GUIDELINES ON RENAL CELL CARCINOMA

(Text update March 2013)

B. Ljungberg, K. Bensalah, A. Bex, S. Canfield, S. Dabestani, F. Hofmann, M. Hora, M.A. Kuczyk, T. Lam, L Marconi, A.S. Merseburger, P.F.A. Mulders, M. Staehler, A. Volpe

Eur Urol 2001 Sep;40(3):252-5
Eur Urol 2007 Jun;51(6):1502-10
Eur Urol 2010 Sep;58(3):398-406

Introduction

The use of imaging techniques such as ultrasound (US) and computerised tomography (CT) has increased the detection of asymptomatic RCC. In addition, during the last 10 years, mortality rates have generally stabilised and declined in some European countries. The peak incidence of RCC occurs between 60 and 70 years of age, with a 1.5:1 ratio of men to women. Aetiological factors include lifestyle factors, such as smoking, obesity and hypertension. The most effective prophylaxis is to avoid cigarette smoking and obesity.

Diagnosis and classification

Many renal masses remain asymptomatic until the late stages of the disease. Currently, more than 50% of renal cell carcinomas (RCCs) are detected incidentally when noninvasive 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 now rare. Clinical symptoms include macroscopic haematuria, palpable mass, arising varicocele or bilateral lower extremity oedema; these symptoms should initiate radiological examinations.

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 investigations of RCC include 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 and adrenals. Abdominal US and magnetic resonance (MR) imaging are supplements to CT. Contrast-enhanced US can be helpful in specific cases (e.g., chronic renal failure with a relative contraindication for iodinated or gadolinium contrast media, complex cystic masses, and differential diagnosis of peripheral vascular disorders such as infarction and cortical necrosis). Magnetic resonance imaging can be used in patients with possible venous involvement, or allergy to intravenous contrast. Chest CT is the most accurate chest staging; a routine chest X-ray should be done as a minimum only.

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.

Total renal function should always be evaluated. In patients with any sign of impaired renal function, a renal scan and total

renal function evaluation should 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: The 2009 TNM classification for RCC	
T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney
T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension
T2	Tumour > 7 cm in greatest dimension, limited to the kidney
T2a	Tumour > 7 cm in greatest dimension but ≤ 10 cm
T2b	Tumour > 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 four different subtypes with genetic and histological differences: clear cell RCC (cRCC, 80-90%), papillary RCC (pRCC, 10-15%), chromophobe RCC (ch RCC4-5%), and collecting duct carcinoma (1%).
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
In a patient with one or more suspicious laboratory or physical findings, the possible presence of RCC should be suspected	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	A
A chest CT is most sensitive for assessment of the lung, but at least a plain chest radiograph should be taken for clinical staging	A
In patients at risk for bone metastases (raised alkaline phosphatase level or bone pain), further evaluation with a bone scan is needed	A
Evaluation of renal function is recommended before treatment decision in any patient in whom renal impairment is suspected	B
Percutaneous biopsy is recommended in active surveillance strategies in order to stratify the follow-up according to tumour histology	B
Percutaneous biopsy is always required before ablative therapy and systemic therapy without previous pathology	A
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 tumors. The

remaining 10-15% of renal tumours include a variety of uncommon carcinomas, a group of unclassified carcinomas, and several benign kidney 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 treated surgically. When possible, a nephron-sparing procedure should be performed in Bosniak type III.	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 only very 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

Guidelines for the primary treatment of RCC

Based on the available oncological and QoL outcomes, the current evidence suggests that localised renal cancers are best managed by nephron-sparing surgery (partial nephrectomy) rather than by radical nephrectomy, irrespective of the surgical approach. 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 or laparoscopic surgery offers a reasonable chance for cure.

If pre-operative imaging is normal, routine adrenalectomy is not indicated. Lymphadenectomy should be restricted to staging because extended lymphadenectomy does not improve survival. 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 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.

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. Currently 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 selected patients with a tumour diameter of up to 7 cm, nephron-sparing surgery has achieved 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 radical nephrectomy has a lower morbidity compared with open surgery. It has become an established surgical procedure for RCC. Whether done retro- or transperitoneally, the laparoscopic approach must duplicate established, open surgical, oncological principles. Long-term outcome data indicate equivalent cancer-free survival rates versus open radical nephrectomy. Thus, 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 and robot assisted nephron-sparing surgery has become available treatment options in experienced hands.

Table 2: 2010 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

Laparoscopic partial resection has a risk for longer intra-operative 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 and more mature data before any conclusive technical recommendations can be made.

Conclusion: Radical nephrectomy, preferably laparoscopic, is recommended for patients with localised RCC, who are not suitable for nephron-sparing surgery. Nephron-sparing surgery is the standard of care despite the surgical approach.

Minimally invasive alternative treatment

Minimally invasive techniques, such as ablation with percutaneous radio-frequency, cryotherapy, microwave, and high-intensity focused US (HIFU), are suggested alternatives to surgery. Potential advantages of these techniques include

Recommendations
Recommended standard
Recommended option in experienced centres
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 recommended for selected patients with small, incidentally found, renal cortical lesions, elderly patients, patients with a genetic predisposition to multiple tumours, patients with a solitary kidney, or patients with bilateral tumours. The oncological efficacy remains to be determined for both cryotherapy and RFA, which are the most often used minimally invasive techniques. Current data suggest that cryoablation, when performed laparoscopically, results in fewer re-treatments and improved local tumour control compared with RFA. For both treatments, tumour recurrence rates are higher compared with nephron-sparing surgery. Further research is needed to determine the oncological success rate and complications associated with these procedures.

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. Although there is no current data supporting adjuvant therapy with targeting agents, three worldwide phase III randomised trials are ongoing. Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery.

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. In a meta-analysis of two randomised studies, comparing nephrectomy + immunotherapy versus immunotherapy alone, increased long term survival was found in patients who underwent prior nephrectomy.

For targeting agents, there is no current knowledge whether cytoreductive surgery is advocated before or after successful medical therapy. However, in the absence of available evidence data, cytoreductive nephrectomy is recommended when possible.

Complete removal of metastases contributes to improved clinical prognosis. Metastasectomy should be carried out in patients with resectable disease and a good 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.

Systemic therapy for mRCC

Chemotherapy

Chemotherapy as monotherapy should not be considered effective in patients with mRCC.

Immunotherapy

Conclusions on immunotherapy for mRCC	LE
Interferon-alpha monotherapy is no longer recommended as first-line therapy for mRCC.	1b
Interferon alpha monotherapy still has a role only in selected cases (good performance status, clear cell type, lung metastases only).	2
Interleukin-2 has more side effects than INF-α.	2–3
High-dose IL-2 is associated with durable complete responses in a limited number of patients.	1b
Interleukin-2 can be considered as monotherapy in selected patients with a good prognosis profile.	1b
A combination of bevacizumab and IFN-α is more effective than IFNα in treatment-naïve, low-risk and intermediate-risk tumours.	1b
Vaccination therapy with tumour antigen 5T4 showed no survival benefit over the first-line standard of care.	1b

Recommendations 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
Bevacizumab + IFN-α is recommended as first-line therapy in low-risk and intermediate-risk patients.	B
Cytokine combinations, with or without additional chemotherapy, do not improve the overall survival in comparison with monotherapy.	A

Drugs targeting VEGF or mammalian target of rapamycin (mTOR)

Recent advances in molecular biology have led to the devel-

opment of several novel agents for the treatment of mRCC (Table x). In sporadic clear cell RCC, HIF accumulation due to von Hippel-Lindau (VHL) inactivation results in overexpression of VEGF and PDGF, both of which promote neoangiogenesis and contributes to the development and progression of RCC. At present, several targeting drugs have been approved both in the USA and in Europe for the treatment of mRCC:

Recommendations for systemic therapy for mRCC

Recommendations	GR
Sunitinib is recommended as first-line therapy in favorable-risk and intermediate-risk patients.	A
Bevacizumab + IFN-α is recommended as first-line therapy in favourable-risk and intermediate-risk patients.	A
Sorafenib is recommended as a second-line treatment for mRCC after cytokine failure.	A
Pazopanib is recommended as first-line or after cytokine failure in favourable-risk and intermediate-risk patients.	A
Temsirolimus is recommended as first-line treatment in poor-risk patients.	A
Everolimus is recommended as second-line treatment after failure of tyrosine kinase inhibitors.	A
Axitinib is recommended as second-line treatment after failure of cytokines or tyrosine kinase inhibitors.	A

Table 3: 2013 EAU evidence-based recommendations for first- and second-line systemic therapy in mRCC. Level of evidence given in [brackets].

Table 3: Recommendations for first and second line systemic therapy in mRCC		
Treatment	**Risk or prior treatment**	**Recommended agent**
First-line	Low- or intermediate-risk mRCC	Sunitinib Bevacizumab + IFN-α Pazopanib
	High-risk mRCC	Temsirolimus
Second-line	Prior cytokine therapy	Sorafenib Pazopanib
	Prior VEGFR therapy Prior mTOR inhibitor therapy	Everolimus Clinical trials

RCC type	MSKCC risk group	1st line therapy	2nd line therapy	3rd line therapy
Clear cell	Favourable or intermediate	sunitinib [1b] IFN-α + beva-cizumab [1b] pazopanib [1b] In selected patients: IFN-α [1b] High-dose IL-2 [1b]	After prior TKI: axitinib [1b] sorafenib [1b] everolimus [1b] After prio cytokines: sorafenib [1b] axitinib [1b] pazopanib [1b]	After prior TKI(s): everolimus [1b]
	Poor	temsirolimus [1b]		
Non-clear-cell	favourable Intermediate	No standard treatment available. Patients should be treated within a clinical trial.		
	Poor			

Surveillance following surgery for RCC

The aim of surveillance is to detect either local recurrence or metastatic disease while the patient is still surgically curable. There is no evidence for whether early versus later diagnosis of recurrence improves survival.

Depending on the availability of new effective treatments, more strict 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 as well as the optimal duration of follow-up. It is therefore a need for a surveillance algorithm that monitors patients after treatment for RCC that

recognises not only the patient's risk profile but also treatment efficacy. An example is given in Table 4.

For patients with metastatic disease, an individual follow-up plan is required.

Table 4: An example of an algorithm for surveillance following treatment for RCC taking into account patient risk profile and 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; CT = computed tomography of chest and abdomen or Magnetic resonance imaging (MRI); cyro = cryotherapy; RFA = radiofrequency ablation.

Recommendations	LE	GR
Surveillance 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.	4	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.	4	C

	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

In high-risk patients, the follow-up examinations should include routine CT/MRI scans.	4	C
There is an increased risk of intrarenal recurrences 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 978-90-79754-71-7), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.