GUIDELINES ON RENAL CELL CARCINOMA

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Introduction

Renal cell carcinoma (RCC) represents 2-3% of all cancers, with the highest incidence occurring in Western countries. In Europe, until recently, there was a general annual increase of 2% in the incidence. However, incidence rates of RCC have now stabilised or declined in some countries (Sweden, Denmark), while other European countries are still showing an upward trend in the incidence of RCC.

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 prominently 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

More than 50% of RCCs are diagnosed incidentally. Asymptomatic RCCs are generally smaller and of a lower stage than symptomatic RCCs. In their natural clinical course, RCCs remain asymptomatic and non-palpable until late. The classic triad of flank pain, gross haematuria and palpable abdominal mass is seldom found (6-10%). Clinical symptoms include macroscopic haematuria, palpable mass, arising varicocele or bilateral lower extremity oedema; these symptoms should initiate radiological examinations.

Paraneoplastic symptoms (e.g. hypertension, weight loss, pyrexia, neuromyopathy, anaemia, polycythaemia, amyloidosis, elevated erythrocyte sedimentation rate and abnormal liver function) are found in approximately 20-30% of patients with RCC. About 20-30% of patients with symptoms present as a result 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 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 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.

Fuhrman grading and RCC subtype classification are recommended. There are several integrated prognostic systems and nomograms that combine dependent prognostic factors, which can be useful for predicting survival and differentiating follow-up. Molecular markers and gene expression profiles appear promising for the prediction of survival, but cannot be recommended yet in routine practice.

Other renal tumours

The common RCC types account for 85-90% of all renal

malignancies. The remaining 10-15% of renal tumours include a variety of uncommon carcinomas, a group of unclassified carcinomas, and several benign kidney tumour masses.

- Except for angiomyolipomas, most of these less common renal tumours cannot be differentiated from RCC by radiological imaging and should therefore be treated in the same way as RCC.
- Renal cysts with a Bosniak classification ≥ III should be surgically treated.
- In oncocytomas verified on biopsy, follow-up can be considered as an option.
- In angiomyolipomas, treatment (surgery, thermal ablation, and selective arterial embolisation) can be considered when the tumour > 4 cm. When possible, a nephron-sparing procedure should be performed.
- A standardised oncological programme does not exist for advanced uncommon types of renal tumours.

Radiological investigations of RCC

Radiological investigations of RCC should 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 alternatives to CT. Contrast-enhanced US can be helpful in specific cases. Magnetic resonance imaging can be reserved for 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. Renal masses may

be classified as solid or cystic by imaging criteria. For evaluating solid renal masses, the presence of enhancement is the most important criteria for differentiating malignant lesions. For evaluating renal cystic masses, the Bosniak classification may be used.

Other diagnostic procedures (bone scan, MR imaging, brain CT) should only be considered if indicated by clinical symptoms or laboratory results in selected cases. Renal arteriography and inferior venacavography have only a limited role in the work-up of selected patients with kidney tumours. The true value of positron emission tomography (PET) in the diagnosis and follow-up of RCC remains to be determined and is currently not standard. In patients with any sign of impaired renal function, an isotope renogram and total renal function evaluation should be considered to evaluate the need to preserve renal function.

Renal biopsy

There is an increasing indication for biopsy of renal tumours, as in ablative therapies and in patients being treated with surveillance or systemic therapy without previous histopathology. Core biopsy has demonstrated a high specificity and sensitivity for determining eventual malignancy, but about 20% of biopsies are non-conclusive. Percutaneous biopsy is rarely required for large renal masses scheduled for nephrectomy since it will not alter management. Fine-needle biopsy has only a limited role in the clinical work-up of patients with renal masses.

Guidelines for the primary treatment of RCC

Until recently, the standard for curative therapy of RCC was radical nephrectomy with complete removal of the tumour-bearing kidney with perirenal fat and Gerota's fascia.

For localised RCCs, nephron-sparing surgery is recommended. Radical nephrectomy is recommended 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 when the patient's general health has significantly deteriorated. 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.
Localised unilateral RCC with a healthy contralateral kidney is an indication for elective surgery.

Nephron-sparing surgery is recommended for patients with localised RCC, as 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 trans-peritoneally, 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 nephrectomy is expected to become a widely available treatment option and should be promoted in centres treating RCC.

In experienced hands, partial laparoscopic nephrectomy may be an alternative to open nephron-sparing surgery in selected patients. The optimal indication for laparoscopic nephron-sparing surgery is a relatively small and peripheral tumour. Laparoscopic partial resection has a longer intra-operative ischaemia time than open partial nephrectomy and therefore carries a higher risk for reduced long-term renal function. It also has a higher surgical complication than open surgery. However, the oncological outcome seems comparable in available series. Robotic-assisted partial nephrectomy has been introduced, but requires further evaluation and more mature data before any conclusive recommendations can be made.

Table 2: 2010 recommendations for primary surgical treatment of RCC according to T stage

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

Conclusion: Radical nephrectomy, preferably laparoscopic, is recommended for patients with localised RCC, who are not suitable for nephron-sparing surgery. Open partial nephron-sparing surgery remains the standard of care. Laparoscopic partial nephrectomy should be limited to experienced centres.

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 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 predisposi-

Recommendations
Recommended standard
Optional 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

tion 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 only 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. In patients with a good performance status (PS), tumour nephrectomy + interferon-alpha (IFN-α) can be recom-

mended. 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 is considered ineffective in patients with RCC.

Immunotherapy

Available data show that immunotherapy with IFN-α is beneficial in only a limited subset of patients; those with good PS, a PFS of > 1 year following initial diagnosis, and preferably the lung as the sole metastatic site. Randomised studies comparing targeting agents in a first-line setting to IFN-α monotherapy have demonstrated superiority for either sunitinib, bevacizumab + IFN-α, or temsirolimus. IFN-α monotherapy only

remains an option in selected patients as first-line therapy for mRCC. High-dose bolus interleukin-2 (IL-2) gives durable complete responses in a limited number of patients; however, the toxicity associated with IL-2 is substantially higher than that with IFN-α . To date, no superiority has been shown for treatment with either IFN-α or IL-2 in mRCC patients. Only patients with cRCC benefit clinically from immunotherapy.

A combination of cytokines, with, or without, additional chemotherapy does not improve overall survival compared with monotherapy.

The MSKCC (Motzer) prognostic criteria can be used for risk stratification including; Karnowsky performance status (< 80), time to diagnosis to treatment with IFN-α (< 12 months), Haemoglobin (< normal), Lactate dehydrogenase (> 1.5 upper normal limit) and corrected serum calcium (> normal). Low risk, 0 risk factor; intermediate, 1-2 risk factors; high risk ≥ 3 risk factors.

Angiogenesis inhibitor drugs

Recent advances in molecular biology have led to the development of several novel agents for the treatment of mRCC. In sporadic and VHL (von Hippel Lindau) cRCC, the accumulation of hypoxia inducible factor (HIF) due to a defective VHL protein results in over-expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), promoting neo-angiogenesis. This process substantially contributes to the development and progression of RCC. At present, four targeting drugs have been approved both in the USA and in Europe for mRCC, while other agents have

shown significant efficacy in randomised controlled trials.

Tyrosine kinase inhibitors (TKIs): several TKIs have shown efficacy in cRCC with increased PFS as both first- and second-line treatments of mRCC.

- Sorafenib is an oral multikinase inhibitor with proven increased PFS as a second-line treatment after failure of systemic immunotherapy.
- Sunitinib is an oral TKI. In a phase III first-line study comparing sunitinib with IFN-α, sunitinib achieved a longer PFS time (11 months vs 5 months) in low- and intermediate-risk patients. In patients who did not receive any post-study treatment, overall survival was longer in the sunitinib-only treated group than in the IFN-α treated only group (28.1 months vs 14.1 months, respectively).
- Pazopanib is an oral TKI targeting VEGF and PDGF receptors and c-Kit. In a prospective randomised trial of pazopanib versus placebo in treatment-naive mRCC patients and cytokine-treated patients, there was a significant improvement in PFS from 4.2 to 9.2 months and tumour response was observed.

VEGF antibodies

- Bevacizumab is a humanised monoclonal antibody that binds VEGF. A double-blind phase III trial showed a median 31% overall response with bevacizumab + IFN-α versus 13% in IFN-α monotherapy. Median PFS increased significantly from 5.4 months with IFN-α to 10.2 months for bevacizumab + IFN-α, but was restricted to low- and intermediate-risk patients.

Mammalian target of rapamycin (mTOR) inhibitors, which affect the mTOR pathway, show significant efficacy in mRCC, in other RCC types besides cRCC, and also in high-risk patients.

- Temsirolimus is a specific inhibitor of mammalian target of rapamycin. A phase III trial demonstrated increased overall survival in poor-risk patients with mRCC given temsirolimus monotherapy compared with IFN-α.
- Everolimus is an oral mTOR inhibitor. A recent phase III study in patients who had failed previous anti-VEGF-R treatment showed a PFS of 4 months with everolimus versus 1.9 months with placebo.

Clinical research continues into the use of these and several other new novel agents for the primary or secondary treatment of mRCC, including monotherapy, in combination with each other or with cytokines, or in the adjuvant setting. Only limited overall survival data are available for these new agents and their role is still under development. In the sunitinib randomised trial, patients crossed over from IFN-α to sunitinib (n = 25), the median survival times were 20.0 versus 26.4 months for sunitinib, respectively ($p = 0.03$). In patients who did not receive any post-study sunitinib, the median overall survival was 14.1 months versus 28.1 months in the sunitinib group. To date, there has been no data on the curative effect of the new agents. These agents appear to promise to stabilise mRCC for a prolonged period of time. However, their clinical use has to be balanced against their toxicity profile and the patient's quality of life.

Table 3: 2010 EAU evidence-based 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

Recommendations for systemic therapy

Tyrosine kinase inhibitors should be considered as first- or second-line treatment for mRCC patients as shown in Table 3. Interferon-α monotherapy only remains as an option in selected patients as first-line therapy for mRCC.

Surveillance following surgery for RCC

Surveillance following surgery for RCC allows the urologist to monitor post-operative complications, renal function, local recurrence after partial nephrectomy or ablative treatment, recurrence in the contralateral kidney, and development of metastases.

The method and timing of investigation has been the subject

of many publications. Using different scoring systems and algorithms, patients can be categorised as at low-, intermediate- or high-risk of developing metastases. Despite extensive research, there is no general recommendation for the method and timing of investigations for surveillance. In fact, there is no evidence for whether early versus later diagnosis of recurrence improves survival. However, follow up remains important to increase knowledge of the disease and should be performed by the urologist, who should record the time elapsed to recurrence or metastatic development. Follow-up also allows metastases to be identified early.

Early identification of metastases increases the possibility of surgical resection and efficacy of systemic treatment at a time when the tumour burden is as low as possible. This is particularly important with ablative therapies, such as cryotherapy and RFA, where the local recurrence rate is higher than conventional surgery and the patient may still be cured by repeat ablative therapy or radical nephrectomy. In metastatic disease, more extended tumour growth can reduce the possibility of surgical resection, which is considered the standard therapy in cases of resectable and preferably solitary lesions. In addition, within clinical trials, an early diagnosis of tumour recurrence might enhance the efficacy of a systemic treatment if the tumour burden is low.

The urologist can therefore be selective in the use of imaging and the need for intensive surveillance. Although there is no evidence-based standard for the follow-up of patients with RCC, there are several scoring systems and nomograms for predicting tumour recurrence and metastases. Using these

nomograms, several stage-based surveillance regimes have been proposed. However, none include ablative therapies. There 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; please note this is not an EAU recommendation.

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

Table 4: Example of a proposed follow-up algorithm for surveillance after treatment for RCC with combined patient risk profile and treatment efficacy

(This is an example of a follow-up scheme; grade of recommendation C)

Treatment and schedule	Risk profile		
	Low	Intermediate	High
Treatment	RN/PN only	RN/PN/cryo/RFA	RN/PN/cryo/RFA
6 months	CXR and US	CT	CT
1 year	CXR and US	CXR and US	CT
2 years	CXR and US	CT	CT
3 years	CXR and US	CXR and US	CT
4 years	CXR and US	CXR and US	CT
5 years	CXR and US	CT	CT

> 5 yrs	Discharge	Yearly CXR and US	CXR/CT in alternate years

CT = CT of chest and abdomen; cryo = cryotherapy; CXR = chest X-ray; PN = partial nephrectomy; RFA = radio-frequency ablation. RN = radical nephrectomy; US = ultrasound of kidneys and renal bed.

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-70-0), available to all members of the European Association of Urology at their website - http://www.uroweb.org.