EAU GUIDELINES ON RENAL CELL CARCINOMA

(Limited update March 2025)

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Introduction

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.

There is no evidence to support primary screening of the general population. Genetic screening of subgroups of patients with a family history of RCC is recommended.

Staging system

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

Table 1: 2017 TNM 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 peri-renal 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		
pTNM 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.*

Recommendations for epidemiology, aetiology and screening	Strength rating
Increase physical activity, eliminate cigarette smoking and, in obese patients, reducing weight are the primary preventative measures to decrease risk of RCC.	Strong
Do not routinely screen people for primary RCC.	Weak

Recommendations for the management of other renal tumours	Strength rating
Manage Bosniak type III cysts the same as localised RCC, or offer active surveillance (AS).	Weak
Manage Bosniak type IV cysts the same as localised RCC.	Strong

Offer AS to patients with biopsy-proven oncocytoma or other oncocytic renal tumours as an acceptable alternative to surgery or ablation.	Weak
Treat angiomyolipoma (AML) with selective arterial embolisation or nephron-sparing surgery, in: • large tumours (a recommended threshold of intervention does not exist); • females of childbearing age; • patients for whom follow-up or access to emergency care may be inadequate; • persistent pain or acute or repeated bleeding episodes.	Weak
Offer systemic therapy (everolimus) to patients with surgically unresectable AMLs which are not amenable to embolisation and require therapy.	Weak

Diagnostic evaluation

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, 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 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 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 renal cell carcinoma.	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 at imaging.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation of solid renal tumours.	Strong

Recommendations for the genetic assessment 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 2017 WHO/ISUP grade classification has replaced the Fuhrman nuclear grade system. The new WHO morphological classification combines both morphologic and molecular analysis. Still, 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, rarer 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 2025 RCC Guidelines publication).

Recommendations for prognostic factors	Strength rating
Use the current Tumour, Node, Metastasis classification system.	Strong
Use the World Health Organization (WHO)/International Society of Urological Pathology (ISUP) grading system and classify renal cell carcinoma type.	Strong
Use prognostic models in localised and metastatic disease.	Strong

Use the 2003 Leibovich scoring model for risk stratification of localised and locally advanced clear cell renal cell carcinoma.	Weak
Use the venous involvement, necrosis, size, stage, and sarcomatoid differentiation (VENUSS) scoring model for risk stratification of localised and locally advanced papillary renal cell carcinoma.	Weak
Do not routinely use molecular markers to assess prognosis.	Strong

WHO/ISUP = World Health Organization/International Society of Urological Pathology.

Disease Management

Patient involvement in kidney cancer treatment

Recommendations for prognostic factors	Strength rating
Employ a shared decision-making approach when deciding on appropriate treatment for RCC.	Strong

Smoking cessation

Recommendations for prognostic factors	Strength rating
Counsel RCC patients to stop smoking.	Strong

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 for the treatment of localised RCC	Strength rating
Offer surgery to achieve cure in localised renal cell cancer.	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

Summary of evidence for radical and partial nephrectomy techniques	**LE**
Laparoscopic radical nephrectomy (RN) has lower morbidity than open RN.	1b
Short-term oncological outcomes for T1-T2a tumours are equivalent for laparoscopic- and open RN.	2a
Partial nephrectomy (PN) 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
Transperitoneal and retroperitoneal laparoscopic PN do not differ in post-operative surgical and medical complications, positive surgical margins (PSMs), and kidney function.	2a
Hospital volume for PN might impact on surgical complications, warm ischaemia time and surgical margins.	3
Immediate completion nephrectomy for PSMs can result in over-treatment in many cases.	3
Off-clamp partial nephrectomy does not improve renal function outcomes in patients with baseline normal renal function.	1b

Recommendations for radical and partial nephrectomy techniques	Strength rating
Offer laparoscopic or robotic 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
Do not attempt off-clamp PN unless indicated.	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.

Active Surveillance and Watchful Waiting

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 contra-indicate 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 for therapeutic approaches as alternative to surgery	Strength rating
Offer active surveillance (AS) or tumour 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
Discuss the harms/benefits with regards to oncological outcomes and complications when TA or AS is offered.	Strong
Offer stereotactic ablative radiotherapy for patients with non-metastatic growing biopsy proven RCC, unfit for surgery.	Weak
Do not routinely offer radiofrequency ablation 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.

Immune checkpoint inhibitors (ICI), restoring immune activity, have shown impressive efficacy in advanced RCC. Previous tyrosine kinase inhibitor (TKI) adjuvant trials have failed to improve disease-free survival (DFS) except one with no effect on overall survival (OS). The Keynote-564 study with adjuvant pembrolizumab was the first ICI trial showing significantly improved DFS in ccRCC with a high risk of relapse. Recently, primary DFS endpoints were not met in three adjuvant ICI studies (IMmotion010, CheckMate 914, PROSPER) while the updated follow-up of the Keynote-564 study remained significant. Differences in effect can be due to heterogeneity in patient selection and different ICIs studied. Pembrolizumab remains recommended in this setting, although OS data are still immature. Treatment decisions should be made with caution and individual patient preference should be carefully considered including a discussion with the patient on the potential risk for over-treatment.

Recommendations for lymph node dissection, the management of RCC with venous tumour thrombus and unresectable tumours	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
Discuss treatment options in patients with locally-advanced unresectable RCC (biopsy and/or systemic therapy/deferred resection, or palliative management) within a multi-disciplinary team to determine treatment goal.	Strong

Neoadjuvant and adjuvant therapy

Summary of evidence for neoadjuvant and adjuvant therapy	LE
Neoadjuvant systemic therapy can reduce vascular thrombus and tumour size in the presurgical setting.	2a
Adjuvant sunitinib, sorafenib, pazopanib, everolimus, girentuximab, or axitinib does not improve overall survival (OS) after nephrectomy.	1b
Adjuvant PD1 inhibition with pembrolizumab defined by the inclusion criteria of the trial* after nephrectomy improves disease-free survival (DFS) and OS.	1b
Adjuvant PD-L1 inhibition with atezolizumab and PD1 inhibition with nivolumab did not improve DFS or OS.	1b

Adjuvant dual PD-1 and CTLA-4 inhibition with nivolumab and ipilimumab did not improve DFS.	1b
Peri-operative treatment with nivolumab did not improve relapse-free survival.	1b
There is uncertainty regarding further systemic therapy in patients who receive adjuvant pembrolizumab and develop a recurrence.	4
The lack of biomarker data is hindering progress in this field.	4

** pT2 G4 or pT3 any G; pT4 any G; pN+ any G; M1, NED after resection of metastases.*

Recommendations for neoadjuvant and adjuvant therapy	**Strength rating**
Do not use neoadjuvant therapy outside a clinical trial setting.	Weak
Offer adjuvant pembrolizumab to clear cell RCC (ccRCC) patients, preferably within twelve to sixteen weeks post-nephrectomy, with a recurrence risk as defined in the Keynote-564 trial: Intermediate-high risk: • pT2, grade 4 or sarcomatoid, N0 M0 • pT3, any grade, N0, M0 High risk: • pT4, any grade, N0, M0 • any pT, any grade, N+, M0 M1 no evidence of disease (NED): • No evidence of disease after resection of oligometastatic sites within one year from nephrectomy.	Strong

If adjuvant therapy is planned: • Discuss the contradictory results of the available adjuvant ICI trials with the patient to facilitate shared decision making. • Inform the patient about the potential risk of overtreatment and immune related side effects if adjuvant therapy is considered.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell RCC.	Weak
Offer vascular endothelial growth factor receptor - tyrosine kinase inhibitor (VEGFR-TKI) to patients developing a recurrence while receiving pembrolizumab or within the first six months after stopping pembrolizumab given for one year.	weak
Do not offer immune checkpoint inhibitor (ICI) mono- or combination therapy in patients with recurrence during or within six months after adjuvant pembrolizumab.	weak

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 for local therapy of advanced/ metastatic RCC	LE
Deferred cytoreductive nephrectomy (CN) with pre-surgical sunitinib in intermediate-risk patients with clear cell metastatic RCC 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 do not benefit from CN.	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

CN = cytoreductive nephrectomy, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, IO = Immune-oncology, MSKCC = Memorial Sloan Kettering Cancer Cente, OS = overall survival, PFS = progression-free survival, VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor.

Recommendations for local therapy of advanced/metastatic RCC	Strength rating
Do not perform cytoreductive nephrectomy (CN) in IMDC/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

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 for local therapy of metastases in metastatic RCC	**LE**
Retrospective comparative studies point towards a benefit of complete metastasectomy in metastatic RCC patients in terms of overall survival, cancer specific survival and delay of systemic therapy.	3
A single-arm prospective and retrospective study support that oligometastases can be observed for up to sixteen months before systemic therapy is required due to progression.	2a

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 relapse-free survival when compared to placebo or observation.	1b

Recommendations for local therapy of metastases in metastatic RCC	**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 metastatic RCC 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

Recommendation for systemic therapy in advanced/metastatic RCC	Strength rating
Do not offer chemotherapy to patients with metastatic RCC.	Strong

Targeted therapies

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

Summary of evidence for single-agent targeted therapy in metastatic clear-cell RCC	LE
Single-agent vascular endothelial growth factor (VEGF)-targeted therapy has been superseded by immune checkpoint-based combination therapy.	1b
Intermittent VEGF therapy can be considered in patients on long term VEGF targeted therapy.	2
Immuno-oncology (IO)-VEGFR tyrosine kinase inhibitors (TKI) combination established a response rate (RR) and progression-free survival (PFS) benefit over single agent VEGFR TKI, but no overall survival (OS) benefit in subgroup analysis.	1a
Pazopanib is non-inferior to sunitinib as first-line management option in metastatic RCC.	1b
Cabozantinib in intermediate- and poor-risk treatment-naive clear cell RCC (ccRCC) leads to better response rates and PFS but not OS when compared to sunitinib.	2b
Tivozanib has been European Medicines Agency approved in first-line setting.	3

Single-agent VEGF-targeted therapies are preferentially recommended after first-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
Belzutifan has a PFS advantage and no OS benefit over everolimus in second and more lines pretreated ccRCC.	1b
Lenvatinib in combination with everolimus improved PFS over everolimus alone in VEGF-refractory disease. Its role after immune checkpoint inhibitors is uncertain. There is a lack of robust data on this combination making its recommendation challenging.	2a

Recommendations for single-agent targeted therapy in metastatic clear-cell RCC	**Strength rating**
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naive vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy.	Strong
Sequence 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
Offer belzutifan as an alternative to everolimus in patients previously treated with second to fourth line therapy for clear cell RCC.	Weak
Intermittent single agent VEGFR tyrosine kinase inhibitor can be offered in case of partial response or stable disease > 6 months.	Weak

Immunotherapy

Interferon-α monotherapy either alone or combined with bevacizumab, as well as single-agent TKI (except for IMDC favourable risk patients) have been superseded as standard treatment of treatment-naive advanced cc-mRCC by ICI combinations and combinations with ICI and targeted therapies.

Summary of evidence for immunotherapy in cc-mRCC	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 metastatic clear cell RCC (cc-mRCC) of IMDC intermediate- and poor risk demonstrated overall survival (OS) and objective response rate (ORR) benefits compared to sunitinib alone.	1b
The updated OS data for Ipilimumab/Nivolumab in IMDC favourable risk patients demonstrates the long-term benefit for this subgroup of patients.	2b
The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naïve patients with cc-mRCC demonstrated progression-free survival (PFS), OS and ORR benefits compared to sunitinib in the intention to treat (ITT) population.	1b
The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naïve patients with cc-mRCC in IMDC favorable subgroups demonstrated PFS and ORR benefits compared to sunitinib, without OS improvememt.	2b
The combination of axitinib plus avelumab did not demonstrate significant OS benefit and axitinib plus toripalimab did not demonstrate significant OS benefit yet, as did benmelstobart plus anlotinib.	1b
The triplet combination cabozantinib, nivolumab, and ipilimumab (CABO-NIVO-IPI) demonsrated a PFS benefit over NIVO-IPI.	1b

Sequencing systemic therapy	
Nivolumab leads to superior OS compared to everolimus in disease progression after one or two lines of vascular endothelial growth factor (VEGR)-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 multi-disciplinary team.	1b
Nivolumab plus ipilimumab was associated with 46% grade III-IV toxicity and 1.5% treatment-related deaths. Tyrosine kinase inhibitor-based immune-oncology combination therapies were associated with grade III-V toxicity ranging between 61-72% and 1% of treatment-related deaths.	1b
In the CONTACT 3 study atezolizomab plus cabozantinib offered no benefit compared to cabozantinib alone in patients who's cancers have previously progressed on immune checkpoint inhibition therapy.	1b

Cabozantinib as a single agent has the most robust data after first line PD1 based combination therapy.	3

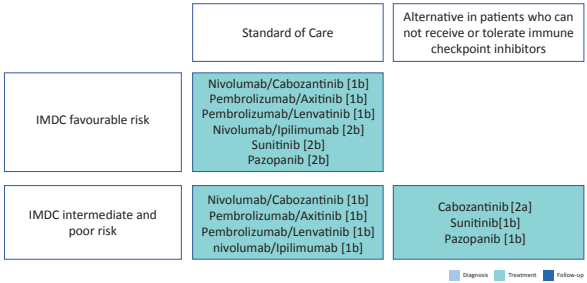
IMDC = International Metastatic RCC Database Consortium.

Recommendations for immunotherapy in cc-mRCC	**Strength rating**
First line Treatment for metastatic clear cell RCC patients	
Offer nivolumab plus ipilimumab, pembrolizumab plus axitinib, lenvatinib plus pembrolizumab or nivolumab and cabozantinib to patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate- or poor risk-disease.	Strong
Offer pembrolizumab plus axitinib, lenvatinib plus pembrolizumab or nivolumab and cabozantinib or nivolumab plus ipilimumab or sunitinib or pazopanib for IMDC favourable risk disease.	Weak
Offer sunitinib or pazopanib to patients with any IMDC risk who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to patients with IMDC intermediate- and poor-risk clear cell metastatic renal carcinoma (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. Re-challenge with combination therapy requires expert support after discontinuation for toxicity.	Weak

Sequencing systemic therapy for metastatic clear cell RCC	
Sequence systemic therapy in treating mRCC.	Strong
Offer carbozantinib or other vascular endothelial growth factor (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
Sequence the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer nivolumab or cabozantinib for those patients who received first line VEGF targeted therapy alone.	Strong
Treatment past progression can be justified but requires close scrutiny and the support of an expert multi-disciplinary team.	Weak
Do not re-challenge patients who stopped immune checkpoint inhibitors because of toxicity without expert guidance and support from a multi-disciplinary team.	Strong
Do not offer programmed death-ligand 1 (PD-L1) combination therapy after progression after immune checkpoint inhibition combination.	Weak

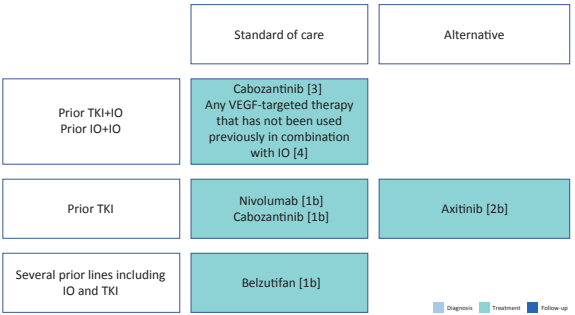
* *While this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib in this population. This justified the same recommendation under exceptional circumstances.*

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



IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium.
[1b] = based on one randomised controlled phase III trial.
[2a] = based on a well-designed study without randomisation, or a subgroup analysis of a randomised controlled 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 for targeted therapy in RCC with sarcomatoid features	Strength rating
Offer immune checkpoint inhibitor combination therapy for advanced clear cell metastatic RCC with sarcomatoid features.	Weak

Treatment of patients with papillary metastatic RCC

Summary of evidence for systemic therapy in papillary metastatic RCC	LE
Cabozantinib improved progression-free survival (PFS) over sunitinib in patients with advanced papillary RCC without additional molecular testing.	2a
Lenvatinib plus pembrolizumab and cabozantinib plus nivolumab demonstrated response rates of 47-54% with median PFS rates > 12 months.	2a
Pembrolizumab resulted in long-term median overall survival in a single-arm study in the papillary RCC subgroup.	2a

Recommendations for systemic therapy in papillary metastatic RCC	Strength rating
Offer cabozantinib to patients with papillary RCC (pRCC) based on a positive randomised controlled trial.	Weak
Offer lenvatinib plus pembrolizumab or nivolumab plus cabozantinib to patients with pRCC based on small single-arm trials.	Weak

Treatment of patients with metastatic non-ccRCC other than papillary RCC

The evidence surrounding systemic therapy for non-ccRCC tumours other than pRCC is especially weak and has relied on subset analysis of randomised phase II trials as well as expanded access programmes.

Summary of evidence for systemic therapy in chromophobe and unclassified RCC	LE
Both mTOR inhibitors and vascular endothelial growth factor (VEGF)-targeted therapies have limited activity in metastatic non-clear cell RCC (non-cc-mRCC). There is a non-significant trend for improved oncological outcomes for sunitinib over everolimus and for cabozantinib over sunitinib.	2a
In non-cc-mRCC, sunitinib improved progression free survival over everolimus in a systematic review of phase II trials and subgroups of patients.	1a
In non—cc-mRCC lenvatinib plus pemrolizumab demonstrated clinical efficacy in different non-ccRCC subgroups.	2a

In non-cc-mRCC cabozantinib plus nivolumab demonstrated clinical efficacy in different non-ccRCC subgroups except for chromophobe RCC which were excluded from the study.	2a
Overall survival rate at twelve months was significantly higher with nivolumab plus ipilimumab compared to standard of care in non-ccRCC patients.	1b

Recommendation for systemic therapy in chromophobe and unclassified RCC	**Strength rating**
Offer sunitinib to patients with other non-clear cell renal cell carcinoma (cc-RCC) subtypes than papillary RCC.	Weak
Offer lenvatinib plus pembrolizumab to patients with non-ccRCC subtypes.	Weak
Offer cabozantinib and nivolumab to patients with non-ccRCC subtypes other than chromophobe RCC.	weak
Offer nivolumab plus ipilimumab in patients with non-ccRCC.	Weak

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

Hereditary and syndrome specific RCC

Summary of evidence	LE
Hereditary RCC syndromes are often suggested by family history, age of onset and presence of other lesions typical for the respective syndromes.	3
Hereditary RCC tumours are predominantly found in the lowest decile, with 70% occurring in individuals aged 46 years or younger.	3
To establish whether gene variants identified in a tumour are germline, germline genetic testing must be performed.	3
In von Hippel-Lindau (VHL) and non-familial hereditary disorders-RCC tumours can be observed until a diameter of 3 cm.	3
Belzutifan leads to an objective response rate of VHL lesions of 64% at 37.8 months.	2
There is currently no approved standard first-line treatment for non-VHL hereditary or syndrom specific RCC.	3

Suspect hereditary or syndrome-specific RCC in patients with positive family history, young onset and bilateral or multiple tumours.	**Strong**
Suspect hereditary or syndrome-specific RCC in patients with positive family history, young onset and bilateral or multiple tumours.	Weak
Offer germline testing to patients < 46 years.	Weak
Offer surveillance in von Hippel-Lindau (VHL) until the largest tumour reaches 3 cm in diameter.	Strong
Offer belzutifan to patients with VHL related renal and other tumours who are not surgical candidates.	Weak

FOLLOW-UP IN 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 radiofrequency ablation (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.

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

Table 2: Proposed follow-up schedule following treatment for localised RCC, taking into account patient risk of recurrence profile and treatment efficacy.

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 (**) (***)
Low risk of recurrence For ccRCC: Leibovich Score 0-2 For non-ccRCC: pT1a-T1b pNx-0 M0 and histological grade 1 or 2.	-	CT	-	CT	-	CT	-	CT once every two yrs	-
Intermediate risk of recurrence For ccRCC: Leibovich Score 3-5 For non-ccRCC: pT1b pNx-0 and/or histological grade 3 or 4.	-	CT	CT	-	CT	-	CT	CT once yr	CT once every two yrs
High risk of recurrence For ccRCC: Leibovich Score ≥ 6 For non-ccRCC: pT2-pT4 with any histological grade or pT any, pN1 cM0 with any histological grade	CT	CT	CT	CT	CT	-	CT	CT once yr	CT once every two yrs

ccRCC = clear cell renal cell carcinoma; CT = computed tomography; mo = months; non-ccRCC = non clear cell renal cell carcinoma; yr = years.

The table above provides recommendations on follow-up strategies for low, intermediate and high risk of recurrence in patients curatively treated for localised RCC either with NSS or RN. Computed tomography in the table refers to imaging of both chest and abdomen. Alternatively, MRI of the abdomen can be performed instead of a CT-scan.

* *Risk of recurrence profiles should be based on validated prognostic models. The EAU RCC Guidelines Panel recommends the 2003 Leibovich model for ccRCC [250]. However, other validated models can be used by physicians based on their own national/regional recommendations. In a similar fashion, for curatively treated localised non-ccRCC, the Panel recommends the use of the University of California Los Angeles integrated staging system (UISS) to determine risk of recurrence [251].*

** *For all risk of recurrence profiles, functional follow-up, mainly monitoring renal and cardiovascular function, may continue according to specific clinical needs irrespective of the length of the oncological follow-up.*

*** *For low-risk profiles at > 3 years and intermediate-risk at > 5 years of follow-up respectively, consider counselling patients about terminating oncological follow-up imaging based on assessment of comorbidities, age, life expectancy and/or patient wishes.*

Summary of evidence for surveillance following radical nephrectomy or partial nephrectomy or ablative therapies in RCC	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 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 follow-up have a better overall survival than patients not undergoing follow-up.	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 support counselling of patients on duration of follow-up.	4
Overall survival is reduced in metastatic RCC patients with symptoms of depression and distress.	2a

Recommendations for surveillance following radical nephrectomy or partial nephrectomy or ablative therapies in RCC	Strength rating
Base follow-up after treatment of localised RCC on the risk of recurrence.	Strong
Base risk of recurrence stratification on validated subtype-specific models such as the Leibovich Score for clear cell RCC (ccRCC), or the University of California Los Angeles integrated staging system for non-ccRCC.	Weak
Intensify follow-up in patients after nephron-sparing surgery 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
Offer psychological evaluation for all patients diagnosed with RCC to provide timely support for distress, depression, or anxiety.	Weak

This short booklet is based on the more comprehensive EAU Guidelines (978-94-92671-29-5), available on the EAU website: http://www.uroweb.org/guidelines/.