuvant radiotherapy is not recommended after radical surgery.

Radiotherapy is used for palliative treatment of renal cancer, such as local tumor recurrence, and metastasis of regional or distant lymph node, bone, brain or lung, to relief pain and improve quality of life.

Radiotherapy technology has developed rapidly in the past 10 years. In some retrospective phase I or II studies, single-dose stereotactic body radiotherapy (SBRT, single high dose once or several fractionated stereotactic radiotherapy) is gradually used to treat renal cancer. Results showed that SBRT offers short-term better therapeutic effects than conventional radiotherapy. Other studies showed that SBRT offers good short-term cancer control with fair safety. However, the sample size was small and long-term follow-up study is lacking. Currently no randomized studies have demonstrated that SBRT is superior to conventional fractionated radiotherapy or other local treatments. Therefore, SBRT used as palliative treatment or in clinical trial can only be performed in medical centers which are capable of technically supporting for precise radiotherapy or have experienced radio-therapists and physicists.

6.7 Common adverse events and managements of targeted therapy

6.7.1 Hypertension

Hypertension is one of the most common side effects in targeted therapy, especially in VEGF or VEGFR inhibitors (*Table 9*).

Table 9 Classification of hypertension related to targeted therapy for RCC

Severity grading*	Clinical characteristics
Grade I	Prehypertension stage (systolic pressure 120–139 mmHg, or diastolic pressure 80–89 mmHg)
Grade II	Stage I hypertension (systolic pressure140–1S9 mmHg, or diastolic pressure 90–99 mmHg); Medical intervention is needed. Recurrent or persistent (>24 h) hypertension with symptomatic diastolic pressure increase >20 mmHg, or blood pressure 140/90 mmHg (normal pressure in the past), monotherapy is needed
Grade III	Stage II hypertension (systolic pressure ≥160 mmHg, diastolic pressure ≥100 mmHg); multi-drug therapy is needed.
Grade IV	Life-threatening hypertension (such as hypertension crisis) requires urgent treatment
Grade V	Death

RCC, renal cell cancer; *, The grading standard adopts the America National Cancer Institute General Terminology Standard for Adverse Events (NCI-CTCAE 4.0); 1 mmHg=0.133 kPa

Table 10 Hematological toxicity grading system of targeted therapy

Severity	Neutropenia	Thrombocytopenia	Anaemia
Grade I	1.5×10^9/L – normal low limit	75×10^9/L – normal low limit	HB 100 g/L – normal low limit
Grade II	(1.0–1.5) $\times10^9$/L	(50–75) $\times10^9$/L	HB 80–100 g/L
Grade III	(0.5–1.0) $\times10^9$/L	(25–50) $\times10^9$/L	HB<80 g/L
Grade IV	<0.5$\times10^9$/L	<25$\times10^9$/L	Life-threatening, urgent treatment
Grade V	–	–	Death

Table 11 Hand-foot syndrome and dermal toxicity grade system of targeted therapy

Severity*	Hand-foot syndrome	Skin rash
Grade I	Painless mild skin changes or inflammation (erythema, edema, hyperkeratosis)	Rash, papule, or erythema without other symptoms
Grade II	Painful skin changes (desquamation, blisters, bleeding, edema, hyperkeratosis), and affecting daily activities	Macula, papule or erythema, without other symptoms, local desquamation and skin lesions; involving area of body surface <50%
Grade III	Severe skin changes (desquamation, blisters, bleeding, edema, hyperkeratosis) with pain, affecting daily activities	Systemic erythema, macula, papules or herpes, desquamation and skin lesions, involving area of body surface >50%
Grade IV	–	Systemic exfoliative, ulcerative or blistering dermatitis
Grade V	–	Death

*, The classification criteria for hand-foot syndrome is based on the National Cancer Institute's General Terminology for Adverse Events (NCI-CTCAE 4.0) and the rash grading standard is NCI-CTCAE 3.0.

6.7.2 Hematological toxicity of targeted therapy for RCC

Common hematological toxicities of targeted therapy for advanced RCC are neutropenia, thrombocytopenia and anemia (*Table 10*).

6.7.3 Hand-foot syndrome and dermal toxicity

Hand-foot syndrome usually manifests as bilateral palms' rash with pain and dysaesthesia, hyperkeratosis, erythema and desquamation are prone to be appeared at location of mechanical stretch (*Table 11*).

6.7.4 Adverse events of gastrointestinal tract of targeted therapy for RCC

Diarrhea, nausea and vomiting (*Table 12*) are common in patients treated with targeted therapy for RCC. Mild diarrhea could be treated with electrolytes and severe diarrhea should be treated with intravenous administration of electrolytes and loperamide, diphenoxylate, etc. Proton pump inhibitor or H-receptor antagonist may prevent nausea-like dyspepsia.

6.7.5 Hypothyroidism

There are 12%–19% of advanced renal cancer patients treated with VEGFR inhibitors have various degree of hypothyroidism (*Table 13*). The incidence increases with treatment time. The grade of hypothyroidism due to targeted therapy is shown in *Table 13*. Thyroid function at the beginning of therapy, as well as thyroid hormone and

Table 12 Classification of gastrointestinal adverse events of targeted therapy for RCC

Severity*	Diarrhea	Nausea	Vomiting
Grade I	Compared with baseline, the number of bowel movements increased by <4 times per day	Loss of appetite, no change in eating habits	Vomiting occurs 1–2 times within 24 h with 5-min interval
Grade II	Compared with baseline, the number of bowel movements increased by 4–6 times per day, intravenous fluid administration <24 h	Reduced oral food intake, no significant weight loss, dehydration or malnutrition	Vomiting occurs 3–5 times within 24 h with 5-min interval
Grade III	Compared with baseline, the number of bowel movements increased by 7 times per day, encopresis, and hospitalization might be necessary, personal life was affected.	Insufficient oral intake of energy and water, nasal feeding, parenteral nutrition or hospitalization might be necessary	Vomiting occurs >6 times within 24 h with 5-min interval. Nasal feeding, parenteral nutrition or hospitalization might be necessary
Grade IV	Life threatening, urgent treatment is needed	–	Life threatening, urgent treatment is needed
Grade V	Death	–	Death

RCC, renal cell cancer; *, The grading standard adopts the National Cancer Institute General Terminology Standard for Adverse Events (NCI-CTCAE 4.0)

Table 13 Hypothyroidism grading system of targeted therapy for RCC

Severity*	Clinical characteristics
Grade I	Asymptomatic; only observed by examination or diagnostic examination; no need of treatment
Grade II	Symptomatic; affecting daily activity; thyroid hormone replacement therapy is required.
Grade III	Severe symptoms; affecting daily activity; hospitalization is required
Grade IV	Life threatening; urgent treatment is needed
Grade V	Death

RCC, renal cell cancer; *, The grading standard adopts the National Cancer Institute General Terminology Standard for Adverse Events (NCI-CTCAE 4.0)

thyroid stimulating hormone during targeted therapy should be closely monitored. Mild asymptomatic elevation of thyroid stimulating hormone needs to be monitored as well. Patients with thyroid stimulating hormone >10 mU/L or clinical signs of hypothyroidism require thyroid hormone replacement therapy. In most cases, thyroid hormone replacement therapy can effectively control symptoms without suspending targeted therapy or adjusting the medication dosage.

6.7.6 Liver toxicity of targeted therapy for RCC

Liver function should be monitored when treated with pazopanib. Liver-protecting drugs are recommended for patients with liver damage, or primary liver diseases should be actively treated (such as hepatitis B and cirrhosis). If ALT increases to >8× upper limit of normal (ULN) during the treatment, therapy should be suspended until ALT restored to baseline again. If ALT increases again to >3× ULN after recovery, or ALT>3× ULN with bilirubin >2× ULN, the targeted drugs should be discontinued permanently.

6.7.7 Interstitial lung disease

Interstitial lung disease is a diffuse lung disease involving pulmonary interstitial, alveolar or bronchioles. The incidence in patients treated with second-line drugs, such as mTOR inhibitor, is about 19.8%. Much attention should be paid to interstitial lung disease and lung infection when patients are treating with targeted therapy. And these drugs should be used cautiously for patients with lung metastases, poor lung function, obstructive pneumonia or other lung infectious diseases. Advanced renal cancer patients with respiratory symptoms should be evaluated carefully and pulmonary imaging and function should be monitored regularly before targeted therapy. Mild interstitial lung disease does not require treatment other than close monitoring. Targeted therapy should be discontinued once severe interstitial lung disease happened and replaced with hormones treatment, such as methylprednisolone.

6.7.8 Cardiotoxicity

The incidence of cardiac adverse events caused by VEGFR inhibitors was 2%–10%. Such adverse events are usually

characterized by a decrease in left ventricular ejection fraction (LVEF) and myocardial ischemia. Baseline LVEF testing should be considered for patients without risk of cardiac diseases. Vital signs and LVEF should be monitored if patients have cardiac risk or cardiovascular adverse events recently. Discontinuing the therapy if patients have congestive heart failure; for asymptomatic congestive heart failure with LVEF <50%, or LVEF lower than 20% of baseline, the dose of targeted drugs should be reduced or targeted therapy should be suspended. If patient's medical history showed prolonged QT, history of antiarrhythmic drugs, bradycardia, or electrolyte abnormalities, etc. Electrocardiogram and blood potassium and magnesium should be checked regularly.

6.8 Treatment of localized RCC

Localized RCC refers to tumor that is confined to the renal capsule, including T1–2N0M0, or clinical stage I and II renal cancer. With the improvement of imaging technology and the popularity of health screening examinations, the proportion of localized renal cancer has exceeded 50%. More studies have shown that partial nephrectomy and radical nephrectomy have similar oncology outcomes in most T1, partial T2, and even a small portion of T3a RCCs, but partial nephrectomy has better protection for renal function.

NSS is recommended as first-line treatment for T1a renal tumor if technology allows. Radical nephrectomy is indicated for patients if anatomical structure is complicated to perform partial nephrectomy (NSS) and contralateral renal function is normal. Open surgery, laparoscopic or robot-assisted technologies are used for partial or radical nephrectomy. Ablation therapy is recommended for patients who do not accept or are not tolerance of surgery; and active surveillance is recommended for those with high risk of surgical mortality and poor life expectancy; NSS or radical nephrectomy is also recommended for T1b renal cancer. Renal tumor complexity, such as tumor size, location, depth and individual differences, should be considered when selecting surgery. Radical nephrectomy is the first-line treatment for T2 renal cancer. Some suitable patients with clinical needs may also choose partial nephrectomy.

Postoperative adjuvant therapy: adjuvant radiotherapy, chemotherapy, immunotherapy and targeted therapy after localized RCC surgery will not reduce recurrence and metastasis rate of the disease. Therefore, postoperative follow-up other than adjuvant therapy is routinely used for T1–2N0M0 RCC patients.

6.9 Treatment of locally advanced RCC

Locally advanced RCC refers to a tumor that extending through the renal capsule and affecting the perirenal or renal sinus fat but it is still confined within the Gerota's fascia. It may be accompanied by regional lymph node metastasis or/and venous tumor thrombus without distant metastasis. It includes T1–2N1M0/ T3N0–1M0 or clinical stage III.

Radical nephrectomy is the first-line treatment for locally advanced RCC. Partial nephrectomy is performed only in specific patients who are technically feasible with specific clinical needs. Some recent retrospective or prospective phase II studies have shown that preoperative neoadjuvant targeted therapy for T2–T3 RCC has certain shrinkage effects on renal cancer mass and it can be used for cT3 tumors with local excision difficulties. However, high-level research is still lacking to confirm it.

Removal of regional lymph nodes or tumor thrombus depends on the extent of the disease and the patients' performance status (PS).

Lymph node dissection: Locally advanced RCC is indicated for partial or radical lymph node dissection, which only plays a role in staging of RCC with clinically negative lymph nodes (cN0). It has no survival benefit for patients. Lymph node dissection is feasible for patients with positive lymph node (cN+), however it is only beneficial for a small number of patients, and the scope of the dissection is still controversial.

Patients with suspicious adrenal metastases should receive adrenalectomy and lymph node dissection.

Postoperative adjuvant therapy for locally advanced RCC: There is no standard adjuvant treatment for postoperative locally advanced RCC. Patients should refer to clinical trial or be followed up closely.

6.10 Treatment of advanced/metastatic RCC

Advanced/metastatic RCC refers to tumor with extension beyond Gerota's fascia accompanied with non-regional lymph node or distant metastasis. These include T4N0-1M0/T1–4N0–1M1, clinical stage IV stage of renal cancer. Systemic treatments combined with palliative surgery or radiotherapy for primary or metastatic lesions are usually

necessary. Appropriate treatment plan requires comprehensive consideration of primary and metastatic lesions, score of risk factors and patient's PS.

6.10.1 Surgical treatment

As an adjuvant therapy for metastatic RCC, surgical treatments include cytoreductive nephrectomy for primary tumor and palliative resection of metastatic lesions. Only a small number of patients can achieve long-term survival through these surgical treatments.

(1) Surgical treatment of primary tumor

Cytoreductive nephrectomy should be performed on the basis of effective systemic treatments. Low-risk patients with good PS should be treated with cytoreductive nephrectomy. Combination of IFN-α or (and) IL-2 therapy may improve the effect with prolonged survival for about five months. Retrospective studies have shown that cytoreductive nephrectomy and metastases resection may still provide survival benefits in the era of targeted therapy. Cytoreductive nephrectomy is currently recommended for mRCC patient with good PS (ECOG score <2, none or slightly related symptoms, low metastatic burden), and surgery can significantly reduce tumor burden. In addition, palliative nephrectomy or renal artery embolization may relieve severe hematuria or pain caused by renal tumor and these approaches can also improve the quality of life. Patients with brain metastases have a poor prognosis, therefore cytoreductive nephrectomy is generally not recommended before systemic therapy.

(2) Surgical treatment of metastases of RCC

Solitary metastasis can be surgically removed if patient is in good PS. Lung is the most common metastatic site for renal cancer, which is usually located in a single lobe. Surgery may prolong patient's survival. Bone is also a common metastatic site for renal cancer. Surgery may remove metastases or prevent and treat bone-related events. Surgical treatment should be performed for patients with primary lesion that has been resected or resectable, also with a single bone metastasis. Surgical treatment is first-line treatment for patients with fracture risk of weight-bearing bone. Prophylactic internal fixation should be applied to avoid bone-related events. Surgical treatment is indicted for patient with pathological fractures or compression symptoms of spinal cord, expecting survival more than 3 months, good PS, and surgery may improve quality of life. The favorable factors for metastases resection include: the time >1 year to discover metastases since nephrectomy; single or multiple resectable metastases; single lung metastasis; and patient's age ≤60 years.

In the era of targeted therapy, cytoreductive nephrectomy and metastases resection for selective mRCC patients may improve patient's survival, but prospective studies are needed to confirm. Currently three prospective randomized controlled clinical trials, TARIBO study (NCT02535351), CARMENA (NCT0093033) and SURTIME (NCT01099423), are undergoing to evaluate the clinical value of cytoreductive nephrectomy in combination with targeted therapy for mRCC patients.

6.10.2 Systemic treatment

(1) Clinical trial

NCCN recommends that clinical trials should be the preferred option for patients with advanced renal cancer.

(2) Systemic treatment of clear-cell RCC (*Table 14*)

1) Targeted therapy is the first-line treatment for clear-cell RCC. Studies found that deletion or inactivation of *VHL* gene was found in most cells of RCC. It results in up-regulation of *HIF* gene, and the latter leads to over-expression of *PDGF*, *VEGF* and *CaIX* genes which could promote the pathogenesis of clear-cell RCC. The biological mechanism of tumorigenesis and development may be the mechanism of molecular targeted therapy.

(3) Systemic treatment of non-clear-cell RCC

Due to small sample size, larger randomized controlled clinical trial data for patients with advanced non-clear-cell RCC are lacking. Expanded clinical studies of sunitinib, sorafenib and everolimus, as well as a small sample of phase II studies have shown that these targeted drugs are effective on non-clear-cell RCC, but their efficacy is not as good as for clear-cell RCC (*Table 15*).

6.10.3 Palliative radiotherapy

For RCC patients with recurrence of local tumor, regional or distant lymph node metastasis, and bone or lung metastasis, palliative radiotherapy can relief pain and improve quality of life.

6.10.4 Treatment principles for metastasis of special sites

The common metastatic sites of RCC are lung (45.2%), bone (29.5%), lymph node (21.8%), liver (20.3%), adrenal gland (8.9%), brain (8.1%), and retroperitoneum (6.9%). Metastases of liver, bone and brain are characterized as compressing peripheral nerves or tissues, affecting quality of life with poor prognosis, and thus special consideration should be given for these situations.

Table 14 Strategy for metastatic or unresectable clear-cell RCC therapy (clinical trial preferred in any of the following situations)

Treatment status	Stratification	Level I recommendation	Level II recommendation	Level III recommendation
First-line treatment	Low and medium risk	Sunitinib (1A evidence) Pazopanib (1A evidence) Sorafenib (2A evidence)	Axitinib (2A evidence) Cabozantinib (2A evidence) bevacizumab + IFN (1A vidence) IFN-α (2A evidence) Large dose of IL-2 (2A evidence)	
	High risk	Clinical trial	Temsirolimus (1A evidence) Cabozantinib (2A evidence) Sunitinib (2A evidence)	Pazopanib Sorafenib Axitinib
Second-line treatment	TKI failed	Axitinib (1A evidence) Everolimus (1A evidence)	Cabozantinib (1A evidence) Nivolumab (1A evidence) Lenvatinib + everolimus (2A evidence) sorafenib (2A evidence) Sunitinib (2A evidence)	Pazopanib Sorafenib + bevacizumab
	Cytokine failure	Axitinib (1B evidence) Sorafenib (1A evidence) Sunitinib (1B evidence) Pazopanib (1B evidence)	Clinical trial	Cabozantinib Lenvatinib + everolimus
Third-line treatment		Clinical trial	Sorafenib (2A evidence) Everolimus (2A evidence) Nivolumab (2A evidence) Cabozantinib (2A evidence)	sorafenib + bevacizum

RCC, renal cell cancer.

Table 15 Medical therapy strategy for metastatic or unresectable non-transparent cell type RCC (clinical trial preferred in any of the following situations)

Treatment status	Stratification	Level I recommendation	Level II recommendation	Level III recommendation
First-line treatment	Non-collecting duct carcinoma	Clinical trial	Sunitinib (1A evidence) Everolimus (2A evidence) Temsirolimus (2A evidence) Cabozantinib (2A evidence)	Sorafenib Pazopanib Axitinib
	Collecting duct carcinoma	Clinical trial	Clinical trial	Sorafenib + cis-platinum Sorafenib + gemcitabine + cis-platinum

RCC, renal cell cancer.

(1) Bone metastasis of RCC

Bone metastasis is common in the spine, pelvis and proximal limbs. The main symptom is progressive pain at these lesions. X-ray manifests osteolytic bone destruction, so the patient is prone to pathological fracture, or even paraplegia caused by compressing the spinal cord. Treatment will include targeted therapy combined with surgery, radiotherapy, bone protectants and other comprehensive therapies.

(2) Brain metastasis of RCC

Radiotherapy is superior to surgical treatment for brain metastases of RCC. And radiotherapy can treat multiple brain metastases. When combined with dexamethasone and dehydrating agents, it significantly reduces the size of tumor and edema, and relieves intracranial hypertension and other neurological symptoms. For patients with good PS and simple brain metastasis (brain metastases ≤3, maximum diameter of brain metastases ≤3 cm), stereotactic radiotherapy (gamma-knife, X-knife, three-dimensional conformal radiotherapy and intensity-modulated radiotherapy) or brain surgery combined with radiotherapy is the first-line treatment; for multiple brain metastases (>3 brain metastases, maximum diameter of brain metastases >3 cm), whole cranial radiotherapy may be considered. Systemic anti-tumor medications are then required based on the patient's tolerance.

(3) Liver metastasis of RCC

The prognosis of renal cancer patients with liver metastases is usually poor. Systemic targeted therapy is the first-line treatment. If systemic therapy is ineffective, combined local

treatment, such as ablation, transcatheter arterial chemoembolization, stereo directional radiotherapy and high-intensity focused ultrasound therapy can be used as part of a comprehensive treatment to control local metastatic lesions.

7. Follow-up

Routine follow-up items include: 1) inquiry of medical history; 2) physical examination; 3) laboratory tests including urinalysis, complete cell blood count, urea nitrogen, creatinine, glomerular filtration rate, lactate dehydrogenase, liver function, alkaline phosphatase and serum calcium. Bone scan if there is an abnormal increase of alkaline phosphatase or (and) symptoms of bone metastasis such as bone pain; 4) chest CT scan; and 5) renal tumor patients with signs of acute nervous system should receive immediate CT or MRI scan on head or spinal cord based on the corresponding segmental symptoms.

7.1 Postoperative follow-up

Patients with pT1N0/NxM0 RCC should undergo abdominal ultrasound, CT or MRI scan as baseline within 3–12 months after surgery, and once every year for 3 consecutive years. Chest CT scan should be performed postoperatively for RCC patients once a year for 3 consecutive years to determine if there is lung metastasis. If patients with pT2–4N0/NxM0 RCC underwent surgery, image examinations should be performed every 6 months for at least 3 years, and then once a year thereafter.

7.2 Follow-up of patients with local treatments for RCC

Abdominal CT or MRI should be performed as baseline within 3–6 months for patients with pT1aN0/NxM0 RCC who undergo local treatment such as cryotherapy and radiofrequency ablation, and once a year every year (including abdominal and chest imaging studies). If the original lesions are enlarged, enhanced, or new lesions appear during follow-up, a biopsy should be required.

7.3 Follow-up of advanced patients

For recurrent/metastatic stage IV RCC patients treated with systemic therapy, CT or MRI scan should be considered on all evaluable lesions (maximum lesion diameter >1 cm) as baseline before systemic treatment. The same imaging examination should be performed every 6 to 16 weeks to compare the size and number of lesions according to the patient's condition and treatment plan to evaluate the efficacy of systemic treatment.

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