GUIDELINES ON RENAL CELL CARCINOMA

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Introduction

This EAU guideline was prepared to help urologists assess the evidence-based management of the malignancy. Renal cell carcinoma (RCC) represents 2-3% of all cancers with the highest incidence found in the more developed countries. There is a general European annual increase in incidence of around 2%, except in Denmark and Sweden. An increased number of incidentally diagnosed RCCs are found by the use of imaging techniques such as ultrasound (US) and computerized tomography (CT). Despite the increased incidental detection rate, the mortality from RCC has so far remained unaffected and parallel to the transient incidence. The peak incidence is found between 60 and 70 years of age, with a 1.5:1 predominance of men over women. Aetiological factors include lifestyle factors, such as smoking, obesity and therapy for hypertension. The most effective prophylaxis is to avoid cigarette smoking and obesity.

Diagnosis and classification

Many RCCs remain asymptomatic and non-palpable until late in their natural course. Asymtomatic RCCs are generally smaller and of lower stage. The classic triad of flank pain, gross haematuria and palpable abdominal mass is now rarely 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, such as hypertension, weight loss, pyrexia, neuromyopathy, anaemia, polycythaemia, amyloidosis, elevated erythrocyte sedimentation rate and abnormal liver function, are found in around 20-30% of patients with RCC. About 20-30% of patients are diagnosed with symptoms present due to metastatic disease.

Staging system

The UICC 2002 TNM (Tumour Node Metastasis) classification is recommended for the staging of RCC.

Table 1: The 2002 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, but not more than 7 cm
	T2	Tumour > 7 cm in greatest dimension, limited to the kidney

	T3	Tumour extends into major veins or directly invades adrenal gland or perinephric tissues but not beyond Gerota fascia
		T3a Tumour directly invades adrenal gland or perinephric tissues[1] but not beyond Gerota fascia
		T3b Tumour grossly extends into renal vein(s)[2] or its segmental branches, or the vena cava below the diaphragm
		T3c Tumour grossly extends into vena cava or its wall above the diaphragm
	T4	Tumour directly invades beyond Gerota fascia
N	**Regional lymph nodes**[3]	
	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 1 regional lymph node
M	**Distant metastasis**	
	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis

[1] *Includes renal sinus (peripelvic) fat*
[2] *Includes segmental (muscle-containing) branches*
[3] *pN0 lymphadenectomy specimens will ordinarily include 8 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.*

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 defines the Fuhrman grade. RCC is composed of four genetically different subtypes. These include conventional (clear cell) (80-90%), papillary (10-15%), chromophobe RCC (4-5%), and collecting duct carcinoma (1%). In general, the RCC types have different clinical courses and responses to therapy. It is recommended to use Fuhrman grading and RCC subtype classification. A number of different integrated prognostic systems and nomograms combining dependent prognostic factors have been developed. These nomograms can be useful for predicting survival and differentiating follow-up.

Radiological investigations of RCC

Radiological investigations should include a high-quality CT scan using contrast medium. This serves to verify the diagnosis and provides information on the function and morphology of the contralateral kidney and assesses tumour extension, including extrarenal spread, venous involvement, enlargement of lymph nodes and adrenals. Abdominal ultrasound and especially magnetic resonance imaging (MRI) are alternatives to CT. MRI can be reserved for patients with possible venous involvement, renal insufficiency or allergy to intravenous contrast. Chest CT is the most accurate chest staging, but a routine chest X-ray should be done as a minimum.

Only if indicated by clinical symptoms or laboratory signs should other diagnostic procedures be considered in selected cases. These include bone scan, MRI, brain CT, renal arteriography, and inferior venacavography. 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

Radical nephrectomy remains the gold standard for curative therapy for patients with localized RCC. Only surgery remains curative, after complete removal of the disease. For smaller RCCs, nephron-sparing surgery is recommended and radical nephrectomy is no longer the standard of care. There is currently no evidence to favour a specific surgical approach. Routine adrenalectomy is not recommended provided the preoperative CT scan is normal. Lymphadenectomy should be restricted for staging purposes since extended lymphadenectomy does not improve survival. Renal cell carcinomas with tumour thrombus and with no metastatic spread have a better prognosis after nephrectomy and complete thrombectomy.

Embolization of the primary tumour is indicated in patients with gross haematuria or local symptoms such as pain, in those who are not fit for surgical intervention, and before surgical resection of large skeletal metastases. There is no benefit in performing tumour embolization 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 that is 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. Elective indication is localized unilateral

RCC with a healthy contralateral kidney. Nephron-sparing surgery is recommended for patients with tumours < 4 cm, providing recurrence-free and long-term survival rates similar to those of radical nephrectomy. Even selected patients with a tumour diameter up to 7 cm have achieved oncological results equivalent to those observed after a radical approach, but it is not recommended as a standard procedure. 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 due to an increased risk of intra-renal recurrences.

Table 2: Primary surgical treatment of RCC according to T stage

T1a	Nephron-sparing surgery	Open
		Laparoscopic
	Radical nephrectomy	
T1b-T2	Radical nephrectomy	Open
		Laparoscopic
	Nephron-sparing surgery	
T3,T4	Radical nephrectomy	Open
		Laparoscopic

Laparoscopic nephrectomy

Laparoscopic radical nephrectomy has become an established surgical procedure with a lower morbidity when compared with open surgery. The laparoscopic approach duplicates established open surgical oncological principles that include early control of the renal vessels before tumour manipulation, wide specimen mobilization external to Gerota's fascia, avoidance of specimen damage or rupture and intact specimen extraction. Laparoscopic radical nephrectomy is today recommended as a standard of care for patients with T1-2 RCCs, and outcome data indicate equivalent cancer-free survival rates when compared with open radical surgery. Laparoscopic nephrectomy can be expected to become a widely available treatment option and should be promoted in centres treating RCC.

Partial laparoscopic nephrectomy might be an alternative to open surgery for very select patients in experienced hands. The optimal indications are in patients with a relatively small and peripheral renal tumour. Although the oncological out-

	Recommended standard
	Optional in experienced centres
	Reasonable in selected patients
	Adequate and recommended but with a higher morbidity
	Recommended standard
	Feasible in selected patients in experienced centres
	Recommended standard for most patients
	Feasible in selected patients

come following laparoscopic partial nephrectomy has been suggested to duplicate that of open techniques, larger studies revealing reliable long-term data are not available. Disadvantages of the laparoscopic approach are the longer warm ischaemia time and increased intra-operative and post-operative complications when compared with open surgery. Open partial nephrectomy currently remains the standard of care. Laparoscopic partial nephrectomy should be limited to experienced centres.

Minimally invasive alternative treatment

Minimally invasive techniques, such as percutaneous radiofrequency (RF), cryotherapy, microwave, and high-intensity focused ultrasound ablation (HIFU) have been suggested as feasible alternatives to surgery. Potential advantages of these techniques might include reduced morbidity, outpatient therapy and the ability to treat high-risk patients not fit for conventional surgery. Thus, such experimental treatments might be recommended for selected patients with small, incidentally found, renal cortical lesion, elderly patients, patients with a

genetic predisposition to multiple tumours, patients with a solitary kidney, or patients with bilateral tumours. The oncological success rate and complications after these procedures have to be defined within clinical trials.

Adjuvant therapy

Adjuvant tumour vaccination might improve the duration of the progression-free survival, especially of those patients with T3 RCC. Cytokine therapy does not improve survival after nephrectomy. 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 the majority of patients with mRCC, nephrectomy is only palliative. In a meta-analysis of two randomized studies, comparing nephrectomy combined with immunotherapy versus immunotherapy only, an increased long-term survival was found in patients subjected to nephrectomy. Tumour nephrectomy can be recommended in patients with a good performance status in combination with interferon-alpha (INF-α) treatment.

Complete removal of metastases contributes to an improvement in clinical prognosis. In patients with metastatic spread, metastasectomy should be performed in cases with resectable disease and a good performance status. Metastasectomy should also be considered in patients with residual and resectable metastatic lesions previously responding to immunotherapy.

Radiotherapy for metastases

Radiotherapy can be used for selected patients with non-resectable brain or osseous lesions and can induce a significant relief from symptoms.

Systemic therapy for mRCC

Chemotherapy

Chemotherapy is generally considered ineffective in patients with RCC.

Immunotherapy

Immunotherapy with INF-α seems beneficial for a subset of patients with good performance status. Interferon-alpha can be considered as the standard of care, but only a limited number of mRCC patients will respond.

Especially with high-dose bolus interleukin-2 (IL2), long-term complete responders have been found. However, the toxicity of IL2 is substantially higher than that of INF-α. The survival efficacy of combinations of these immunotherapies is generally not better than that obtained with monotherapy. Since only clear cell RCC seems to respond to immunotherapy, it is recommended that only patients with clear cell RCC are treated with IL2 or INF-α.

Angiogenesis inhibitor drugs

Recently, drugs targeted on the angiogenesis pathways have been the subject of investigation in RCC. The inhibition by antibodies to vascular epithelial growth factor and downstream tyrosine kinases have shown efficacy in studies on clear

cell RCC. The position of the new agents is still under investigation with regard to primary or secondary treatment of mRCC and combinations with each other or with cytokines.

Surveillance following surgery for RCC

Surveillance after surgery allows the urologist to monitor postoperative complications, renal function, local recurrence, recurrence in the contralateral kidney and development of metastases. The main reason for identifying metastases early is to enhance the possibility of surgical resection and furthermore to enhance the efficacy of systemic treatment when the tumour burden is as low as possible. There is no general recommendation on the method and timing of investigations for surveillance. Using different scoring systems and algorithms, patients can be divided into low, intermediate and high risk of developing metastases. This allows the urologist to be selective in the use of imaging and the need for intensive surveillance. There is no evidence-based standard for the follow-up of patients with RCC.

Table 3: Example of a follow-up regime

(NB: This should not be considered as an EAU follow-up recommendation)

Low-risk patients (pT1a N0 M0 G1-2)	Clinical follow-up, surveillance with annual chest X-ray, without routine CT. But surveillance may also be omitted due to few events
Intermediate-risk patients (pT1b-2 N0 M0, and pT1a N0 M0G3-4)	Surveillance with CT of the thorax or chest X-ray every 6 months for 2 years and annually for 5 years
High-risk patients (all pT3-4 N1-2 M0)	More intensive follow-up with CT of the abdomen and the chest at 3 months, every 6 months for 2 years and thereafter annually for 5 years.
Metastatic disease	Individual follow-up has to be planned

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 90-70244-37-3), available to all members of the European Association of Urology at their website - http://www.uroweb.org.