EAU GUIDELINES ON RENAL CELL CARCINOMA

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Epidemiology

The widespread use of imaging techniques such as ultrasound (US) and computed tomography (CT) has increased the detection of asymptomatic renal cell carcinoma (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 extends into the renal vein or its segmental branches, or invades the pelvicalyceal system or invades perirenal and/or renal sinus 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.
**Adapted based on the American Joint Committee on Cancer (AJCC), 8th Edn. 2017.*

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 (CT) imaging, unenhanced, and during the nephrographic phase 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 supplementary 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 is an alternative to abdominal CT and is useful in patients with allergy to intravenous contrast. It can also be used for the work-up of patients with possible venous involvement. 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 (advantageous), 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 for the diagnosis of RCC	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Omit chest CT in patients with incidentally noted cT1a disease due to the low risk of lung metastases in this cohort.	Weak
Use magnetic resonance imaging (MRI) to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, including MRI and contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses, in case the results of contrast-enhanced CT are indeterminate.	Strong
Offer brain CT/MRI in metastatic patients when systemic therapy or cytoreductive nephrectomy is considered.	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 unless a significant solid component is visible on imaging.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation of solid renal tumours.	Strong

Recommendations for genetic assessment in case of RCC	**Strength rating**
Perform a genetic evaluation in patients aged ≤ 46 years, with bilateral or multifocal tumours and/or a first or second-degree relative with RCC and/or a close blood relative with a known pathogenic variant and/or specific histologic characteristics which suggest the presence of a hereditary form of RCC.	Strong
Refer patients to a cancer geneticist or to a comprehensive clinical care centre in case of suspected hereditary RCC.	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 has replaced the Fuhrman nuclear grade system. The three most common RCC types, with genetic and histological differences, are: clear-cell RCC (ccRCC) (70-85%), papillary RCC (pRCC) (10-15%), and chromophobe RCC (chRCC) (4-5%). The various RCC types have different clinical courses and responses to therapy. Other, more rare RCC variants are addressed in the full RCC Guidelines document.

Prognostic factors

In all RCC types, prognosis worsens with stage and histopathological grade. Histological factors include tumour grade, RCC subtype, sarcomatoid features, lymphovascular invasion, tumour necrosis, and invasion of the peri-renal fat and collecting system. Clinical factors include performance status, local symptoms, cachexia, anaemia, platelet count, neutrophil/lymphocyte ratio, C-reactive protein and albumin (see Tables 6.3 and 6.4 in the 2022 RCC Guidelines publication).

Recommendations	Strength rating
Use the current Tumour, Node, Metastasis classification system.	Strong
Use the WHO/ISUP grading system and classify RCC type.	Strong
Use prognostic models in localised and metastatic disease.	Strong
Do not routinely use molecular markers to assess prognosis.	Strong

Disease Management

Treatment of localised RCC

Localised RCCs 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 as the survival benefit of extended LN dissection (LND) 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 (QoL) 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.

Recommendations	Strength rating
Offer surgery to achieve cure in localised RCC.	Strong
Offer partial nephrectomy (PN) to patients with T1 tumours.	Strong
Offer PN to patients with T2 tumours and a solitary kidney or chronic kidney disease, if technically feasible.	Weak
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Do not offer an extended lymph node dissection to patients with organ-confined disease.	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 nephrectomy.	1b
Short-term oncological outcomes for T1-T2a tumours are equivalent for laparoscopic- and open RN.	2a
Partial nephrectomy can be performed, either by open-, pure laparoscopic- or robot-assisted approach, based on surgeon's expertise and skills.	2b
Robot-assisted and laparoscopic PN are associated with shorter length of hospital stay and lower blood loss compared to open PN.	2b
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared to RN.	3
Transperitoneal and retroperitoneal laparoscopic PN do not differ in post-operative surgical and medical complications, positive surgical margins and kidney function.	2a
Hospital volume for PN might impact on surgical complications, warm ischaemia time and surgical margins.	3
Radical nephrectomy for positive surgical margins after PN can result in over-treatment in many cases.	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
Intensify follow-up in patients with a positive surgical margin, especially in upstaged pT3a patients.	Weak

Alternatives to surgery

Most population-based analyses show a significantly lower cancer-specific mortality in patients treated with surgery compared to non-surgical management.

Surveillance

Elderly and comorbid patients with incidental small renal masses may have significant competing-cause mortality exceeding RCC-specific mortality. Therefore, in selected patients initial monitoring of small renal masses (active surveillance [AS]), followed, if required, by treatment for progression is appropriate. 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

Cryoablation or radiofrequency ablation (RFA) techniques are associated with less morbidity as compared to PN, at the cost of higher recurrence rates.

Recommendations	Strength rating
Offer active surveillance (AS), or thermal ablation (TA) to frail and/or comorbid patients with small renal masses.	Weak

Perform a percutaneous renal mass biopsy prior to, and not concomitantly with TA.	Strong
When TA or AS are offered, discuss with patients about the harms/benefits with regards to oncological outcomes and complications.	Strong
Do not routinely offer TA for tumours > 3 cm and cryoablation for tumours > 4 cm.	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.

There are no data supporting the use of adjuvant targeting agents following surgery. The first adjuvant trial of immune checkpoint inhibitors (ICIs) reported improved disease-free survival after one-year pembrolizumab therapy vs. placebo, with similar QoL or symptom scores for either group. Based on this data, a weak recommendation for adjuvant pembrolizumab in high-risk ccRCC patients is provided.

Treatment of advanced/metastatic RCC

Management of RCC with venous tumour thrombus

Recommendations	Strength rating
During nephrectomy remove clinically enlarged lymph nodes for staging, prognosis and follow-up implications.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong
In case of metastatic disease, discuss surgery within the context of a multidisciplinary team.	Weak

Management of RCC with neoadjuvant or adjuvant therapy

Summary of evidence	LE
Adjuvant tyrosine kinase inhibitor therapy does not improve OS after nephrectomy.	1b
In one single RCT, in selected high-risk patients, adjuvant sunitinib improved DFS but not OS.	1b
Adjuvant sorafenib, pazopanib, everolimus, girentuximab or axitinib does not improve DFS or OS after nephrectomy.	1b
Adjuvant pembrolizumab after nephrectomy in patients with high-risk RCC improves PFS.	1b
In one RCT, in selected intermediate/high- or high-risk patients or M1 patients without evidence of disease, adjuvant pembrolizumab improved DFS.	1b
Adjuvant RCTs are ongoing to evaluate the benefit of adjuvant immunotherapy after nephrectomy in high-risk patients.	1b

Recommendations	Strength rating
Do not offer adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab or axitinib.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk ccRCC.	Weak
Offer adjuvant pembrolizumab to patients with ccRCC following surgery with curative intent with a risk of recurrence as defined in the trial.*	Weak

**pT2 G4 or pT3 any G; pT4 any G; pN+ Any G.*

Advanced/metastatic RCC – local therapy

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 oligometastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary.

Summary of evidence	LE
Deferred CN with pre-surgical sunitinib in intermediate-risk patients with cc-mRCC shows a survival benefit in secondary endpoint analyses 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 VEGFR-TKI.	1a

Cytoreductive nephrectomy in 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
Patients with their primary tumour in place treated with IO-based combination therapy have better PFS and OS in exploratory subgroup analyses compared to treatment with sunitinib.	2b

Recommendations	**Strength rating**
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform immediate CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Start systemic therapy without CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Discuss delayed CN with patients who derive clinical benefit from systemic therapy.	Weak
Perform immediate CN in patients with a good performance status 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

MSKCC = Memorial Sloan-Kettering Cancer Center.

Local therapy of metastases in metastatic RCC

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 studies included in a Panel systematic review were retrospective, non-randomised comparative studies, resulting in a high risk of bias associated with non-randomisation, attrition, and selective reporting.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of OS, CSS and delay of systemic therapy.	3
A single-arm prospective and retrospective study supports that oligometastases can be observed for up to 16 months before systemic therapy is required due to progression.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g., pain).	3
Tyrosine kinase inhibitors treatment after metastasectomy in patients with no evidence of disease did not improve RFS when compared to placebo or observation.	1b

Recommendations	Strength rating
To control local symptoms, offer 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
Do not offer tyrosine kinase inhibitor treatment to mRCC patients after metastasectomy and no evidence of disease.	Strong
Perform a confirmatory axial scan of disease status prior to metastasectomy to rule out rapid progressive metastatic disease which requires systemic treatment.	Weak
Before initiating systemic therapy for oligometastases that cannot be resected, discuss with your patient a period of observation until progression is confirmed.	Weak

Systemic therapy for advanced/metastatic RCC

Chemotherapy

Recommendation	Strength rating
Do not offer chemotherapy to patients with mRCC.	Strong

Targeted therapies

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

Summary of evidence	LE
Single-agent VEGF-targeted therapy has been superseded by immune checkpoint-based combination therapy.	1b
Pazopanib is non-inferior to sunitinib in front-line mRCC.	1b

Cabozantinib in intermediate- and poor-risk treatment-naïve ccRCC leads to better response rates and PFS but not OS when compared to sunitinib.	2b
Tivozanib has been EMA approved, but the evidence is still considered inferior over existing choices in the front-line setting.	3
Single-agent VEGF-targeted therapies are preferentially recommended after front-line PD-L1-based combinations. Re-challenge with treatments already used should be avoided.	3
Single-agent cabozantinib or nivolumab are superior to everolimus after one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS after VEGF-targeted therapy when compared to placebo. This is no longer widely recommended before third-line therapy.	1b
Lenvatinib in combination with everolimus improved PFS over everolimus alone in VEGF-refractory disease. Its role after ICIs is uncertain. There is a lack of robust data on this combination making its recommendation challenging.	2a

Recommendations	**Strength rating**
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naïve vascular endothelial growth factor receptor (VEGFR)-refractory cc-mRCC after one or two lines of therapy.	Strong
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak

Offer VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab or cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Offer cabozantinib after VEGF-targeted therapy in cc-mRCC.	Strong
Sequence systemic therapy in treating mRCC.	Strong
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak

IMDC = International Metastatic RCC Database Consortium.

Immunotherapy

Interferon-α monotherapy and combined with bevacizumab, has been superseded as standard treatment of advanced cc-mRCC by ICI combinations and combinations with ICI and targeted therapies.

Summary of evidence	**LE**
Treatment-naïve patients	
Currently, PD-L1 expression is not used for patient selection.	2b
The combination of nivolumab and ipilimumab in treatment-naïve patients with cc-mRCC of IMDC intermediate- and poor risk demonstrated OS and ORR benefits compared to sunitinib.	1b

The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naïve patients with cc-mRCC across all IMDC risk group demonstrated PFS, OS and ORR benefits compared to sunitinib.	1b
Nivolumab plus ipilimumab, pembrolizumab plus axitinib, nivolumab plus cabozantinib and lenvatinib plus pembrolizumab should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	4
The combination of nivolumab plus ipilimumab in the IMDC intermediate- and poor-risk population of treatment-naïve patients with cc-mRCC leads to superior survival compared to sunitinib.	2b
Sequencing systemic therapy	
Nivolumab leads to superior OS compared to everolimus in disease progression after one or two lines of VEGF-targeted therapy.	1b
Axitinib, cabozantinib or lenvatinib can be continued if immune-related adverse events result in cessation of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus pembrolizumab. Re-challenge with immunotherapy requires expert support.	4
Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	4
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	1b

Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity and 1.5% treatment-related deaths. Tyrosine kinase inhibitor-based IO combination therapies were associated with grade 3-5 toxicity ranging between 61-72% and 1% of treatment-related deaths.	1b

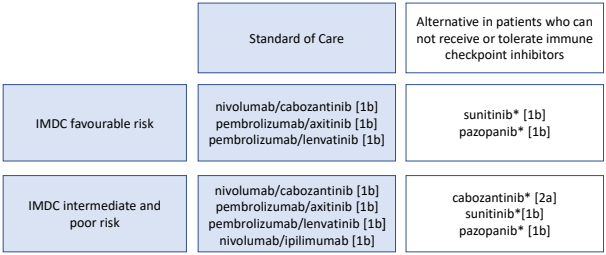
Recommendations	Strength rating
Treatment-naïve patients	
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naïve vascular endothelial growth factor receptor (VEGFR)-refractory cc-mRCC after one or two lines of therapy.	Strong
Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC.	Strong
Administer nivolumab plus ipilimumab, pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab and cabozantinib in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	Weak
Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable-, intermediate-, and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong*

Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible.	Weak
Sequencing systemic therapy	
Offer axitinib, cabozantinib or lenvatinib as subsequent treatment to patients who experience treatment-limiting immune-related adverse events after treatment with the combination of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	Weak
Do not re-challenge patients who stopped immune checkpoint inhibitors because of toxicity without expert guidance and support from a multidisciplinary team.	Strong

* *While this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib in this population. This justified the same recommendation under exceptional circumstances.*

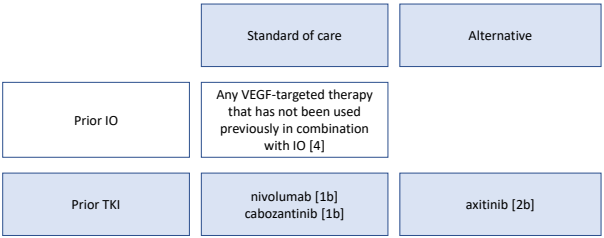
IMDC = International Metastatic RCC Database Consortium.

Figure 1: Updated EAU Guidelines recommendations for the first-line treatment of cc-mRCC



IMDC = International Metastatic RCC Database Consortium.
**pazopanib for intermediate-risk disease only.*
[1b] = based on one randomised controlled phase III trial.
[2a] = based on one randomised controlled phase II trial.

Figure 2: EAU Guidelines recommendations for later-line therapy



IO = immunotherapy; TKI = tyrosine kinase inhibitors;
VEGF = vascular endothelial growth factor.
[1b] = based on one randomised controlled phase III trial.
[2b] = subgroup analysis of a randomised controlled phase III trial.
[4] = expert opinion.

Therapy for renal tumours with sarcomatoid features

Immune checkpoint inhibitor-combination therapy was superior to sunitinib in terms of PFS and OS in a subset analysis of a trial including patients with ccRCC and sarcomatoid differentiation.

Recommendation	Strength rating
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak

Therapy for non-cc-mRCC

In non-cc-mRCC, both mTOR inhibitors and VEGF-targeted therapies have limited activity. There is a non-significant trend for improved oncological outcomes for sunitinib over everolimus.

Recommendation	Strength rating
Offer sunitinib to patients with other non-ccRCC subtypes than papillary RCC.	Weak

Therapy for papillary mRCC

Summary of evidence	LE
Cabozantinib improved PFS over sunitinib in patients with advanced pRCC without additional molecular testing.	2a
Savolitinib improved PFS over sunitinib in patients with MET-driven advanced pRCC.	2a
Pembrolizumab resulted in long-term median OS in a single-arm study in the pRCC subgroup.	2a

Recommendations	Strength rating
Offer cabozantinib to patients with advanced papillary RCC (pRCC) without molecular testing.	Weak
Offer savolitinib to patients with MET-driven advanced pRCC.	Weak
Offer pembrolizumab to patients with advanced pRCC without molecular testing.	Weak

Therapy of rare tumours

Renal medullary carcinoma

Renal medullary carcinoma (RMC) is one of the most aggressive RCCs and most patients (~67%) will present with metastatic disease. Due to the infiltrative nature and medullary epicentre of RMC, RN is favoured over PN even in early-stage disease. Renal medullary carcinoma is refractory to monotherapies with targeted anti-angiogenic regimens including TKIs and mTOR inhibitors. The mainstay systemic treatments for RMC are cytotoxic combination regimens which produce partial or complete responses in ~29% of patients. Patients should be enrolled in clinical trials, particularly after failing first-line cytotoxic chemotherapy.

Hereditary tumours - Von-Hippel-Lindau-disease-associated RCC

Patients with Von-Hippel-Lindau disease often develop RCC and tumours in other sites and commonly undergo several surgical resections in their lifetime. In patients who do not require immediate surgery, a hypoxia-inducible factor 2α (HIF-2α) inhibitor has shown favourable efficacy results and has been approved by the FDA.

Recurrent RCC

Locally recurrent disease in the treated kidney can occur

either after PN, or ablative therapy. After RN or nephron-sparing treatment approaches, recurrence may occur in the renal fossa 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 as well as systemic therapy.

Recommendation	Strength rating
Offer local treatment of locally recurrent disease when technically possible and after balancing adverse prognostic features, comorbidities and life expectancy.	Weak

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:

- post-operative 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, considering patient risk profile and treatment efficacy (expert opinion [LE: 4])

Risk profile (*)	Oncological follow-up after date of surgery								
	3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	> 3 yr	> 5 yr (optional)
Low risk of recurrence	-	CT	-	CT	-	CT	-	CT every two yrs	-
Intermediate risk of recurrence	-	CT	CT	-	CT	-	CT	CT once yr	CT every two yrs
High risk of recurrence	CT	CT	CT	CT	CT	-	CT	CT once yr	CT every two yrs

**Leibovich Score 0-2 / 3-5 / ≥ 6; for non-ccRCC: pT1NX-0, grade 1-2 / pT1b, grade 3-4 / vs. high risk: pT2-4, grade 1-4, or pT any, N1, grade 1-4.*

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 or ablative therapies in RCC

Summary of evidence	LE
Functional follow-up after curative treatment for RCC is useful to prevent renal and cardiovascular deterioration.	4

Oncological follow-up can detect local recurrence or metastatic disease while the patient may still be 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 follow-up have a better OS than patients not undergoing surveillance.	3
Prognostic models provide stratification of RCC risk of recurrence based on TNM and histological features.	3
In competing-risk models, risk of non-RCC-related death exceeds that of RCC recurrence or related death in low-risk patients.	3
Life expectancy estimation is feasible and may help in counselling patients on duration of follow-up.	4

Recommendations	**Strength rating**
Base follow-up after treatment of localised RCC on the risk of recurrence.	Strong
Perform functional follow-up (renal function assessment and prevention of cardiovascular events) both in nephron-sparing (NSS) and radical nephrectomy patients.	Weak
Intensify follow-up in patients after NSS for tumours > 7 cm or in patients with a positive surgical margin.	Weak
Consider curtailing follow-up when the risk of dying from other causes is double that of the RCC recurrence risk.	Weak

Base risk of recurrence stratification on validated subtype-specific models such as the Leibovich Score for ccRCC or the University of California Los Angeles integrated staging system for non-ccRCC.	Weak

SSIGN = (Mayo Clinic) stage, size, grade, and necrosis score.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-16-5), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.