GUIDELINES ON RENAL CELL CARCINOMA

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Introduction

The use of imaging techniques such as ultrasound (US) and computed tomography (CT) has increased the detection of asymptomatic renal cell cancer (RCC). In addition, during the last 10 years, mortality rates have stabilised and even declined in some European countries. 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, such as smoking, obesity and hypertension. The most effective prophylaxis is to avoid cigarette smoking and obesity.

Diagnosis and classification

Many renal masses remain asymptomatic until the late stages of the disease. Currently, more than 50% of RCCs are detected incidentally when imaging is used to investigate a variety of nonspecific symptoms and other abdominal diseases. The classic triad of flank pain, gross haematuria and palpable abdominal mass is rare. Clinical symptoms include visible (gross) haematuria, palpable mass, arising varicocele or bilateral lower extremity oedema; these symptoms should initiate radiological examination.

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 and other investigations of RCC

Radiological investigation includes CT imaging, before and after intravenous contrast, to 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 imaging (MRI) are supplements to CT. Contrast-enhanced US can be helpful in specific cases (e.g. chronic renal failure with a relative contraindication for iodinated or gadolinium contrast media, complex cystic masses, and differential diagnosis of peripheral vascular disorders such as infarction and cortical necrosis). In patients with possible venous involvement, or allergy to intravenous contrast MRI can be used. 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 increasingly being used:

1. For histological diagnosis of radiologically indeterminate renal masses;
2. To select patients with small renal masses for surveillance approaches;
3. To obtain histology before ablative treatments;
4. To select the most suitable form of targeted pharmacologic therapy 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 (eGFR) should always be undertaken to optimise the treatment decision.

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 ≤ 10cm
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 lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in more than one regional lymph node

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.

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 (cRCC 80-90%), papillary RCC (pRCC 10-15%), and chromophobe RCC (chRCC 4-5%). Generally, the RCC types have different clinical courses and responses to therapy.

Recommendations for the diagnosis and staging of RCC	GR
The Fuhrman grading system and classification of RCC subtype should be used.	B
Contrast-enhanced abdominal CT and MRI are recommended for the work-up of patients with RCC. These are the most appropriate imaging modalities for renal tumour staging prior to surgery.	B
A chest CT is recommended for staging assessment of the lungs and mediastinum.	C
Bone scan is not routinely recommended.	C
Evaluation of renal function is recommended before treatment decision in any patient in whom renal impairment is suspected.	C
Percutaneous biopsy is recommended in patients in whom active surveillance is pursued.	C
Percutaneous biopsy is always required before ablative therapy and systemic therapy without previous pathology.	C
When biopsy is indicated, good-quality needle cores should be obtained with a coaxial technique in order to increase the safety of the procedure and maximize its diagnostic yield.	B

Other renal tumours

The RCC types account for 85-90% of all renal tumours. The remaining 10-15% include a variety of uncommon carcinomas, a group of unclassified carcinomas, and several benign renal tumour masses.

Recommendations for "other renal tumours"	LE	GR
Except for angiomyolipomas, most of these less common renal tumours cannot be differentiated from RCC on the basis of radiology and should therefore be treated in the same way as RCC.	3	C
Bosniak cysts ≥ type III should be regarded as RCC and be treated accordingly.	3	C
In oncocytomas verified on biopsy, follow-up is an option.	3	C
In angiomyolipomas, treatment (surgery, thermal ablation, and selective arterial embolisation) can be considered in well selected cases. A nephron-sparing procedure is preferred.	3	C
In advanced uncommon types of renal tumours, a standardised oncological treatment approach does not exist.	4	C

Primary treatment of RCC

Current evidence suggests that localised renal tumours are best managed by nephron-sparing surgery (partial nephrectomy) rather than by radical nephrectomy, irrespective of the surgical approach used. Radical nephrectomy with complete removal of the tumour-bearing kidney with perirenal fat and Gerota's fascia is currently recommended only for patients with localised RCC, who are not suitable for nephron-sparing surgery due to locally advanced tumour growth, when partial resection is technically not feasible due to an unfavourable localisation of the tumour or local growth. Complete resection of the primary RCC either by open-, laparoscopic- or robot-assisted surgery offers a reasonable chance for cure.

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 who have RCCs with tumour thrombus and no metastatic spread, prognosis is improved after nephrectomy and complete thrombectomy.

Embolisation of the primary tumour is indicated in patients with visible (gross) haematuria or local symptoms (e.g. pain), in patients unfit for surgical intervention, and before surgical resection of large skeletal metastases. No benefit is associated with tumour embolisation before routine radical nephrectomy.

Low level data suggests that tumour thrombus in the setting of non-metastatic disease should be excised. Adjunctive procedures such as tumour embolization or IVC filter do not appear to offer any benefits in the treatment of tumor thrombus.

Recommendations for the primary treatment of RCC	GR
Surgery is recommended to achieve cure in localised RCC.	B
Ipsilateral adrenalectomy is not recommended when there is no clinical evidence of invasion of the adrenal gland.	B
Lymph node dissection is not recommended in localised tumour without clinical evidence of lymph node invasion.	A
In patients with clinically enlarged lymph nodes, lymph node dissection can be performed for staging purposes or local control.	C
Excision of the kidney tumour and caval thrombus is recommended in patients with non-mRCC.	C

Nephron-sparing surgery

Absolute indications for partial nephrectomy are anatomical

or functional solitary kidney or bilateral RCC. Relative indications are a functioning opposite kidney affected by a condition that might impair renal function and hereditary forms of RCC with a high-risk of developing a tumour in the contralateral kidney. Also localised unilateral RCC with a healthy contralateral kidney is an indication for nephron-sparing surgery since recurrence-free and long-term survival rates are similar to those for radical nephrectomy. Even in patients with a tumour diameter of up to 7 cm, nephron-sparing surgery can achieve results equivalent to those of a radical approach. If the tumour is completely resected, the thickness of the surgical margin (> 1 mm) does not correlate with the likelihood of local recurrence. If RCCs of larger size are treated with nephron-sparing surgery, follow-up should be intensified, as there is an increased risk of intrarenal recurrences.

Laparoscopic radical- and partial nephrectomy

Laparoscopic- and robot-assisted radical nephrectomy has a lower morbidity compared with open surgery.
It has become an established surgical procedure for RCC. Whether the nephrectomy was done retro- or transperitoneally, the laparoscopic approach must duplicate established, open surgical and oncological principles. Equivalent cancer-free survival rates are achieved versus open radical nephrectomy and laparoscopic radical nephrectomy is now considered the standard of care for patients with T1 and T2 RCCs, who are not treatable by nephron-sparing surgery. Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial resection is indicated.

Laparoscopic partial resection has a risk for longer intraoperative ischaemia time than open partial nephrectomy and therefore carries a higher risk for reduced long-term renal function. The oncological outcome seems comparable in available series. Robotic-assisted partial nephrectomy

requires further evaluation but preliminary data suggest lower estimated blood loss and a shorter warm ischaemia time compared with pure laparoscopic surgery.

Table 2: 2014 recommendations for primary surgical treatment of RCC according to T-stage

Stage	Surgery	
T1	Nephron-sparing surgery	Open
		Laparoscopic/ Robot-assisted
	Radical nephrectomy	Laparoscopic
		Open
T2	Radical nephrectomy	Laparoscopic
		Open
	Nephron-sparing surgery	
T3,T4	Radical nephrectomy	Open
		Laparoscopic

Therapeutic approaches as alternatives to surgery

Active surveillance (initial monitoring of tumour size by serial abdominal imaging with delayed intervention reserved for those tumours that show clinical progression during follow-up) can be considered in the management of small renal masses in elderly and comorbid patients with limited life expectancy and high surgical risk. In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).

Other alternatives to surgery for these patients are minimally-invasive techniques, such as ablation with percutaneous radio-frequency, cryotherapy, microwave, and high-intensity focused US. Potential advantages of these techniques include

Recommendations
Recommended
Recommended
Recommended standard only in patients not suitable for nephron-sparing surgery
Optional in patients not suitable for nephron-sparing surgery
Recommended standard
Adequate and recommended, but carries a higher morbidity
Feasible in selected patients in experienced centres
Recommended standard
Feasible in selected patients

reduced morbidity, outpatient therapy, and the ability to treat high-risk patients not fit for conventional surgery.

These experimental treatments might be used for selected patients as in elderly and /or comorbid patients. The oncological efficacy remains to be determined for both cryotherapy and radiofrequency ablation (RFA), which are the most frequently used minimally-invasive techniques. Data suggest that for both treatments, tumour recurrence rates are higher compared with nephron-sparing surgery.

Recommendations for minimally-invasive alternative treatment	GR
Due to the low quality of the available data no recommendation can be made on RFA and cryoablation.	C
In the elderly and/or comorbid patients with small renal masses and limited life expectancy, active surveillance, RFA and cryoablation can be offered.	C

RFA = radiofrequency ablation.

Adjuvant therapy

Adjuvant tumour vaccination may improve the duration of the progression-free survival (PFS), which is especially important in patients at high-risk of metastases, e.g. T3 RCC. Cytokine therapy does not improve survival after nephrectomy.

Recommendations for adjuvant therapy	GR
Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery.	A

Surgical treatment of metastatic RCC (mRCC)

Nephrectomy of the primary tumour is curative only if surgery can excise all tumour deposits. For most patients with mRCC, nephrectomy is palliative. For targeting agents cytoreductive nephrectomy is recommended before or after successful medical therapy, when possible.

Complete removal of metastases contributes to improved clinical prognosis. Metastasectomy should be carried out in patients with resectable disease and a good performance status (PS). It should also be considered in patients with residual and respectable metastatic lesions, who have previously responded to systemic therapy.

Radiotherapy for metastases

For selected patients with non-resectable brain or osseous lesions, radiotherapy can induce significant symptom relief.

Recommendations for surgical treatment of mRCC	GR
Cytoreductive nephrectomy is recommended in appropriately selected patients with mRCC.	C
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, patient preference and alternative techniques to achieve local control, must be considered.	C
In individual cases, stereotactic radiotherapy for bone metastases, and stereotactic radiosurgery for brain metastases can be offered for symptom relief.	C

Systemic therapy for mRCC (Table 2)

Chemotherapy

Chemotherapy as monotherapy is not considered effective in patients with mRCC.

Immunotherapy

In general, interferon-alpha (IFN-α) monotherapy is inferior to targeted therapy in mRCC. IL-2 monotherapy may have a role in selected cases (good PS, clear-cell type, lung metastases only), since high-dose IL-2 is associated with durable complete responses in a limited number of patients. However, IL-2 has more side effects than IFN-α. A combination of bevacizumab and IFN-α is more effective than IFN-α in treatment-naïve, low-risk and intermediate-risk tumours.

No recommendations can be made at present for vaccination therapy.

Recommendation for immunotherapy	GR
Monotherapy with IFN-α or high-dose bolus IL-2 can only be recommended as a first-line treatment for mRCC in selected patients with clear cell histology and good prognostic factors.	A

INF-α = interferon-alpha.

Table 2: European Association of Urology 2014 evidence-based mRCC

RCC type	MSKCC risk group (3)	First-line	LE^	
Clear cell*	favourable, intermediate and poor	sunitinib pazopanib bevacizumab + IFN-α (favourable-intermediate only)	1b 1b 1b	
Clear cell*	poor¶	temsirolimus	1b	
Non-clear cell§	any	sunitinib everolimus temsirolimus	2a 2b 2b	

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

** Doses: IFN-α, 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg biweekly intravenously; sunitinib 50 mg daily orally for a period of 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 > grade 2 toxicity, blood pressure higher than 150/90 mmHg, or the patient is receiving antihy-*

Targeting agents

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.

recommendations for systemic therapy in patients with

	Second-line*	**LE^**	**Third-line***	**LE^**	**Later lines**	**LE**
	after VEGFR: axitinib sorafenib# everolimus after cytokines: sorafenib# axitinib pazopanib	 2a 2a 2a 1b 2a 2a	after VEGFR: everolimus after mTOR: sorafenib	 2a 1b	any targeted agent	4
	any targeted agent					
	any targeted agent	4				

pertensive medication. Everolimus, 10 mg daily orally.

§ No standard treatment available. Patients should be treated in the framework of clinical trials. If a trial is not available, a decision can be made in consultation with the patient to perform treatment in line with clear-cell renal cell carcinoma.

¶ Poor risk criteria in the NCT00065468 trial consisted of MSKCC (3) risk plus metastases in multiple organs.

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

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

Recommendations *for systemic therapy in mRCC*	GR
Systemic therapy for mRCC should be based on targeted agents	A
Sunitinib and pazopanib are recommended as first-line therapy for advanced/metastatic clear-cell RCC.	A
Bevacizumab + IFN-α is recommended as first-line therapy for advanced/metastatic RCC in favourable-risk and intermediate-risk clear-cell RCC.	A
Temsirolimus is recommended as a first-line treatment in poor-risk RCC patients.	A
Axitinib is recommended as a second-line treatment for mRCC.	A
Everolimus is recommended for clear-cell RCC patients who have failed VEGF-targeted therapy.	A
Pazopanib and sorafenib are alternatives to axitinib and are recommended as second-line therapy after failure of prior cytokines.	B
Sequencing of targeted agents is recommended.	A

Surveillance following surgery for RCC

Table 3: An example of an algorithm for surveillance following treatment efficacy

Risk profile	Treatment	Surveillance		
		6 months	1 year	
Low	RN/PN only	US	CT	
Intermediate	RN/PN/cryo/RFA	CT	US	
High	RN/PN/cryo/RFA	CT	CT	

RN = radical nephrectomy; PN = partial nephrectomy;
US = ultrasound of abdomen, kidneys and renal bed;

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 and other morbidities.

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; nor 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 3. For patients with metastatic disease, individualised follow-up is indicated

treatment for RCC taking into account patient risk profile and

	2 years	**3 years**	**4 years**	**5 years**	**After 5 years**
	US	CT	US	CT	Discharge
	CT	US	CT	CT	CT alternate 2 years
	CT	CT	CT	CT	CT alternate years

CT = computed tomography of chest and abdomen; cyro = cryotherapy; RFA = radiofrequency ablation.

Recommendations for follow-up in RCC	GR
Follow-up after treatment for RCC should be based on a patient's risk factors and the type of treatment delivered.	C
For low-risk disease, CT/MRI can be used infrequently.	C
In the intermediate-risk group, 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
There is an increased risk of intrarenal recurrences in patients treated with minimal invasive therapy, in larger-size (> 7 cm) tumours treated with nephron-sparing surgery, or when there is a positive margin. Follow-up should be intensified in these patients.	C

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-65-6), available to all members of the European Association of Urology at their website - http://www.uroweb.org/guidelines/online-guidelines/.