EAU GUIDELINES ON RENAL CELL CARCINOMA

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Comment on methodology

The EAU Guidelines Office is introducing a new rating system for their recommendations. This will be a phased introduction, with the Renal Cell Cancer (RCC) Panel being the first Panel to employ this methodology. For further information, please consult the large text document. These changes will be visible in the recommendation boxes.

Epidemiology

The use of imaging techniques such as ultrasound (US) and computerised tomography (CT) has increased the detection of asymptomatic 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.

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 fat), 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 (6-10%) 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 (MR) imaging 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 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.

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.

Recommendations for the diagnostic assessment of renal cell cancer	grade	
Use multi-phasic contrast-enhanced computed tomography (CT) for general staging and detection of RCC.	strong	⇑⇑
Use axial abdominal imaging and CT of the chest for staging of RCC.	strong	⇑⇑
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 use bone scan and/or positron-emission tomography (PET)-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 considered for 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.	weak	⇓

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 most aggressive pattern observed defines the Fuhrman grade.

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.

Recommendations	grade	
Use the current Tumour, Node, Metastasis classification system.	strong	↑↑
Use grading systems and classify RCC subtype.	strong	↑↑

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 collecting system. Clinical factors include performance status (PS), local symptoms, cachexia, anaemia, platelet count, neutrophil/lymphocyte ratio, C-reactive protein and albumin.

Recommendations	grade	
Use prognostic systems in the metastatic setting.	strong	↑↑
In localised disease, do not routinely use integrated prognostic systems or nomograms for patient selection. Prognostic systems or nomograms can provide a rational for enrolling patients into clinical trials.	weak	↓
Do not use molecular prognostic markers in routine clinical practice.	weak	↓
In patients receiving targeted treatments, use molecular prognostic markers to predict response.	weak	↑

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 (eLND) 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 renal cancers are 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	**grade**	
Offer surgery to achieve cure in localised RCC.	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	↓↓
Consider an extended lymph node dissection in patients with adverse clinical features including a large diameter of the primary tumour or sarcomatoid histological features.	weak	↑

Radical- and partial nephrectomy techniques

Summary of evidence	LE
Laparoscopic radical nephrectomy has lower morbidity than open surgery.	1b
Oncological outcomes for T1-T2a tumours are equivalent between laparoscopic and open radical nephrectomy.	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 radical nephrectomy.	3

Recommendations	grade	
Offer laparoscopic radical nephrectomy to patients with T2 tumours and localised masses not treatable by partial nephrectomy.	strong	↑↑
Do not perform radical nephrectomy in patients with T1 tumours for whom partial nephrectomy is indicated.	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	grade	
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 controversial.

In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain.

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.

At present there is no evidence for the use of adjuvant therapy following surgery.

Treatment of advanced / metastatic RCC

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 combined with interferon-α improves survival in patients with metastatic RCC (mRCC) and good performance status.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3

Recommendations	grade	
Offer cytoreductive nephrectomy to favourable- and intermediate-risk patients with metastatic RCC.	weak	↑

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	grade	
Consider local therapy for metastatic disease (including metastasectomy) in patients with a favourable risk profile in whom complete resection is achievable or when local symptoms need to be controlled.	weak	↑
Stereotactic radiotherapy for clinically relevant bone or brain metastases can be considered for local control and symptom relief.	weak	↑

Systemic therapy for advanced/metastatic RCC

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

Recommendations	grade	
Do not offer chemotherapy as first-line therapy in patients with metastatic clear-cell RCC.	strong	↓↓
Consider offering a combination of gemcitabine and doxorubicin to patients with sarcomatoid or rapidly progressive RCC.	weak	↑

Immunotherapy

Interferon-alpha may only be effective in some patient subgroups, including patients with ccRCC, favourable-risk criteria, as defined by the Memorial Sloan-Kettering Cancer Center and lung metastases only. Interleukin-2, vaccines and targeted immunotherapy have no place in the standard treatment of advanced/mRCC.

Summary of evidence	LE
Interferon-α monotherapy is inferior to vascular endothelial growth factor (VEGF)-targeted therapy or mTOR inhibition in mRCC.	1b

Interleukin-2 monotherapy may have an effect in selected cases (good PS, ccRCC, lung metastases only).	2
IL-2 has more side-effects than IFN-α.	2-3
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 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 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

Recommendations	**grade**	
Offer nivolumab after one or two lines of vascular endothelial growth factor-targeted therapy in metastatic RCC.	strong	↑↑
Do not offer monotherapy with interferon-α or high-dose bolus interleukin-2 as first-line therapy in metastatic RCC.	weak	↓

Targeted therapies

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

Summary of evidence	LE
VEGF and TKIs increase PFS and/or OS as both first-line and second-line treatments for clear-cell mRCC.	1b
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-naive patients.	1b
Bevacizumab plus IFN-α is more effective than IFN-α in treatment-naïve low- and intermediate-risk patients.	1b
Pazopanib is superior to placebo in both 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 poor-risk mRCC.	1b
Cabozantinib is superior to everolimus in terms of PFS and OS in patients failing one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS in patients who have previously failed or are intolerant of VEGF-targeted therapy when compared to placebo.	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 VEFG-targeted therapies (sunitinib or sorafenib) can be used in non-clear cell RCC.	3
No combination has proven to be better than single-agent therapy, with the exception of the combination of lenvatinib plus everolimus.	1a

Recommendations	grade	
Offer sunitinib or pazopanib as first-line therapy for metastatic ccRCC.	strong	↑↑
Consider offering bevacizumab + interferon-α as first-line therapy for metastatic RCC in favourable and intermediate-risk ccRCC.	weak	↑
Consider offering temsirolimus as first-line treatment in poor-risk RCC patients.	weak	↑
Offer cabozantinib for ccRCC after one or two lines of vascular endothelial growth factor (VEGF)-targeted therapy in metastatic RCC.	strong	↑↑
Offer axitinib or everolimus to ccRCC patients who failed VEGF-targeted therapy, and when nivolumab or cabozantinib are not safe, tolerable or available.	strong	↑↑
Sequence targeted agents in treating metastatic RCC.	strong	↑↑
Sunitinib can be offered as first-line therapy for non-clear-cell mRCC.	weak	↑

EAU 2017 evidence-based recommendations for systemic therapy in pati				
RCC type	**MSKCC risk group**	**First-line**	**LE^**	
Clear cell*	Favourable, intermediate and poor	sunitinib pazopanib bevacizumab + IFN-α (favourable-intermediate only)	1b 1b 1b	
Clear cell*	poor¶	temsirolimus sunitinib pazopanib	1b 2b 1b	
Non-clear cell §	any	sunitinib	1b^^	

IFN-α = interferon alpha; LE = level of evidence; MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin inhibitor; RCC = renal cell carcinoma; TKI= tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

* Doses: IFN-α - 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg bi-weekly intravenously; sunitinib 50 mg daily orally for four weeks, followed by two weeks of rest (37.5 mg continuous dosing did not show significant differences); temsirolimus 25 mg weekly intravenously; pazopanib 800 mg daily orally. Axitinib 5 mg twice daily, to be increased to 7 mg twice daily, unless greater than Grade 2 toxicity, blood pressure higher than 150/90 mmHg, or the patient is receiving antihypertensive medication. Everolimus, 10 mg daily orally.

ents with mRCC						
	Second-line after VEGF therapy*	**LE^**	**Third-line***	**LE^**	**Later lines**	**LE**
	based on OS: nivolumab cabozantinib based on PFS: axitinib sorafenib# everolimus&	 2b 2b 2b 2b 2b	**After VEGF therapy:** nivolumab cabozantinib everolimus& **after VEGF and mTOR therapy:** sorafenib **after VEGF and nivolumab:** cabozantinib axitinib everolimus	 2b 2b 2b 1b 4 4 4	any targeted agent	4
	any targeted agent	4				
	Any targeted agent	4				

§ No standard treatment available. Patients should be treated in the framework of clinical trials or a decision can be made in consultation with the patient to perform treatment in line with ccRCC.

¶ Poor risk criteria in the NCT00065468 trial consisted of MSKCC risk plus metastases in multiple organs. Evidence for subsequent therapies unclear, making this option less appealing.

Sorafenib was inferior to axitinib in a RCT in terms of PFS but not OS.

^ Level of evidence was downgraded in instances when data were obtained from subgroup analysis within an RCT.

& Everolimus was inferior in terms of OS to nivolumab and in terms of PFS to cabozantinib and should not routinely be given where other superior agents are available.

^^ Based on a systematic review.

Recurrent RCC

Locally recurrent disease can occur either after nephrectomy, partial nephrectomy, 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 is rare. Surgical resection of local recurrent disease may be offered. 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 identify:

- 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

Risk profile	Surveillance						
	6 mo	1 y	2 y	3 y	4 y	5 y	> 5 y
Low	US	CT	US	CT	US	CT	Discharge
Intermediate	CT	CT	CT	US	CT	CT	CT once every 2 years
High	CT	CT	CT	CT	CT	CT	CT once every 2 years

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

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

Summary of evidence	LE
Surveillance can detect local recurrence or metastatic disease while the patient is still surgically curable.	4
After nephron-sparing surgery 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

Recommendations	grade	
Base follow-up after RCC on the risk of recurrence.	strong	↑↑
Intensify follow-up in patients after NSS 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: 978-90-79754-91-5), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.