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Imaging Recommendations for Diagnosis, Staging, and Management of Renal Tumors

Chandan J Das[1] Ankita Aggarwal[2] Prabhjot Singh[3] B Nayak[3] Taruna Yadav[4] Anupam Lal[5] Ujjwal Gorsi[5] Atul Batra[6] Shamim Ahmed Shamim[7] Bijit Kumar Duara[8] Kevin Arulraj[3] Seema Kaushal[9] Amlesh Seth[3]

[1] Department of Radiodiagnosis and Interventional Radiology, AIIMS, New Delhi, India
[2] Department of Radiodiagnosis, VMMC and SJH, New Delhi, India
[3] Department of Urology, AIIMS, New Delhi, India
[4] Department of Radiodiagnosis, Jodhpur, Rajasthan, India
[5] Department of Radiodiagnosis, PGI, Chandigarh, India
[6] Department of Medical Oncology, AIIMS, IRCH, New Delhi, India
[7] Nuclear Medicine, AIIMS, New Delhi, India
[8] Department of Radiodiagnosis, GMCH, Guwahati, Assam, India
[9] Department of Pathology, AIIMS, New Delhi, India

Address for correspondence Chandan J Das, MD, DNB, FRCP Edin, Department of Radiodiagnosis and Interventional Radiology AIIMS, Aurobindo Marg, New Delhi, 110029, India

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Abstract

Renal cell carcinomas accounts for 2% of all the cancers globally. Most of the renal tumors are detected incidentally. Ultrasound remains the main screening modality to evaluate the renal masses. A multi -phase contrast enhanced computer tomography is must for characterizing the renal lesions. Imaging plays an important role in staging, treatment planning and follow up of renal cancers. In this review , we discuss the imaging guidelines for the management of renal tumors.

Keywords
- CT scan
- MRI
- PET-CT scan
- renal cell carcinoma
- ultrasound

Introduction

Continuous advancements in various imaging modalities have revolutionized the imaging algorithm of renal masses. A majority of renal masses are detected incidentally when the patient is scanned for unrelated complaints. Radiologists need to be able to characterize renal mass on imaging. The foremost step is to differentiate between cystic and solid masses as up to 90% of solid tumors are malignant, whereas purely cystic lesions are usually benign or indolent.

Imaging is also important for staging, treatment planning, and follow-up of malignant renal masses. Ultrasound (US) is the screening modality for the evaluation of renal masses but cannot distinctly differentiate between benign and malignant lesions accurately and is also operator dependent. Contrast-enhanced US (CEUS) is a valuable addition and is especially useful in characterizing complex cystic lesions and the identification of pseudotumors. Multiphasic contrast-enhanced computed tomography (CT) is the current gold standard for the evaluation of renal masses and multiparametric magnetic resonance imaging (MRI) is used mainly as a problem-solving tool.

Risk Factors and Etiopathogenesis

Renal cell carcinoma (RCC) accounts for 2% of all cancers globally and is responsible for 2% of cancer deaths. It is the seventh most common cancer in men and the tenth most common in women[1].

Risk factors and etiopathogenesis include:[2]

1. Obesity: Obesity is a risk factor for kidney cancer in both men and women. The mechanisms by which obesity influences renal carcinogenesis are unclear, with chronic

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inflammation in adipose tissue and immune dysregulation potentially promoting carcinogenesis.
2. Smoking: Ever-smokers have a higher risk of renal cancer than never-smokers with a dose-dependent increase in risk related to the number of cigarettes smoked per day.
3. Hypertension: Hypertension is an independent risk factor for RCC.
4. Acquired cystic disease: Patients on long-term hemodialysis due to end-stage renal disease develop renal cysts and have an increased risk of renal cancer
5. Occupational exposure: Exposure to metal dyes increases the risk of developing RCCs.
6. Genetic susceptibility: Many genetic syndromes are associated with the development of RCC.

Epidemiology and Clinical Presentation

Abdominal mass, pain abdomen, and hematuria are the three cardinal clinical signs to suspect RCC. However, this constellation of symptoms is rarely seen at presentation these days and rather suggests advanced disease. About half of the RCCs are detected incidentally; such masses are small in size and pretend to have a good prognosis. Other common manifestations can be fever, leukocytosis, and weight loss. A variety of paraneoplastic syndromes may occur like polycythemia due to secretion of erythropoietin, hypercalcemia due to oversecretion of parathormone-related hormone peptide, hypertension due to renin, or Cushing syndrome due to adrenocorticotropic hormone.[3]

Clinical/ Diagnostic Workup

The initial workup of patients with suspected RCC includes history, physical examination, and blood investigations including a complete blood count with differential white blood count, serum calcium, liver functions, and renal functions. The workup allows the patient with metastatic RCC to be classified into favorable, intermediate, and poor risk categories, as per the International Metastatic RCC Database Consortium (IMDC) classification[4.] The factors include

1. Less than 1 year from the time of diagnosis to systemic therapy
2. Karnofsky performance status less than 70
3. Hemoglobin less than lower limit of normal
4. Corrected calcium more than upper limit of normal
5. Neutrophils more than upper limit of normal
6. Platelets more than upper limit of normal

The presence of none, 1 to 2, and 3 or more of the above factors categorizes the patient into favorable, intermediate, and poor risk categories, respectively. The choice of appropriate systemic therapy is based on the IMDC risk categories. For example, intermediate and poor-risk patients are treated with immune checkpoint inhibitor combinations (nivolumab and ipilimumab) or a combination of an immune checkpoint inhibitor with vascular endothelial growth factor tyrosine kinase inhibitor (VEGF TKI) pembrolizumab and lenvatinib/axitinib, nivolumab and cabozantinib, and avelumab and axitinib), while good risk patients are treated with VEGF TKIs (sunitinib or pazopanib) or a combination of immune checkpoint inhibitor and VEGF TKIs.[5]

Imaging Guidelines

RCC may be detected by an abdominal US either incidentally or in symptomatic patients. US serves as the most convenient and reliable screening tool for the detection of renal mass. It can accurately detect simple and minimally complicated cysts (Bosniak categories 1 and II). No further imaging is required in such cases. The accuracy of US falls in complex renal cysts from Bosniak 2F onwards. Differentiation of benign versus malignant masses cannot be confidently made by B mode US.

The last decade has seen an upsurge in renal applications of CEUS and it has shown fair potential in the characterization of renal tumors, especially in patients with chronic kidney disease or allergy to CT or MRI contrast. CEUS has shown great potential specifically in the differentiation of pseudotumors from renal tumors. The same enhancement characteristics along with the normal vascular pattern of the mass as the background normal kidney favor pseudotumors.[6,7] In addition, characterization of indeterminate masses, classification of the cystic renal mass into one of the Bosniak categories,[8,9] postablative treatment assessment,[10,11] differentiating bland versus malignant thrombus,[12,13] and renal transplant evaluation are other potential applications of CEUS.[14] Subtyping of the RCC by CEUS requires more studies for validation. Further characterization of the renal mass requires a dedicated tailored imaging protocol.

As per the guidelines issued by the American Association of Urology, high-quality, multiphasic, cross-sectional imaging is mandatory in any patient detected to have renal mass. This is essential for the optimum characterization and staging of the mass. Multiphasic CT forms the mainstay for the diagnosis of renal tumors. Morphology of the lesion, presence, and dynamic nature of enhancement are the important criteria in these modalities for differentiating benign from malignant masses.[14,15] In all suspected cases, a renal protocol is followed. Patient is given neutral oral contrast. A noncontrast scan is done followed by a postcontrast nephrographic phase at 40 to 70 seconds, a corticomedullary phase at 100 to 120 seconds, and an excretory phase at 7 to 10 minutes. Renal carcinoma is best identified in the nephrographic phase. The various subtypes of RCC can be better appreciated in the corticomedullary phase. The involvement of the pelvicalyceal system can be seen in the excretory phase. The split bolus technique is a newer modification that is currently followed in our institute as well. Conventional CT includes four phases in total that amounts to a high radiation dose. The split bolus technique has allowed a reduction in the number of phases with reduced total radiation dose and comparable imaging quality.

A baseline multiphasic CT is required in all diagnosed cases of RCC. The first step is to determine whether the mass is cystic or solid. If the mass is cystic, depending upon the

complexity of the lesion, it should be classified in one of the Bosniak categories. Bosniak classification, version 2019, is used on a renal mass protocol CT or MRI for predicting the risk of malignancy in cystic renal masses and guides treatment in each category. Any cystic lesion can be classified into one of the five categories namely I, II, IIF, III, and IV. Risk of malignancy increases from category IIF onwards. Bosniak III cysts can be managed with either active surveillance or primary surgery.[14,16,17] When the attenuation of the renal lesion is between −10 and +20 Hounsfield unit (HU), it is likely to be a simple cyst. If the attenuation is greater than 70 HU, it is likely to be a proteinaceous or hemorrhagic cyst. No further investigation is required for Bosniak category 1, II cysts. Bosniak category II F cysts require active surveillance and Bosniak category III and IV cysts should be considered for surgery.[18] If it is solid, it should be characterized as malignant (RCC, metastasis, lymphoma) or benign (angiomyolipoma [AML] or oncocytoma). About 90% of the solid masses are malignant. When the attenuation is between 20 and 70 HU on plain CT, contrast enhancement of greater than 15 to 20HU with less than 5% fat is highly suspicious for RCC.[16]

Such lesions mandate urological consultation for possible surgical management. Once the mass is characterized and labeled to be malignant, further staging is done to decide on the appropriate management. Essential points to consider for the staging of the mass are the size of the mass, the morphology of the mass including complexity, enhancement, and presence of fat, exophytic or endophytic nature of the mass, crossing the polar lines, involvement of PCS, invasion of perinephric fat, amount of perinephric fat, involvement of renal vein/IVC, invasion of adrenal/ surrounding organs, lymphadenopathy, distant metastasis and status of the contralateral kidney. TNM staging (8th edition) has been elaborated in ►**Table 1**.

In patients with the cT1a stage, a chest radiograph is sufficient.[16] Chest CT is recommended in all renal tumors beyond the cT1a stage for detection of lung metastases or mediastinal lymphadenopathy[12,14] as the lungs are the most common site of distant metastasis.[19,20] A bone scan is done when the patient has bony pain or elevated alkaline phosphatase. If the patient has neurological symptoms, then brain CECT or CE MRI is done to rule out metastasis. MRI is also recommended in asymptomatic patients with metastatic RCC.[14,21]

Multiparametric MRI serves as a complementary tool in the evaluation of solid renal masses. Increasingly, MRI is being used as the first modality for better characterization of

Table 1 TNM staging (8th edition)

T—Primary tumor
· **T1**—tumor < 7 cm or less in greatest dimension, limited to the kidney
o **T1a:** tumor confined to kidney, <4 cm
o **T1b:** tumor confined to kidney, >4 cm but <7 cm
· **T2:** limited to kidney >7 cm
o **T2a:** tumor confined to kidney, >7 cm but not >10 cm
o **T2b:** tumor confined to kidney, >10 cm
· T3: tumor extension into major veins or perinephric tissues, but not into ipsilateral adrenal gland or beyond Gerota fascia
o **T3a:** T3a tumor extends into the renal vein or its segmental branches, or tumor invades the pelvicalyceal system or tumor invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia
o **T3b:** Tumor extends into the vena cava below diaphragm
o **T3c:** T3c tumor extends into vena cava above the diaphragm or invades the wall of the vena cava
· **T4:** Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
N—Regional lymph nodes
· NX regional lymph nodes cannot be assessed
· **N0:** no nodal involvement
· **N1:** metastatic involvement of regional lymph node(s)
M
· **M0:** no distant metastases
· **M1:** distant metastases
Stage groupings
Stage I T1 N0 M0
Stage II T2 N0 M0
Stage III T3 N0 M0 T1, T2, T3 N1 M0
Stage IV T4 Any N M0 Any T Any N M1

small renal masses, complex renal cysts, evaluation of tumor thrombus, and as a problem-solving modality in the differentiation of indeterminate renal masses diagnosed on CECT, for example, in cases of hemorrhagic cysts and papillary RCC. It is helpful in the characterization of the renal mass in case it is indeterminate on CT.[22,23] A minute amount of fat can be better appreciated in MRI than CT. Multiparametric MRI is preferable due to increased detection of small areas of subtle soft tissue enhancement with the added advantage of using subtraction techniques. It is also advocated in patients with allergy to CT contrast agents and in young or pregnant patients (where radiation exposure should be avoided).[12,24] Due to excellent soft tissue resolution, plain MRI should be done in cases when both CT and MRI contrast agents are contraindicated.[25] The standard MRI protocol done for renal mass includes T1-weighted (T1W), T2W, diffusion-weighted imaging, In and opposed phase, precontrast, and postcontrast Volumetric interpolated breath-hold examination (VIBE) images. Multiparametric MRI can be used to calculate clear cell likelihood score in small renal masses that denotes the likelihood of a renal mass is clear cell RCC.[16]

Further subtyping of RCC can be done based on their imaging characteristics. Clear cell renal cell carcinoma (cRCC) constitutes 65 to 70% of all cases of RCC.[26] The cRCC on imaging appears a large heterogenous encapsulated mass with areas of necrosis and intracytoplasmic fat. It is an intensely enhancing mass that shows steep enhancement in the corticomedullary and nephrographic phase with washout in the delayed phase (►**Fig. 1**). Papillary carcinoma, on the other hand, constitutes 10 to 15% of all RCCs.[26] These are peripheral-based, encapsulated, homogeneous masses having low signal on the T2W sequence. The enhancement is slow and less as compared with the cRCC in all the phases (►**Fig. 2**). Chromophobe RCC is the least common of the

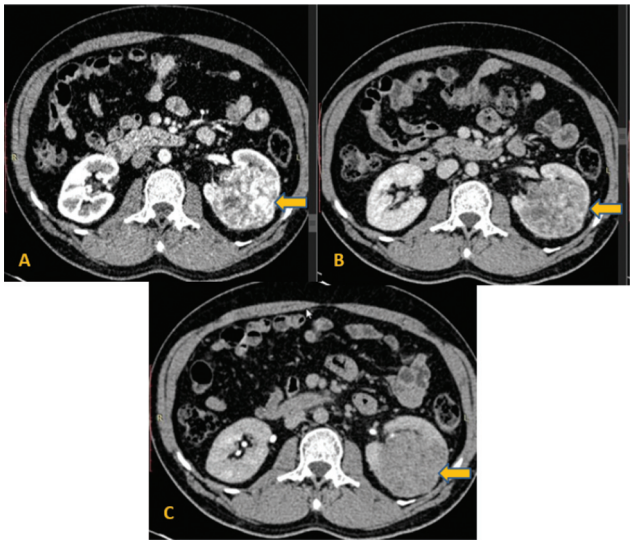

Fig. 1 Multiphase computed tomography axial images of the abdomen show an exo-endophytic mass arrow in the left kidney, showing marked enhancement in the corticomedullary phase **(A)** with relative washout in the nephrographic **(B)** and delayed phases **(C)**. Diagnosis of clear cell renal cell carcinoma was made, confirmed on postsurgical histopathology.

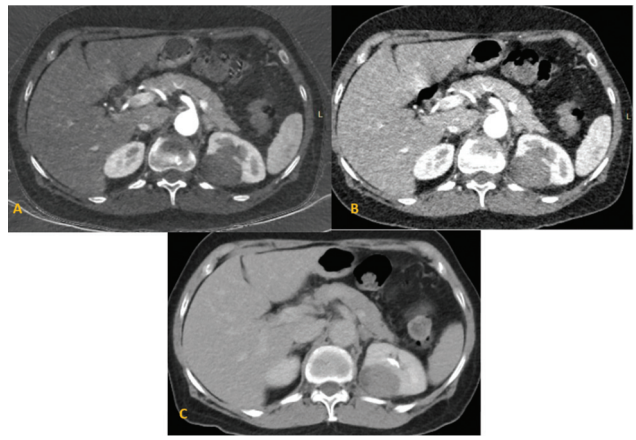

Fig. 2 Multiphase computed tomography axial images of the abdomen show an exo-endophytic mass in the right kidney, showing hypoenhancement in the corticomedullary phase **(A)** nephrographic **(B),** and delayed phases **(C)**. Diagnosis of papillary renal cell carcinoma was made, confirmed on histopathology.

three, constituting 6 to 11% among all the RCCs.[27] These are also peripheral-based, may show a pseudocapsule, and are fairly large. Postcontrast images show moderate wash-in and washout contrast. A central area of necrosis may be present which can show segmental inversion.[28]

Key imaging mimics of RCC are oncocytoma and fat-poor AML.[16] Due to their hypervascular nature, they are often confused with RCC due to which the patient unnecessarily undergoes surgical treatment.[29] Fat-rich AML is easy to diagnose with fat as the major component. They are hyperechoic on US and the fat component in the mass shows low attenuation (<10 HU). However, it is the lipopenic variety of AML (5%) that poses a diagnostic dilemma. Subtle points of differentiation from RCC include the homogenous nature of the mass, iso to hyperechoic on US, hyperdense on noncontrast CT, no calcification (common in RCC), T2W hypointense (RCC is T2W heterogenous hyperintense) and has rapid washout or persistent delayed enhancement on postcontrast study.[30,31] Second common benign neoplasm of the kidney is the oncocytoma that closely resembles chromophobe variety of RCC. Oncocytoma usually occurs in elderly patients, and are well-defined, homogenous masses, showing stellate scar with spoke wheel enhancement and segmental enhancement inversion on postcontrast images in different phases.[32]

In the pediatric age group, the most common tumor of the kidney (~80% cases) is Wilms tumor having a good prognosis.[33] It presents as a large heterogenous mass with hemorrhage and necrosis and infrequent areas of calcification. One should always look for multifocal/ bilateral disease (in hereditary syndromes), an extension of the mas into vascular structures, invasion of surrounding structures, lymphadenopathy, ascites, and distant metastasis.[21]

Positron Emission Tomography

Positron emission tomography (PET) is not recommended for the staging of RCC. 18F-fluoro-2-deoxy-2-d-glucose, the

substrate utilized for PET imaging, is excreted through the kidneys. The renal mass may fallaciously get obscured. The primary role of PET is in the re-evaluation of RCC post-treatment and also to detect recurrent or metastatic disease.[34] Quantitative PET helps evaluate the grade of the tumor, thereby helping in prognostication.[35]

Synoptic reporting formats for radiograph, US, CT, MRI, PET-CT scan are provided in ►**Table 2**. Also, a concise imaging algorithm for renal mass has been detailed in ►**Fig. 3**.

Renal Biopsy

A renal mass biopsy is not required for preoperative diagnosis in all cases. Only if the solid mass is suspected to be metastatic, inflammatory, infectious, or hematological, then a biopsy should be performed. A biopsy may not be done for elderly patients who are not fit for surgery and will be managed conservatively. Also, in young patients who are reluctant to conservative management if the biopsy does not show malignancy, a biopsy can be avoided.

Hereditary RCC constitutes around 4 to 6% of all cases of RCC. A high degree of suspicion should be kept when the patient presents at a young age with multiple RCCs and has a family history of RCC. The principle of management in such cases is to preserve as much renal parenchyma and hence nephron-sparing surgeries are preferred. Active surveillance and screening of other family members are also suggested.

Principles of Management

RCC is primarily a surgical disease. Despite immune-based and targeted therapy, a cure is rarely seen without complete surgical excision.[36,37] Management depends on the disease extent that is classified into localized, locally advanced, or metastatic.[38] The standard of care for localized RCC is surgical resection with the choice of surgical procedure depending upon the extent of disease, age, and comorbidity. For patients with T1 disease ($\leq$7cm), a partial nephrectomy (PN) is recommended if technically feasible. PN is also recommended for T2 disease ($>$7 cm limited to the kidney) with a solitary functioning kidney or chronic kidney disease and in bilateral renal tumors. For T2 and T3a disease (involving the perirenal tissues/renal sinus/collecting system/renal vein) and T1 disease not amenable for PN, radical nephrectomy (RN) is the standard of care.[39] The cancer-specific survival in organ-confined disease (T1 and T2) is 70 to 90% that drops to 40 to 70% in T3a disease.[40,41] Both minimally invasive and open approaches to PN and RN are available with the intent being intact removal of the specimen. Patients with inferior vena cava (IVC) thrombus (T3b/T3c) are managed aggressively with RN and IVC thrombectomy with survival rates of 45 to 60%.[42] T4 disease (extension beyond Gerota fascia or into the adrenals) portends a poorer prognosis with a survival rate of up to 30% and is managed with en bloc surgical excision to achieve negative margins.[38,43] Adjuvant therapy with systemic targeted agents does not increase overall survival and is currently not recommended for all cases.[39] Metastatic RCC carries a poor prognosis (10%

Table 2 Synoptic reporting formats for radiograph, ultrasound, CT, MRI, PET-CT scan

Ultrasound
· Presence of mass lesion
· Size
· Growth rate (if previous imaging done)
· Solid or cystic
· Simple or complex cyst
· Echogenicity of the lesion
· Necrosis
· Axial location
· Craniocaudal location
· Margins of lesion
· Capsule present or absent
· Vascularity on color and spectral doppler—present or absent, if present wave form and velocity
· Extent of the lesion
· Distance to collecting system
· Perinephric extension
· Involvement of surrounding organs
· Renal arterial and venous anatomy
· Renal vein/IVC thrombus
· Whether bland or tumor thrombus
· Tumor thrombus if present extent
· Lymphadenopathy
· Obvious metastases (liver, other abdominal organs)
· Status of opposite kidney
MPCT
· Presence of mass lesion
· Size
· Growth rate (if previous imaging done)
· Solid or cystic
· Bosniak classification if cystic
· Macroscopic fat
· Necrosis
· Presence and degree of enhancement
· Axial location
· Craniocaudal location
· Margins of lesion
· Capsule present or absent
· Extent of the lesion
· Distance to collecting system
· Perinephric extension
· Involvement of surrounding organs
· Renal arterial and venous anatomy
· Renal vein/IVC thrombus

Table 2 (*Continued*)

Ultrasound
· Whether bland or tumor thrombus
· Tumor thrombus if present extent
· Lymphadenopathy
· Distant metastases (lung, liver, bone)
MRI
· Presence of mass lesion
· Size
· Growth rate (if previous imaging done)
· Solid or cystic
· Bosniak classification if cystic
· Signal on T1W,T2W sequences, diffusion restriction
· Macroscopic fat
· Necrosis
· Microscopic fat
· Presence and degree of enhancement
· Possible histology
· Axial location
· Craniocaudal location
· Margins of lesion
· Capsule present or absent
· Extent of the lesion
· Distance to collecting system
· Perinephric extension
· Involvement of surrounding organs
· Renal arterial and venous anatomy
· Renal vein /IVC thrombus
· Whether bland or tumor thrombus
· Tumor thrombus if present extent
· Caval wall invasion
· Lymphadenopathy
· Distant metastases (lung, liver, bone)
PET-CT with IV contrast:
Presence of mass lesion
Size
FDG avid
SUVmax
Solid or cystic
Necrosis
Presence and degree of enhancement
Axial location
Craniocaudal location
Margins of lesion
Capsule present or absent
Extent of the lesion
Distance to collecting system
Perinephric extension
Involvement of surrounding organs
Renal vein/IVC thrombus
Tumor thrombus
Tumor thrombus if present extent
Lymphadenopathy
Distant metastases (lung, liver, bone)

(*Continued*)

Table 2 (*Continued*)

Abbreviations: FDG, 18F-fluoro-2-deoxy-2-d-glucose; IVC, inferior vena cava; MPCT, multiphase computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value; T1W, T1-weighted.

survival at 5 years) and is primarily managed with targeted systemic therapy.[44] RN with metastasectomy can be considered in patients with resectable primary and oligometastases, whereas cytoreductive nephrectomy is considered in select patients based on risk stratification.[39] Algorithm for RCC management is provided in ►**Fig. 4**.

Follow-Up Imaging and Management of Recurrent Disease

Surgery is the standard of care for localized RCC with a cancer-specific survival of 70 to 90%.[40] Although rare, the recurrence rates following radical (RN) and PN are 3 and 2%, respectively.[45,46] Early diagnosis and management of local recurrences improve survival.[47] Hence, a risk-stratified approach is recommended for surveillance following surgery considering the stage, surgical procedure, cost, and radiation exposure. Patients are divided into low-risk (T1N0) and moderate-to-high-risk categories (T2-T4N0 or N1). For low-risk disease, a baseline abdominal scan (CT or MRI) at 3 to 12 months is recommended. If the baseline scan is negative, yearly repeat imaging for 3 years is done for cases who underwent a PN. Further imaging after a negative baseline scan for patients who underwent an RN is performed at the discretion of the surgeon. A yearly chest X-ray for 3 years is recommended in addition. For moderate- and high-risk diseases, a more intensive protocol is recommended. A baseline abdominal scan (CT/MRI) at 3 to 6 months followed by repeat imaging 6 monthly for 3 years and annually thereafter up to year 5 is optimal. Chest imaging with CT is also done at the same interval for up to 5 years. Further imaging of the abdomen and chest can be done beyond 5 years at the discretion of the clinician.[48] Local recurrences following PN can be due to incomplete resection, tumor emboli, nodal, or tumor multifocality.[49] Options include a repeat PN, salvage nephrectomy, thermal ablation, or cryotherapy. Residual renal parenchyma, comorbidities, life expectancy, and tumor prognostic factors are to be considered

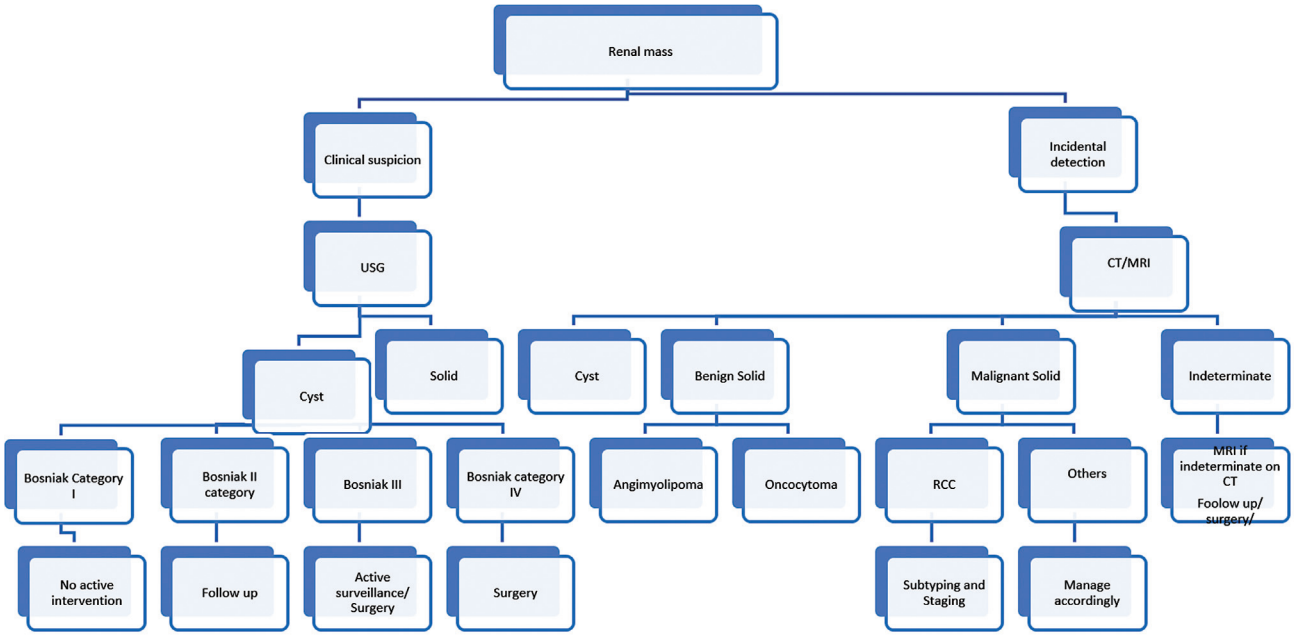

Fig. 3 Imaging algorithm. CT, computed tomography; MRI, magnetic resonance imaging; RCC, renal cell carcinoma; USG, ultrasonography.

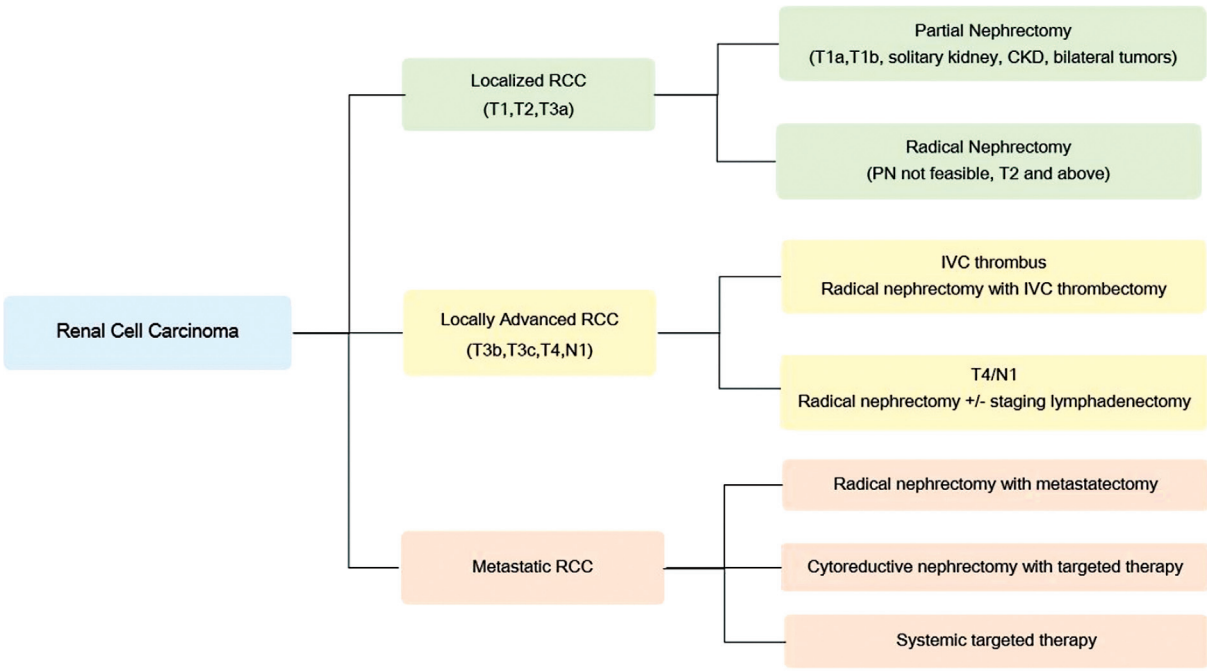

Fig. 4 Algorithm for renal cell carcinoma (RCC) management. CKD, chronic kidney disease; IVC, inferior vena cava.

before offering patients a repeat PN as it is complex and has significant postoperative morbidity (20%). The 5-year survival in these patients was found to be more than 95%.[50] Following RN, the median time to local recurrence was 20 to 36 months.[47] Surgical excision with negative margins is the only option associated with improved cancer-specific survival of 63% at 3 years.[51,52] For patients unfit for surgery, ablative therapies like cryoablation, radiofrequency, or microwave ablation can be tried pending further validation.[53] Following metastasectomy for local recurrences, adjuvant systemic therapy is recommended and in patients where the recurrence is unresectable, management is focused on palliation in the form of systemic therapy and radiation.[39]

Summary of Recommendations

- A contrast-enhanced, triple-phase helical CT scan is the preferred imaging study for evaluating renal masses.

- Chest CT should be done for the staging of renal cancers except in cT1a renal tumors.
- A multiparametric MRI can be performed as a problem-solving tool in characterizing indeterminate renal masses.
- The contrast-enhanced US can be helpful in specific cases.
- Characterization of small renal mass and response assessment following targeted therapy for advanced RCC are key challenges for current imaging modalities.

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