EAU GUIDELINES ON RENAL CELL CARCINOMA

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Introduction

The use of imaging techniques such as ultrasound (US) and computerised tomography (CT) have 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. The most effective prophylaxis is to avoid cigarette smoking and obesity.

Histological diagnosis

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

Summary of evidence	LE
Except for AML, most other renal tumours cannot be differentiated from RCC by radiology and should be treated in the same way as RCC.	3
In biopsy-proven oncocytomas, watchful waiting is an option.	3
In advanced uncommon renal tumours, a standardised oncological treatment approach does not exist.	3

Recommendations	GR
Bosniak cysts ≥ type III should be regarded as RCC and treated accordingly. Treat Bosniak type III or IV cysts the same as RCC.	C
Treat most AMLs with active surveillance. Treat with selective arterial embolisation or NSS for: • large tumours (recommended threshold of intervention does not exist, the formerly recommended size of > 4 cm wide is disputed); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate.	C
In AML > 3 cm not requiring surgical intervention, medical treatment with everolimus can be considered.	C
Treat all tumours with the radiologic appearance of RCC in the same way.	C
Offer watchful waiting to patients with biopsy-proven oncocytomas.	C
For advanced uncommon renal tumours, develop individualised oncological treatment plans for each patient.	C

AML = angiomyolipoma; NSS = nephron-sparing surgery.

Staging system

The current UICC 2009 TNM (Tumour Node Metastasis) classification is recommended for the staging of RCC (Table 1).

Table 1: The 2009 TNM staging classification system

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney
T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension
T2	Tumour > 7 cm in greatest dimension, limited to the kidney
T2a	Tumour > 7 cm in greatest dimension 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's fascia
T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia
T3b	Tumour grossly extends into the vena cava below diaphragm
T3c	Tumour grossly extends into vena cava or its wall above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
N - Regional LNs	
NX	Regional LNs cannot be assessed
N0	No regional LN metastasis
N1	Regional LN metastasis

M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

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

Diagnostic evaluation

Many renal masses remain asymptomatic until the late disease stages. More than 50% of RCCs are detected incidentally by non-invasive imaging used to investigate various non-specific symptoms and other abdominal diseases. 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.

Radiological investigations of RCC

Computed tomography (CT) 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 extrarenal 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 chest staging and is recommended in the primary work–up of patients with suspected RCC.

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 estimation should always be undertaken to optimise the treatment decision.

Recommendations for the diagnostic assessment of renal cell carcinoma	**GR**
Contrast-enhanced multi-phasic abdominal CT and MRI are recommended for the work-up of patients with RCC and are considered equal both for staging and diagnosis.	B
Contrast-enhanced multi-phasic abdominal CT and MRI are the most appropriate imaging modalities for renal tumour characterisation and staging prior to surgery.	C
A chest CT is recommended for staging assessment of the lungs and mediastinum.	C
Bone scan is not routinely recommended.	C

Renal tumour biopsy is recommended before ablative therapy and systemic therapy without previous pathology.	C
Percutaneous biopsy is recommended in patients in whom active surveillance is pursued.	C
Obtain percutaneous renal tumour biopsy with a coaxial technique.	C

CT = computed tomography; MRI = magnetic resonance imaging.

Histopathological classification

Fuhrman nuclear grade is the most commonly used grading system. The most aggressive pattern observed defines the Fuhrman grade. RCC comprises different subtypes with genetic and histological differences. The three most common RCC types are: clear cell RCC (80-90%), papillary RCC (10-15%), and chromophobe RCC (4-5%). Generally, the various RCC types have different clinical courses and responses to therapy.

Recommendations	**GR**
Use the current TNM classification system.	B
Use grading systems and classify RCC type.	B

TNM = tumour node metastasis (classification); WHO = World Health Organization.

Prognostic factors

In all RCC types, prognosis worsens with stage and histopathological grade. The 5-year overall survival (OS) for all types of RCC is 49%. Clinical factors include performance status, localised symptoms, cachexia, anaemia, and platelet count.

Summary of evidence	LE
In RCC patients, TNM stage, Fuhrman nuclear grade, and RCC subtype (WHO, 2004), provide important prognostic information.	2

TNM = tumour node metastasis (classification); WHO = World Health Organization.

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 deterioration in patient health.

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 lymph node 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 NSS rather than RN, irrespective of the surgical approach. Before routine nephrectomy, tumour embolisation has no benefit.

Summary of evidence	LE
PN achieves similar oncological outcomes to RN for clinically localised tumours (cT1).	1b
Ipsilateral adrenalectomy during RN or PN has no survival advantage.	3
In patients with localised disease without evidence of LN metastases, there is no survival advantage of LND in conjunction with RN.	1b
In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.	3

Recommendations	GR
Surgery is recommended to achieve cure in localised RCC.	B
PN is recommended in patients with T1a tumours.	A
Favour PN over RN in patients with T1b tumour, whenever feasible.	B
Ipsilateral adrenalectomy is not recommended when there is no clinical evidence of invasion of the adrenal gland.	B
LND is not recommended in localised tumour without clinical evidence of lymph node invasion.	A

LND = lymph node dissection; PN = partial nephrectomy; RN = radical nephrectomy.

Radical- and partial nephrectomy techniques

Summary of evidence	LE
Laparoscopic RN has lower morbidity than open surgery.	1b
Oncological outcomes for T1-T2a tumours are equivalent between laparoscopic and open RN.	2a
PN can be performed, either with an open, pure laparoscopic- or robot-assisted approach, based on surgeon's expertise and skills.	2b

Recommendations	GR
Laparoscopic RN is recommended for patients with T2 tumours and localised masses not treatable by PN.	B
RN should not be performed in patients with T1 tumours for whom PN is indicated.	B

PN = partial nephrectomy; RN = radical nephrectomy.

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 is appropriate to initially monitor small renal masses, followed, if required, by treatment for progression.

Cryoablation and radiofrequency ablation

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

Summary of evidence	LE
Population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management. However, the same benefit in cancer-specific mortality is not confirmed in analyses focusing on older patients (> 75 years).	3
In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).	3
Quality of the available data does not allow definitive conclusions regarding morbidity and oncological outcomes of cryoablation and RFA.	3
Low quality studies suggest a higher local recurrence rate for minimally invasive therapies compared to PN.	3

Recommendations	GR
Due to the low quality of available data no recommendation can be made on radiofrequency ablation and cryoablation.	C
In the elderly and/or comorbid patients with small renal masses and limited life expectancy, active surveillance, radiofrequency ablation and cryoablation may be offered.	C

PN = partial nephrectomy; RFA = radiofrequency.

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 IFN-α improves survival in patients with mRCC and good PFS.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3

Recommendation	GR
Cytoreductive nephrectomy is recommended in appropriately selected patients with mRCC.	C

IFN-α = interferon-alpha; PFS = progression-free survival; mRCC = metastatic renal cell cancer.

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	GR
No general recommendations can be made. The decision to resect metastases has to be taken for each site, and on a case-by-case basis; performance status, risk profiles, profiles and patient preference. Alternative techniques to achieve local control such as stereotactic radiotherapy and radiofrequency ablation must be considered.	C
Stereotactic radiotherapy for bone metastases and stereotactic radiosurgery for brain metastases may be offered for local control and symptom relief.	C

Systemic therapy for advanced / metastatic RCC

Summary of evidence	LE
In mRCC, 5-fluorouracil combined with immunotherapy has equivalent efficacy to IFN-α.	1b
In mRCC, chemotherapy is otherwise not effective.	3

Recommendation	GR
In patients with clear-cell mRCC, chemotherapy should not be offered.	B

IFN-α = interferon alpha; mRCC = metastatic renal cell cancer.

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
IFN-α monotherapy is inferior to VEGF-targeted therapy or mTOR inhibition in mRCC.	1b
IL-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 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-IL2.	1b
Bevacizumab plus IFN-α is more effective than IFN-α treatment-naïve, low-risk and intermediate-risk tumours.	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	GR
Nivolumab is strongly recommended after one or two lines of VEGF-targeted therapy in mRCC.	A
Monotherapy with IFN-α or HD bolus IL-2 is not routinely recommended as first-line therapy in mRCC.	A

ccRCC = clear cell RCC; HD = high-dose; IFN-α = interferon alpha; IL-2 = interleukin-2; mRCC = metastatic renal cell cancer; OS = overall survival; PS = performance status.

Targeted therapies

Novel agents for the treatment of mRCC include drugs targeting VEGF, other receptor kinases and mammalian target of rapamycin (mTOR). 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 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-naïve patients.	1b

Bevacizumab plus IFN-α is more effective than IFN-α in treatment-naïve low-risk and intermediate-risk patients.	1b
Pazopanib is superior to placebo in both naïve mRCC patients and post-cytokine patients.	1b
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
Nivolumab is superior to everolimus in terms of OS and adverse events in patients failing one or two lines of VEGF-targeted therapy.	1b
Cabozantinib is superior to everolimus in terms of PFS in patients failing one or more lines of VEGF-targeted therapy.	1b

EAU 2016 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	

Everolimus prolongs PFS in patients who have previously failed or are intolerant of VEGF-targeted therapy.	1b
Sorafenib has broad activity in a spectrum of settings in clear-cell renal cancer 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.	1a

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

Clear cell*	poor¶	temsirolimus	1b	
Non-clear cell §	any	sunitinib everolimus temsirolimus	2a 2b 2b	

IFN-α = interferon alpha; MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin inhibitor; RCC = renal cell carcinoma; TKI= tyrosine kinase inhibitor.

* Doses: IFN-α - 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg biweekly intravenously; sunitinib 50 mg daily orally for 4 weeks, followed by 2 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.

Recommendations - Systemic therapy in mRCC	**GR**
Systemic therapy for mRCC should be based on targeted and immune agents.	A
Sunitinib and pazopanib are recommended as first-line therapy for advanced/metastatic clear-cell RCC.	A
Bevacizumab + IFN-α are recommended as first-line therapy for advanced/metastatic RCC in favourable-risk and intermediate-risk cRCC.	A
Temsirolimus is recommended as first-line treatment in poor-risk RCC patients. Data on subsequent therapies is lacking in this setting.	A
Cabozantinib should be given for cRCC patients who failed one or two lines of VEGF-targeted therapy based on a PFS advantage over everolimus.	A
Nivolumab is strongly recommended for cRCC patients who failed one or two lines of VEGF-targeted therapy based on and OS advantage over everolimus.	A

	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.

Axitinib can be given as second-line treatment for mRCC after cytokines or first-line VEGF where other drugs are not safe, tolerable or available.	A
Everolimus can be given for cRCC patients who failed VEGF-targeted therapy where other drugs are not safe, tolerable or available.	A
Sequencing of targeted agents is strongly recommended.	A
Sunitinib or everolimus can be given as first-line therapy for non-clear cell mRCC.	B

ccRCC = clear cell RCC; HD = high-dose; IFN-α = interferon alpha; IL-2 = interleukin-2; mRCC = metastatic renal cell cancer; OS = overall survival; PS = performance status; VEFG = vascular endothelial growth factor.

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 intrarenal or in addition regional, e.g. venous tumour thrombi or retroperitoneal lymph node metastases. Isolated local recurrence is rare. In cases where complete surgical removal is not feasible due to advanced tumour growth and pain, palliative treatments including radiation treatment can be considered.

Summary of evidence	LE
Isolated recurrence in the local renal fossa is rare.	3
Patients who undergo resection of local recurrences in the absence of sarcomatoid features may benefit from durable local control and improved survival.	3

Recommendation	GR
Surgical resection of local recurrent disease may be offered.	C

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. There is no evidence whether early versus later diagnosis of recurrence improves survival. Surveillance also 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

		Surveillance						
Risk profile	**Treatment**	**6 mo**	**1 y**	**2 y**	**3 y**	**4 y**	**5 y**	**> 5 y**
Low	RN/PN only	US	CT	US	CT	US	CT	Discharge
Intermediate	RN/PN/ cryo/RFA	CT	CT	CT	US	CT	CT	CT once every 2 y
High	RN/PN/ cryo/RFA	CT	CT	CT	CT	CT	CT	CT once every 2 y

Cryo = cryotherapy; CT = computed tomography of chest and abdomen, or MRI = magnetic resonance imaging; PN = partial nephrectomy; RFA = radiofrequency ablation; RN = radical nephrectomy; 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 NSS, there is an increased risk of recurrence in larger (> 7 cm) tumours, or when there is a positive surgical margin.	C

Recommendations	GR
Follow-up after RCC should be based on the risk of recurrence.	C
For low-risk disease, CT/MRI can be used infrequently.	C
In intermediate-risk patients, intensified follow-up should be performed, including CT/MRI scans at regular intervals in accordance with a risk-stratified nomogram.	C
In high-risk patients, the follow-up examinations should include routine CT/MRI scans.	C
Follow-up should be intensified in patients after NSS for tumours > 7 cm or with a positive surgical margin.	C
Risk stratification can be based on pre-existing classification systems such as the UISS integrated risk assessment score: http://urology.ucla.edu/body.cfm?id=443.	C

CT = computed tomography; MRI = magnetic resonance imaging; NSS = nephron-sparing surgery; PN = partial nephrectomy; RN = radical nephrectomy.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN: 978-90-79754-98-4), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.