EAU GUIDELINES ON RENAL CELL CARCINOMA

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Epidemiology

The use of imaging techniques such as ultrasound (US) and computed tomography (CT) has increased the detection of asymptomatic renal cell cancer (RCC). The peak incidence of RCC occurs between 60 and 70 years of age, with a 3 : 2 ratio of men to women. Aetiological factors include lifestyle factors, such as smoking, obesity and hypertension. Having a first-degree relative with RCC is associated with a significantly increased risk of RCC.

Staging system

The current UICC 2017 TNM (Tumour Node Metastasis) classification is recommended for the staging of RCC (Table 1).

Table 1: The 2017 TNM staging classification system

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 7 cm or less in greatest dimension, limited to the kidney
	T1a Tumour ≤ 4 cm or less
	T1b Tumour > 4 cm but ≤ 7 cm
T2	Tumour > 7 cm in greatest dimension, limited to the kidney
	T2a Tumour > 7 cm but ≤ 10 cm
	T2b Tumours > 10 cm, limited to the kidney
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia
	T3a Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic), but not beyond Gerota fascia
	T3b Tumour grossly extends into the vena cava below diaphragm
	T3c Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour 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 regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

M - Distant Metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
TNM stage grouping			
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

A help desk for specific questions about TNM classification is available at http://www.uicc.org/tnm.

Clinical Diagnosis

Many renal masses remain asymptomatic until late disease stages. The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare and correlates with aggressive histology and advanced disease.

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs. A few symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough.

Imaging

Computed tomography imaging, before and after intravenous contrast, can verify the diagnosis and provide information on the function and morphology of the contralateral kidney and assess tumour extension, including extra-renal spread, venous involvement, and enlargement of lymph nodes (LNs) and adrenals.

Abdominal US and magnetic resonance imaging (MRI) are supplements to CT. Contrast-enhanced US can be helpful in specific cases (e.g., chronic renal failure with a relative contraindication for iodinated or gadolinium-based

contrast media, complex cystic masses, and differential diagnosis of peripheral vascular disorders such as infarction and cortical necrosis).

Magnetic resonance imaging can be used in patients with possible venous involvement, or allergy to intravenous contrast. Chest CT is the most accurate for chest staging and is recommended in the primary work-up of patients with suspected RCC.

In younger patients who are worried about the radiation exposure of frequent CT scans, MRI may be offered as alternative for follow-up imaging.

Biopsy

Percutaneous renal tumour biopsies are used:

- to obtain histology of radiologically indeterminate renal masses;
- to select patients with small renal masses for active surveillance;
- to obtain histology before, or simultaneously with, ablative treatments;
- to select the most suitable form of medical and surgical strategy in the setting of metastatic disease.

In patients with any sign of impaired renal function, a renal scan and total renal function evaluation using estimated glomerular filtration rate should always be undertaken to optimise the treatment decision.

Renal biopsy is not indicated for comorbid and frail patients who can be considered only for conservative management (watchful waiting) regardless of biopsy results.

Recommendations	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Use magnetic resonance imaging to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, mainly contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses.	Weak
Do not routinely use bone scan and/or positron-emission tomography CT for staging of RCC.	Weak
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	Strong
Perform a percutaneous biopsy in select patients who are considering active surveillance.	Weak
Use a coaxial technique when performing a renal tumour biopsy.	Strong
Do not perform a renal tumour biopsy of cystic renal masses.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation for solid renal tumours.	Strong

Histological diagnosis

A variety of renal tumours exist, and about 15% are benign. All kidney lesions require examination for malignant behaviour.

Histopathological classification

The new WHO/ISUP classification will replace the Fuhrman nuclear grade system in due time but will need validation.

The three most common RCC subtypes, with genetic and histological differences, are: clear cell RCC (80-90%), papillary RCC (10-15%), and chromophobe RCC (4-5%). The various RCC types have different clinical courses and responses to therapy.

Prognostic factors

In all RCC types, prognosis worsens with stage and histopathological grade. Histological factors include tumour grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the perirenal fat and collecting system. Clinical factors include performance status, local symptoms, cachexia, anaemia, platelet count, neutrophil/lymphocyte ratio, C-reactive protein and albumin.

Recommendations	Strength rating
Use the current Tumour, Node, Metastasis classification system.	Strong
Use grading systems and classify RCC subtype.	Strong
Use prognostic systems in the metastatic setting.	Strong
In localised disease, use integrated prognostic systems or nomograms to assess risk of recurrence.	Strong

Disease Management

Treatment of localised RCC

Localised renal cancers are best managed with partial nephrectomy (PN) rather than radical nephrectomy (RN), irrespective of the surgical approach. Partial nephrectomy is unsuitable in some patients with localised RCC due to:

- locally advanced tumour growth;
- unfavourable tumour location;
- significant health deterioration.

If pre-operative imaging and intra-operative findings are normal, routine adrenalectomy is not indicated. Lymphadenectomy should be restricted to staging because the survival benefit of extended LN dissection is unclear in patients with localised disease. In patients who have RCCs with tumour thrombus and no metastatic spread, prognosis is improved after nephrectomy and complete thrombectomy.

Nephron-sparing surgery versus radical nephrectomy

Based on current available oncological and quality of life outcomes, localised RCC is best managed by nephron-sparing surgery (NSS) rather than RN, irrespective of the surgical approach. Before routine nephrectomy, tumour embolisation has no benefit. In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.

Recommendations	Strength rating
Offer surgery to achieve cure in localised renal cell cancer.	Strong
Offer partial nephrectomy to patients with T1 tumours.	Strong
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Offer an extended lymph node dissection to patients with adverse clinical features, including a large diameter of the primary tumour.	Weak
Offer embolisation to patients unfit for surgery presenting with massive haematuria or flank pain.	Weak

Radical- and partial nephrectomy techniques

Summary of evidence	LE
Laparoscopic RN has lower morbidity than open surgery.	1b
Short-term oncological outcomes for T1-T2a tumours are equivalent for laparoscopic and open RN.	2a
Partial nephrectomy can be performed, either with an open, pure laparoscopic or robot-assisted approach, based on surgeon's expertise and skills.	2b
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared with RN.	3

Recommendations	Strength rating
Offer laparoscopic radical nephrectomy (RN) to patients with T2 tumours and localised masses not treatable by partial nephrectomy (PN).	Strong
Do not perform minimally invasive RN in patients with T1 tumours for whom a PN is feasible by any approach, including open.	Strong
Do not perform minimally invasive surgery if this approach may compromise oncological, functional and peri-operative outcomes.	Strong

Alternatives to surgery

Surveillance

Elderly and comorbid patients with incidental small renal masses have a low RCC-specific mortality and significant competing-cause mortality. In selected patients with advanced age and/or comorbidities, active surveillance (AS) is appropriate to initially monitor small renal masses, followed, if required, by treatment for progression. The concept of AS differs from the concept of watchful waiting. Watchful waiting is reserved for patients whose comorbidities contraindicate any subsequent active treatment and who do not require follow-up imaging, unless clinically indicated.

Cryoablation and radiofrequency ablation

Currently there are no data showing oncological benefit of cryoablation or radiofrequency ablation (RFA) techniques over PN.

Recommendation	Strength rating
Offer active surveillance, radiofrequency ablation and cryoablation to elderly and/or comorbid patients with small renal masses.	Weak

Treatment of locally advanced RCC

Management of clinically positive lymph nodes (cN+)

In the presence of clinically positive LNs (cN+), LND is always justified but the extent of LND is still controversial.
Low level data suggest that tumour thrombus in the setting of non-metastatic disease should be excised. Adjunctive procedures such as tumour embolisation or inferior vena cava filter do not appear to offer any benefits in the treatment of tumour thrombus.

In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain. At present there is no evidence for the use of adjuvant therapy following surgery.

Treatment of advanced/metastatic RCC

Management of RCC with venous tumour thrombus

Recommendations	Strength rating
In patients with clinically enlarged lymph nodes (LNs), perform LN dissection for staging purposes or local control.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong

Cytoreductive nephrectomy

Tumour nephrectomy is curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligo-metastatic resectable disease. For

most patients with metastatic disease, cytoreductive nephrectomy is palliative and systemic treatments are necessary.

Summary of evidence	**LE**
Cytoreductive nephrectomy (CN) followed by sunitinib is non-inferior to sunitinib alone in patients with clear-cell metastatic RCC (mRCC).	1a
Deferred CN with presurgical sunitinib in intermediate-risk patients with metastatic ccRCC leads to a survival benefit in secondary endpoint analysis and selects out patients with inherent resistance to systemic therapy.	2b
Sunitinib alone is non-inferior compared to immediate CN followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI).	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3
Patients with MSKCC or IMDC poor risk (≥ 4 risk factors) do not benefit from local therapy.	1a

Recommendations	Strength rating
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform immediate CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI).	Weak
Start systemic therapy without CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.	Weak
Discuss delayed CN in MSKCC inter-mediate-risk patients under VEGFR-TKI therapy who derive long-term sustained benefit and/or minimal residual metastatic burden.	Weak
Perform immediate CN in patients with good performance who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak

IMDC = The Metastatic Renal Cancer Database Consortium: MSKCC = Memorial Sloan-Kettering Cancer Center.

Local therapy of metastases in mRCC

A systematic review of the local treatment of metastases from RCC in any organ was undertaken. The heterogeneity of the data will only allow for cautious recommendations.

Summary of evidence	LE
All included studies were retrospective non-randomised comparative studies, resulting in a high risk of bias associated with non-randomisation, attrition, and selective reporting.	3
With the exception of brain and possibly bone metastases, metastasectomy remains by default the only local treatment for most sites.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of overall survival, cancer-specific survival and delay of systemic therapy.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3

Recommendations	Strength rating
To control local symptoms, offer local ablative therapy, including metastasectomy, to patients with metastatic disease and favourable disease factors and in whom complete resection is achievable.	Weak
Offer stereotactic radiotherapy for clinically relevant bone or brain metastases for local control and symptom relief.	Weak

Systemic therapy for advanced/metastatic RCC

Chemotherapy

Summary of evidence	LE
In mRCC, 5-fluorouracil combined with immunotherapy has equivalent efficacy to interferon-α.	1b
In mRCC, chemotherapy is otherwise not effective with the exception of gemcitabine and doxorubicine in sarcomatoid and rapidly progressive disease.	3

Recommendation	Strength rating
Do not offer chemotherapy as first-line therapy in patients with clear-cell metastatic RCC.	Strong

Immunotherapy

Interferon-α may only be effective in some patient subgroups, including patients with ccRCC, favourable-risk criteria, and lung metastases only. Interleukin-2 (IL-2), vaccines and targeted immunotherapy have no place in the standard treatment of advanced/mRCC.

Immune checkpoint inhibition of programmed death receptor (PD-1) and ligand (PD-L1) inhibition have been investigated in mRCC. Randomised data support the use of nivolumab (a PD-1 inhibitor) in VEGF-refractory disease. A combination of two immune checkpoint inhibitors ipilimumab and nivolumab versus sunitinib in a phase III study on mRCC showed superior survival for a combination of ipilimumab and nivolumab in intermediate- and poor-risk patients

Summary of evidence	LE
Interferon-α monotherapy is inferior to VEGF-targeted therapy or mammalian target of rapamycin (mTOR) inhibition in mRCC.	1b
Interleukin (IL)-2 monotherapy may have an effect in selected cases (good performance status, ccRCC, lung metastases only).	2a
Interleukin-2 has more side-effects than IFN-α.	2b
High-dose (HD)-IL-2 is associated with durable complete responses in a limited number of patients. However, no clinical factors or biomarkers exist to accurately predict a durable response in patients treated with HD-IL-2.	1b
Bevacizumab plus IFN-α is more effective than IFN-α in treatment-naïve, low-risk and intermediate-risk ccRCC.	1b
Vaccination therapy with tumour antigen 5T4 showed no survival benefit over first-line standard therapy.	1b
Cytokine combinations, with or without additional chemotherapy, do not improve overall survival (OS) compared with monotherapy.	1b
Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.	1b
The combination of nivolumab and ipilimumab in treatment-naïve patients with clear-cell-mRCC of IMDC intermediate-and poor-risk leads to superior survival compared to sunitinib.	1b
The combination of nivolumab and ipilimumab in the intention to treat population of treatment-naïve unselected patients with clear-cell-mRCC leads to superior survival compared to sunitinib.	2b

Due to the exploratory nature of PD-L1 tumour expression, the small sample size, the lack of OS data and the premature results in this subpopulation, definitive conclusions cannot be drawn relative to the userfulness of PD-L1 expression.	2b
Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity and 1.5% treatment-related deaths.	1b

Recommendations	**Strength rating**
Offer ipilimumab plus nivolumab to treatment-naïve patients with clear-cell-mRCC of IMDC intermediate and poor risk.	Strong
Administer nivolumab plus ipilimumab in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	Weak
Offer nivolumab after one or two lines of vascular endothelial growth factor-targeted therapy in mRCC.	Strong
Do not offer monotherapy with interferon-α (INF-α) or high-dose bolus interleukin-2 as first-line therapy in mRCC.	Weak
Do not use bevacizumab plus INF-α in treatment-naïve clear-cell favourable- and intermediate-risk RCC patients.	Weak
Do not use PD-L1 tumour expression as a predictive biomarker.	Weak
Do not rechallange patients who stop nivolumab plus ipilimumab because of toxicity, with the same drugs in the future without expert guidance and support from a multidisciplinary team.	Strong

IMDC = The Metastatic Renal Cancer Database Consortium.

Targeted therapies

At present, several targeting drugs have been approved both for the treatment of mRCC.

Summary of evidence	LE
VEGF-targeted therapies increase progression-free survival (PFS) and/or OS as both first-line and second-line treatments for patients with clear-cell mRCC.	1b
Cabozantinib in intermediate-and poor-risk treatment-naïve clear-cell RCC leads to better response rates and PFS but not OS when compared to sunitinib.	1b
Tivozanib has recently been approved but the evidence is still considered inferior over existing choices.	3
Axitinib has proven efficacy and superiority in PFS as a second-line treatment after failure of cytokines and VEGF-targeted therapy in comparison with sorafenib.	1b
Sunitinib is more effective than IFN-α in treatment-naïve patients.	1b
In treatment-naïve patients, bevacizumab in combination with INF-α has not been tested against nivolumab plus ipilimumab and the evidence for subsequent therapies is unclear.	3
Pazopanib is superior to placebo in both treatment-naïve mRCC patients and post-cytokine patients.	1b
First-line pazopanib is not inferior to sunitinib in clear-cell-mRCC patients.	1b
Temsirolimus monotherapy prolongs OS compared to IFN-α in treatment-naïve poor-risk mRCC.	1b
In treatment-naïve patients temsirolimus has not been tested against nivolumab plus ipilimumab and the evidence for subsequent therapies is unclear.	3

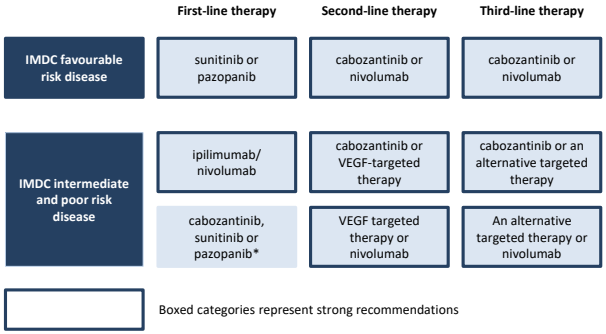
Cabozantinib is superior to everolimus in terms of PFS and OS in patients after one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS after VEGF-targeted therapy when compared to placebo or when the patient cannot tolerate these therapies.	1b
Sorafenib has broad activity in a spectrum of settings in ccRCC patients previously treated with cytokine or targeted therapies. It is inferior to axitinib in both sunitinib or cytokine pre-treated patients.	4
Both mTOR inhibitors (everolimus and temsirolimus) and VEGF-targeted therapies (sunitinib or sorafenib) have limited oncological efficacy in non-clear cell RCC. There is a non-significant trend for improved oncological outcomes for sunitinib, over everolimus.	2a
Lenvatinib in combination with everolimus modestly improved PFS over everolimus alone.	2a

Recommendations	**Strength rating**
Use sunitinib or pazopanib in treatment-naïve patients with clear-cell-mRCC of IMDC favourable risk.	Strong
Use cabozantinib in treatment-naïve patients with clear-cell-mRCC of IMDC intermediate and poor risk.	Weak
Do not offer bevacizumab plus interferon-α to treatment-naïve clear-cell favourable- and intermediate-risk RCC patients.	Weak
Do not offer tivozanib to treatment-naïve clear-cell-mRCC patients.	Weak
Do not offer temsirolimus to treatment-naïve clear-cell poor-risk RCC patients.	Weak

Offer vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKIs) as second-line to patients refractory to nivolumab plus ipilimumab.	Weak
Offer cabozantinib for ccRCC after one or two lines of VEGF-targeted therapy in mRCC.	Strong
Offer axitinib, everolimus or lenvatinib plus everolimus to ccRCC patients who failed VEGF-targeted therapy, and when nivolumab or cabozantinib are not safe, tolerable or available.	Strong
Sequence systemic therapy in treating mRCC.	Strong
Offer sunitinib as first-line therapy for non-clear-cell-mRCC.	Weak
Do not offer sorafenib as second-line treatment to patients with mRCC.	Weak

IMDC = The Metastatic Renal Cancer Database Consortium.

Figure 1: Updated EAU Guidelines recommendations for the treatment of first-line clear-cell metastatic renal cancer.



IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium; VEGF = vascular endothelial growth factor.
*pazopanib for intermediate-risk disease only.

Recurrent RCC

Locally recurrent disease can occur either after nephrectomy, PN, or after ablative therapy. After nephron-sparing treatment approaches the recurrence may be intra-renal or regional, e.g. venous tumour thrombi or retroperitoneal LN metastases. Isolated local recurrence in the true renal fossa after RN is rare.

Patients can benefit from a complete surgical resection of local recurrent disease. In cases where complete surgical removal is not feasible due to advanced tumour growth and pain, palliative treatments including radiation treatment can be considered.

Surveillance following surgery for RCC

The aim of surveillance is to detect either local recurrence or metastatic disease while the patient is still surgically curable. Surveillance after treatment for RCC allows the urologist to assess:

- postoperative complications;
- renal function;
- local recurrence;
- recurrence in the contralateral kidney;
- development of metastases.

Depending on the availability of new effective treatments, more intensive follow-up schedules may be required, particularly as there is a higher local recurrence rate after cryotherapy and RFA. At present there is no evidence-based standard for the follow-up of patients with RCC, or for the optimal duration of follow-up. An example of a surveillance algorithm monitoring patients after treatment for RCC that recognises not only the patient's risk profile but also treatment efficacy is provided in Table 2. For patients with metastatic disease, individualised follow-up is indicated.

Table 2: Proposed surveillance schedule following treatment for RCC, taking into account patient risk profile and treatment efficacy (expert opinion [LE: 4])

Risk profile	Surveillance				
	6 mo	**1 y**	**2 y**	**3 y**	**> 3 y**
Low	US	CT	US	CT	CT once every 2 years; counsel about recurrence risk of ~10%
Intermediate / High	CT	CT	CT	CT	CT once every 2 years

CT = computed tomography of chest and abdomen, alternatively use magnetic resonance imaging for the abdomen; US = ultrasound of abdomen, kidneys and renal bed.

Summary of evidence and recommendations for surveillance following RN or PN orablative therapies in RCC

Summary of evidence	LE
Surveillance can detect local recurrence or metastatic disease while the patient is still surgically curable.	4
After NSS, there is an increased risk of recurrence for larger (> 7 cm) tumours, or when there is a positive surgical margin.	3
Patients undergoing surveillance have a better overall survival than patients not undergoing surveillance.	3
Repeated CT scans do not reduce renal function in chronic kidney disease patients.	3

Recommendations	Strength rating
Base follow-up after RCC on the risk of recurrence.	Strong
Intensify follow-up in patients after nephron-sparing surgery for tumours > 7 cm or in patients with a positive surgical margin.	Weak
Base risk stratification on pre-existing classification systems such as the University of California Los Angeles integrated staging system integrated risk assessment score: (http://urology.ucla.edu/body.cfm?id=443).	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-04-2), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.