Guidelines on
Renal Cell Carcinoma

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1. INTRODUCTION

The EAU Guideline Group for renal cell carcinoma (RCC) have prepared these guidelines to help urologists assess the evidence-based management of RCC and to help them incorporate the guidelines recommendations into their clinical practice. Publications concerning RCC are mostly retrospective analyses, which include some larger multicentre studies and well-designed controlled studies. As only a few randomised controlled trials are available, there is some lack of data with a strong evidence base. In recent years, a number of randomised studies have been performed, mostly concerning the medical treatment of metastasised RCC resulting in high evidence-based recommendations.

Where possible, a level of evidence (LE) and/or grade of recommendation (GR) have been assigned (1). Recommendations are graded in order to provide transparency between the underlying evidence and the recommendation given (Tables 1 and 2).

There is clearly a need for re-evaluation at regular intervals by the RCC Guideline Group of the information provided in these guidelines. It has to be emphasised that the current guidelines contain information for the treatment of an individual patient according to a standardised general approach. The information should be considered as providing recommendations without legal implications.

The current document provides a full text update, with a summary of the amendments provided below.

1.1 Summary of the 2010 RCC guidelines update

A new chapter “Other renal tumours” has been added which discusses other tumours of the kidney with the exception of renal pelvic carcinoma. The content of the other chapters has been completely revised based on the findings of a structured literature search.

1.2 Methodology

Structured literature searches using an expert consultant were designed for each section of this document. Searches were carried out in the Cochrane Library database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, Medline, and Embase on the Dialog-Datastar platform. The controlled terminology of the respective databases was used and both MesH and EMTREE were analysed for relevant entry terms.

The search strategies covered the last 3 years for Medline and Embase. Prior to publication of this document an update search was carried out.

Also other data sources were consulted such as the Database of Abstracts of Reviews of Effectiveness (DARE) as well as relevant reference lists from other guidelines producers (National Institute for Clinical Excellence [NICE], American Urological Association [AUA]).

Publication history information: The RCC Guidelines were first published in 2000, with partial updates in 2001 and 2007 followed by a full text update in 2009, and a partial update in 2010.

Table 1: Level of evidence

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

Modified from Sackett et al. (1).

Table 2: Grade of recommendation

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

Modified from Sackett et al. (1).

1.3 References

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2. EPIDEMIOLOGY AND AETIOLOGY

Renal cell carcinoma represents 2-3% of all cancers (1), with the highest incidence occurring in Western countries. Generally, during the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe, though in Denmark and Sweden a continuing decrease has been observed (2). In 2006, it was estimated that there were 63,300 new cases of RCC and 26,400 kidney cancer-related deaths within the European Union (3). In Europe, overall mortality rates for RCC have increased up until the early 1990s, with rates generally stabilising or declining thereafter (4). There has been a decrease in mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend with increasing rates (4).

Renal cell carcinoma is the commonest solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. It comprises different RCC types with specific histopathological and genetic characteristics (5). There is a 1.5:1 predominance of men over women, with peak incidence occurring between 60 and 70 years of age. Aetiological factors include lifestyle factors such as smoking, obesity, and hypertension (6-10). Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC (11,12). The most effective prophylaxis is to avoid cigarette smoking and obesity.

Due to the increased detection of tumours by imaging techniques such as ultrasound and computed tomography (CT), the number of incidentally diagnosed RCCs has increased. These tumours are more often smaller and of lower stage (13-15).

2.1 Conclusion

Several verified risk factors have been identified including smoking, obesity and hypertension. Cigarette smoking is a definite risk factor for RCC (LE: 2a).

2.2 Recommendation

	GR
The most important primary prevention for RCC is to eliminate cigarette smoking and to avoid obesity.	B

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3. DIAGNOSIS AND STAGING

3.1 Symptoms

Many renal masses are asymptomatic and non-palpable until the late stages of the disease (1). Currently, more than 50% of RCCs are detected incidentally by using imaging to investigate a variety of non-specific symptom complexes (2-4) (LE: 2b). The classic triad of flank pain, gross haematuria, and palpable abdominal mass is now rare (6-10%) (5,6) (LE: 3).

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs (Table 3) (LE: 4). A few symptomatic patients present with symptoms due to metastatic disease, such as bone pain or persistent cough (1,7) (LE: 2b).

Table 3: Most common paraneoplastic syndromes

Hypertension
Cachexia
Weight loss
Pyrexia
Neuromyopathy
Amyloidosis
Elevated erythrocyte sedimentation rate
Anaemia

Abnormal liver function
Hypercalcaemia
Polycythaemia

3.1.1 ***Physical examination***

Physical examination has only a limited role in diagnosing RCC. However, the following findings should initiate radiological examinations:

- palpable abdominal mass;
- palpable cervical lymphadenopathy;
- non-reducing varicocele;
- bilateral lower extremity oedema, which suggests venous involvement.

3.1.2 ***Laboratory findings***

The most commonly assessed laboratory parameters are serum creatinine, glomerular filtration rate, haemoglobin, erythrocyte sedimentation rate, alkaline phosphatase, lactate dehydrogenose (LDH), and serum corrected calcium (1,8,9) (LE: 4).

Separate bilateral renal function should be estimated in the following situations (10-12) (LE: 2b):

- When renal function is clinically important, e.g. in patients with a solitary kidney tumour or bilateral tumours;
- When renal function is compromised, as indicated by an increased concentration of serum creatinine;
- In patients at risk of future renal impairment from co-morbid disorders, e.g. diabetes, chronic pyelonephritis, renovascular disease, stone or renal polycystic disease.

3.2 Radiological investigations

Most renal tumours are diagnosed by abdominal ultrasound or CT performed for various reasons (LE: 4). Imaging can be used to classify renal masses into solid or cystic.

3.2.1 ***Presence of enhancement***

For solid renal masses, the most important criterion for differentiating malignant lesions is the presence of enhancement (13) (LE: 3). The traditional approach for detection and characterisation of renal masses is to use ultrasound, CT, or magnetic resonance imaging (MRI). Most renal masses can be diagnosed accurately by using imaging alone. Contrast-enhanced ultrasound can be helpful in specific cases (e.g. chronic renal failure with relative contraindication for iodinated or gadolinium contrast media (14-16) (LE: 3).

3.2.2 ***Computed tomography or magnetic resonance imaging***

Computed tomography or MRI are used to characterise a renal mass. Imaging must be performed both before and after administration of intravenous contrast material to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield unit (HU) readings from before and after contrast administration. A change of 20 HU or greater is strong evidence of enhancement (17) (LE: 3). To maximise differential diagnosis and detection, the evaluation should include images from the nephrographic phase, because this phase allows optimum depiction of renal masses that typically do not enhance to the same degree as renal parenchyma.

Abdominal CT allows diagnosis of RCC and provides information on:

- function and morphology of the contralateral kidney (10) (LE: 3);
- primary tumour extension with extrarenal spread;
- venous involvement;
- enlargement of locoregional lymph nodes;
- condition of adrenal glands and the liver (LE: 3).

Abdominal contrast-enhanced CT angiography is a useful tool in selected cases to obtain detailed information about the kidney vascular supply (18). If CT results are indeterminate, MRI may provide additional information to:

- demonstrate enhancement in renal masses;
- investigate locally advanced malignancy;
- investigate venous involvement if there is a badly defined extension of inferior vena cava tumour thrombus on CT scan (19-22) (LE: 3).

Magnetic resonance imaging is also indicated in patients with an allergy to intravenous contrast and in

pregnancy without renal failure (23,24) (LE: 3). Evaluation of the tumour thrombus can also be performed with Doppler ultrasound (25) (LE: 3).

*3.2.3 **Other investigations***

Renal arteriography and inferior venacavography have only a limited role in the work-up of selected patients with RCC (LE: 3). In patients with any sign of impaired renal function, an isotope renogram and total renal function evaluation should be considered in order to optimise the treatment decision, e.g. the need to preserve renal function (10-12) (LE: 2a). The true value of positron emission tomography (PET) in the diagnosis and follow-up of RCC remains to be determined and currently PET is not a standard investigation (26,27) (LE: 1b).

*3.2.4 **Metastatic RCC investigations***

Chest CT is the most accurate investigation for chest staging (25,28-34) (LE: 3). However, at the very least, routine chest radiography, as a less accurate alternative to chest CT imaging, must be done for metastatic evaluation (LE: 3). There is a consensus that most bone and brain metastases are symptomatic at diagnosis so that a routine bone or brain CT scan is not generally indicated (35,36). However, if indicated by clinical or laboratory signs and symptoms, other diagnostic procedures may be used, such as a bone scan, brain CT, or MRI (37,39) (LE: 3).

*3.2.5 **Bosniak classification of renal cystic masses***

For the evaluation of renal cystic masses, the Bosniak classification classifies renal cysts into five categories based on CR imaging appearance in an attempt to predict the risk of malignancy (38) (LE: 3). The Bosniak system also advocates treatment for each category (Table 4).

Table 4: The Bosniak classification of renal cysts (38**)**

Bosniak category	**Features**	**Work-up**
I	A simple benign cyst with a hairline-thin wall that does not contain septa, calcification, or solid components. It measures water density and does not enhance with contrast material.	Benign
II	A benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions of < 3 cm, which are sharply marginated and do not enhance.	Benign
IIF	These cysts might contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall can be seen. There may be minimal thickening of the septa or wall. The cyst may contain calcification that might be nodular and thick, but there is no contrast enhancement. There are no enhancing soft-tissue elements. This category also includes totally intrarenal, non-enhancing, high-attenuation renal lesions of ≥ 3 cm. These lesions are generally well-marginated.	Follow-up. A small proportion are malignant.
III	These lesions are indeterminate cystic masses that have thickened irregular walls or septa in which enhancement can be seen.	Surgery or follow-up. Malignant in > 50% lesions.
IV	These lesions are clearly malignant cystic lesions that contain enhancing soft-tissue components.	Surgical therapy recommended. Mostly malignant tumour.

3.3 Renal biopsy

Renal tumour biopsies are increasingly being used in diagnosis, in follow-up surveillance, and in ablative therapies (40-45) (LE: 3). In most series, a core biopsy demonstrates high specificity and high sensitivity for the presence of malignancy (40-44), though it should be noted that 10-20% of biopsies are non-conclusive.

Biopsy aims to determine eventual malignancy, type, and grade of the evaluated renal mass.
A percutaneous mass biopsy is rarely required for large renal masses scheduled for nephrectomy.
The positive predictive value of imaging findings is so high that a negative biopsy result does not alter management (45) (LE: 3).

Biopsy is also indicated in metastatic patients before starting systemic therapy (46) (LE: 3).

3.4 Histological diagnosis

The histological diagnosis in RCC is established after surgical removal of renal tumours or after biopsy specimen examinations (40-42). The Fuhrman classification system for nuclear grade (grade 1, 2, 3 and 4) in RCC (47,48) has been the most generally accepted classification, and is an important, independent prognostic factor for RCC (LE: 3).

According to the World Health Organization (WHO) (49) there are at least three major histological subtypes of RCC:

- clear cell (cRCC, 80-90%);
- papillary (pRCC, 10-15%);
- chromophobe (chRCC, 4-5%) (LE: 3).

These RCC types can be differentiated by histological and molecular genetic changes (Table 5) (LE: 3). Papillary RCC can further be divided into two different subtypes: type 1 and type 2 with an adverse clinical course (Table 5) (50,51) (LE: 3).

Table 5: Major histological subtypes of RCC

Histological subtype	Percentage of RCC	Histological description	Associated molecular genetic changes
Clear cell (cRCC)	80-90%	Most cRCC are composed predominantly of cells containing clear cytoplasm, although eosinophilic cytoplasm predominates in some cells. The growth pattern may be solid, tubular, and cystic.	Identified by the specific deletion of chromosome 3p and mutation of the VHL gene. Other changes are duplication of the chromosome band 5q22, deletion of chromosome 6q, 8p, 9p, and 14q.
Papillary (pRCC)	10-15%	Most pRCCs have small cells with scanty cytoplasm, but also basophilic, eosinophilic, or pail-staining characteristics. A papillary growth pattern predominates, although there may be tubular papillary and solid architectures. Necrotic areas are common. Papillary RCC can be divided into two different subtypes: type 1 with small cells and pale cytoplasm and type 2 with large cells and eosinophilic cytoplasm, the latter having a worse prognosis.	The most consistent genetic alterations are trisomies of chromosomes 3q, 7, 8, 12, 16, 17, and loss of the y chromosome.
Chromophobe (chRCC)	4-5%	The cells of chRCC may have pail or eosinophilic granular cytoplasm. Growth usually occurs in solid sheets.	The genetic characteristic is a combination of loss of chromosomes 1, 2, 6, 10, 13, and 17.

3.5 Conclusion

The proportion of small and incidental renal tumours has significantly increased in most countries, though a large number of patients with RCC still present with clinical symptoms, such as palpable mass, haematuria, and paraneoplastic and metastatic symptoms (LE: 3). Accurate staging of RCC with abdominal and chest CT or MRI is obligatory (LE: 3). Chest CT is the most sensitive approach for chest staging. There is no role for routine bone scan or CT of the brain in the standard clinical work-up of asymptomatic patients.

Recently, there has been an increasing indication for fine-needle biopsy for evaluation and ablative therapies in small renal tumours (40-45) (LE: 3).

3.6 Recommendations

	GR
In a patient with one or more laboratory or physical findings, the possible presence of RCC should be suspected.	B
A plain chest x-ray can be sufficient for assessment of the lung in low-risk patients, but chest CT is most sensitive.	A
Abdominal CT and MRI are recommended for the work-up of patients with RCC and are the most appropriate imaging modalities for Tumour Node Metastasis (TNM) classification prior to surgery.	A
In high-risk patients for bone metastases (raised alkaline phosphatase or bone pain), further evaluation using an imaging approach should be done.	A
Evaluation of renal function is recommended.	B
Percutaneous biopsy is always indicated before ablative- and systemic therapy without previous histopathology.	B
Percutaneous biopsy is recommended in surveillance strategies to stratify follow-up.	B

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4. CLASSIFICATION AND PROGNOSTIC FACTORS

4.1 Classification

The TNM stage classification system is generally recommended for clinical and scientific use (1). However, the TNM classification requires continuous improvements (2). The 2009 version has introduced significant changes based on recent prognostication literature (Table 6).

- The pT1 substratification, introduced in 2002, has been validated by several studies and is no longer a matter of controversy (3-5) (LE: 3). Even though it has been less extensively studied, the tumour size stratification of T2 tumours has been recently introduced within the 2009 TNM classification.
- Since the 2002 version of the TNM classification, tumours with renal sinus fat invasion have been classified as pT3a. However, accumulating data suggest that renal sinus fat invasion carries a worse prognosis than perinephric fat invasion and therefore should not be included in the same pT3a stage group (LE: 3) (6-8).
- Many studies have suggested that adrenal invasion has a very poor prognostic value and that RCCs with this feature should be classified as pT4 tumours (9,10) (LE: 3). This change has been introduced in the latest TNM version (1).
- In previous TNM classifications, the pT3b group included both renal vein and inferior vena cava invasions. As the result of many studies into the independent prognostic value of vena cava compared to renal vein invasion alone (11-13), these two groups have now been separated in the latest version of the TNM classification (1).
- The accuracy of the N1-N2 subclassification has been questioned (14) (LE: 3). For adequate M-staging of patients with RCC, accurate pre-operative imaging (currently, chest and abdominal CT) should be performed (15,16) (LE: 4).

4.2 Prognostic factors

Factors influencing prognosis can be classified into: anatomical, histological, clinical, and molecular.

*4.2.1 **Anatomical factors***

Anatomical factors include tumour size, venous invasion, renal capsule invasion, adrenal involvement, lymph node, and distant metastasis. These factors are commonly gathered together in the universally used TNM staging classification system (Table 6).

Table 6: The 2009 TNM staging classification system (1)

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 but ≤ 10 cm in greatest dimension
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 the diaphragm
	T3c	Tumour grossly extends into vena cava 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 1 regional lymph node	
M - Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	
TNM 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	N2 M0
	Any T	Any N M1

A help desk for specific questions about TNM classification is available at http://www.uicc.org/tnm.

*4.2.2 **Histological factors***

Histological factors include Fuhrman grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system. Fuhrman nuclear grade is the most widely accepted histological grading system in RCC (17). Although affected by intra- and inter-observer discrepancies, it is an independent prognostic factor (18). Recently, it has been suggested that a simplified two- or three-strata Fuhrman grading system could be as accurate as the classical four-tiered grading scheme (19,20) (LE: 3).

According to the WHO classification (21), three major histological subtypes of RCC exist: conventional (clear cell) (80-90%), papillary (10-15%) and chromophobe (4-5%). In univariate analysis, there is a trend towards a better prognosis for patients with chromophobe versus papillary versus conventional (clear cell) RCC (22,23). However, the prognostic information provided by the RCC subtype is lost when stratified to tumour stage (23,24) (LE: 3).

Among papillary RCCs, two subgroups with different outcomes have been identified (25):
Type 1 are low-grade tumours with a chromophilic cytoplasm and a favourable prognosis.
Type 2 are mostly high-grade tumours with an eosinophilic cytoplasm and a great propensity for developing metastases (LE: 3).

The RCC type classification has been confirmed at the molecular level by cytogenetic and genetic analyses (26-28) (LE: 2b).

*4.2.3 **Clinical factors***

Clinical factors include patient performance status, localised symptoms, cachexia, anaemia, and platelet count (29-32) (LE: 3).

*4.2.4 **Molecular factors***

Numerous molecular markers being investigated include: carbonic anhydrase IX (CaIX), vascular endothelial growth factor (VEGF), hypoxia inducible factor (HIF), Ki67 (proliferation), p53, PTEN (phosphatase and tensin homolog) (cell cycle), E-cadherin, and CD44 (cell adhesion) (33,34) (LE: 3). To date, none of these markers has been shown to improve the predictive accuracy of current prognostic systems and their use is therefore not recommended in routine practice. Finally, even though gene expression profiling seems a promising method, it has not helped so far to identify new relevant prognostic factors (35).

*4.2.5 **Prognostic systems and nomograms***

Post-operative prognostic systems and nomograms that combine independent prognostic factors have been developed and externally validated (36-42). These systems may be more accurate than TNM stage or Fuhrman grade alone for predicting survival (LE: 3). An important advantage of nomograms is their ability to measure predictive accuracy (PA), which enables all new predictive parameters to be objectively evaluated. Before being adopted, every new prognostic variable or system should be able to demonstrate that its PA is superior to conventional post-operative histo-prognostic schemes (43). Recently, new pre-operative nomograms with excellent PAs have been designed (44,45). Table 7 summarises the current most relevant prognostic systems.

4.3 Conclusion

In patients with RCC, TNM stage, nuclear grade according to Fuhrman, and RCC subtype (WHO, 2004; (21)), should be performed because they contribute important prognostic information (LE: 2). Prognostic systems should currently be used in a metastatic setting and are still investigational in localised disease (LE: 2).

4.4 Recommendations

	GR
The current TNM classification system is recommended because it has consequences for prognosis and therapy.	B
The Fuhrman grading system and classification of RCC subtype should be used.	B
A stratification system should be used in a metastatic setting for selecting the appropriate first-line treatment.	B
In localised disease, the use of integrated prognostic systems or nomograms is not routinely recommended, even though these systems can provide a rationale for enrolling patients into clinical trials.	B
No molecular prognostic marker is currently recommended for routine clinical use.	B

Table 7: Summary of the anatomical, histological, and clinical variables included in the most commonly used prognostic models for localised and metastatic RCC

Prognostic Models		Variables												
		TNM Stage	ECOG PS	Karnofsky PS	RCC related symptoms	Fuhrman grade	Tumor necrosis	Tumor size	Delay between diagnosis and treatment	LDH	Corrected calcium	Hemoglobin	Neutrophil count	Platelet count
Localised RCC	UISS	X	X			X								
	SSIGN	X				X	X	X						
	Post operative Karakiewicz's nomogram	X			X	X		X						
Metastatic RCC	MSKCC prognostic system			X					X	X	X	X		
	Heng's model			X					X		X	X	X	X

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status; RCC = renal cell carcinoma; SSIGN = Stage Size Grade Necrosis; TNM = tumour node metastasis; UISS = University of California Los Angeles integrated staging system.

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5. OTHER RENAL TUMOURS

Detailed morphological studies, which use contemporary immunohistochemical and molecular techniques, have resulted in the current classification of renal epithelial neoplasms, as outlined in the 2004 WHO monograph (1). The common clear cell (cRCC), papillary (pRCC) and chromophobe RCC (chRCC) types account for 85-90% of the renal malignancies. The remaining 10-15% of renal tumours include a variety of uncommon, sporadic, and familial carcinomas, some of which have recently been described, and a group of unclassified carcinomas.

5.1 Bellini duct carcinoma (collecting-duct carcinoma)

Collecting-duct carcinoma is a very rare type of RCC, often presenting at an advanced stage of disease. Up to 40% of patients have metastatic spread at initial presentation and most patients die within 1–3 years from the time of primary diagnosis. To date, the largest case series (n = 81) to consider outcome showed that regional lymph node metastases were present in 44% of patients at diagnosis and distant metastases were present in 32%. The survival rate was 48% at 5 years and 14% at 10 years (2-4).

5.2 Sarcomatoid RCC

Sarcomatoid RCC represents high-grade transformation in different RCC types, without being a distinct histological entity. Sarcomatoid changes in RCC carry a worse prognosis (5).

5.3 Unclassified RCC

Unclassified RCC is a diagnostic category for RCC that cannot be assigned to any other category of RCC-type carcinoma (1).

5.4 Multilocular cystic RCC (cRCC)

There are no strict histopathological criteria for this subtype. In the WHO 2004 classification (1), multilocular cRCC is an independent entity, but it is essentially a well-differentiated cRCC. This subtype accounts for up to about 3.5% of surgically treated kidney tumours (6). To date, metastases of this tumour have not been

described (6,7). According to the Bosniak classification, which is based on imaging criteria, multilocular cRCC presents as a Bosniak type II or III cystic lesion (8-10). However, this type of Bosniak lesion can also be due to a mixed epithelial and stromal tumour of the kidney (MESTK), a cystic nephroma, or a multilocular cyst, all of which are benign lesions. In many cases, a pre-operative biopsy and intra-operative frozen-section analysis does not lead to a correct diagnosis. Fortunately, all these tumours are treated with the same operative strategy. For this reason, if technically feasible, a nephron-sparing procedure is the procedure of choice for a complex multicystic renal mass with enhanced density is observed (LE: 3) (GR: B) (6,7,9,10).

5.5 Papillary adenoma

Papillary adenomas are tumours with papillary or tubular architecture of low nuclear grade and 5 mm in diameter or smaller (1). Because they are so small, they are only found incidentally in a nephrectomy specimen.

5.6 Renal medullary carcinoma

Renal medullary carcinoma is a devastating malignancy that primarily affects young men with sickle cell trait. It is also extremely rare, comprising approximately 2% of all primary renal tumours in young people aged 10 to 20 years old. Metastatic disease is seen at presentation in 95% of patients (2,11,12).

5.7 Translocation carcinoma

Renal translocation carcinomas are uncommon tumours, which usually occur in children and young adults. Most translocation carcinomas (about 90%) involve the transcription factor E3 (TFE3) located on Xp11.2 and seem to follow a relatively indolent course, despite often being at an advanced stage at presentation (2). Another rare group of RCCs that show a translocation (t (6; 11) (p21; q12)) has also been reported (2,13).

5.8 Mucinous tubular and spindle cell carcinoma

This tumour is associated with the loop of Henle. Most mucinous tubular and spindle-cell carcinomas behave in a low-grade fashion (1,2,14).

5.9 Carcinoma associated with end-stage renal disease

Cystic degenerative changes (acquired cystic kidney disease [ACKD]) and a higher incidence of RCC are typical features of ESKD (end-stage kidney disease). The incidence of ACKD is about 50% in patients undergoing dialysis, but also depends on the duration of dialysis, gender (three times more common in men), and the diagnostic criteria of the method of evaluation. RCCs of native end-stage kidneys are found in about 4% of patients. The lifetime risk of developing RCCs is at least 10 times higher than in the general population. Compared with sporadic RCCs, the RCCs associated with ESKD and ACKD are characterised by multicentricity and bilaterality, being found in younger patients (mostly male), and by less aggressive behaviour. In transplanted patients, however, it is usually quite aggressive, probably as a result of immunosuppression (15-20).

Although the histological spectrum of tumours within ACKD is similar to that in sporadic RCC, the most predominant form is pRCC, being found in 41-71% of ACKD-associated RCC versus 10% in sporadic RCC. The remaining tumours are mostly cRCC (2,19,20). Tickoo et al. (21) recently described two new renal tumours associated with ESKD: ‘acquired cystic disease-associated RCC‘ and ‘clear-cell pRCC‘. To date, these entities have not generally been accepted. The malignant potential of RCCs in ESKD is still a matter of discussion compared to sporadic RCCs. Patients with ESKD should undergo an annual ultrasound evaluation of the kidneys (16-19).

5.10 Metanephric tumours

Metanephric tumours are divided into metanephric adenoma, adenofibroma, and metanephric stromal tumour. These are very rare benign tumours and surgical excision is sufficient (1).

5.11 Renal epithelial and stromal tumours

Renal epithelial and stromal tumours (REST) is a new concept that brings together two benign mixed mesenchymal and epithelial tumours: cystic nephroma and mixed epithelial and stromal tumours (22). Imaging reveals that most REST cystic lesions are Bosniak type III and less frequently Bosniak type II or IV (8,10). Even though aggressive behaviour has been reported in very few cases, both neoplasms are generally considered to be benign and surgical excision as curative (22).

5.12 Oncocytoma

Renal oncocytomas are benign tumours (1) that comprise about 3-7% of all renal tumours (23). Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard (24). Although only a percutaneous biopsy can lead to a pre-

operative diagnosis, it has a low specificity for oncocytoma because oncocytotic cells are also found in cRCC, the granular-cell variant of RCC, and in the eosinophilic variant of pRCC (type 2) (25). 'Watchful waiting' can be considered in selected cases of histologically verified oncocytoma (LE: 3) (GR: C) (25,26).

5.13 Hereditary kidney tumours

Hereditary kidney tumours can be found as part of the following entities: Von Hippel-Lindau syndrome, hereditary pRCC, Birt-Hogg-Dubé syndrome, hereditary leiomyomatosis, tuberous sclerosis, and constitutional chromosome 3 translocation (1,27).

5.14 Mesenchymal tumours

Mesenchymal tumours include different types of sarcomas and are relatively rare, except for angiomyolipoma.

*5.14.1 **Angiomyolipoma***

Angiomyolipoma (AML) is a benign mesenchymal tumour composed of a variable proportion of adipose tissue, spindle and epitheloid smooth muscle cells, and abnormal thick-walled blood vessels. It can occur sporadically, which is four times more likely in women. It also occurs in tuberous sclerosis, when it is multiple, bilateral, larger, and likely to cause spontaneous haemorrhage. It accounts for approximately 1% of surgically removed tumours. Ultrasound, CT, and MRI often lead to diagnosis due to the presence of adipose tissue. Biopsy is rarely useful. Pre-operatively, it may be difficult to differentiate between tumours composed predominantly of smooth muscle cells and epithelial tumours. Epithelioid AML is a potentially malignant variant of AML (1).

The main complications of renal AML are retroperitoneal bleeding or bleeding into the urinary collection system, which can be life-threatening (28). The bleeding tendency is related to the angiogenic component of the tumour that includes irregular and aneurysmatic blood vessels (28). The major risk factors for bleeding are tumour size, the grade of angiogenic component of the tumour, and the presence of tuberous sclerosis (28,29).

Primary indications for intervention include symptoms such as pain, bleeding, or suspected malignancy. Prophylactic intervention is justifiable for:

- large tumours (the recommended threshold of intervention is ≥ 4 cm wide (28,30);
- females of childbearing age;
- patients in whom follow-up or access to emergency care may be inadequate (29) (LE: 3) (GR: C).

Most cases of AML can be managed by conservative nephron-sparing approaches, though some cases of AML may require complete nephrectomy (29) (LE: 3). Of the standard surgical interventions, selective arterial embolisation (SAE) and radiofrequency ablation (RFA) can be used (28,31). Although SAE is effective at controlling haemorrhage in the acute setting, it has limited value in the longer-term management of AML (31).

5.15 New histological entities

New histological entities have recently been described, for which there currently is very little clinical data. The entities include:

- thyroid-like follicular tumour/carcinoma of the kidney (32);
- RCC associated with neuroblastoma (1);
- renal angiomyoadenomatous tumour (33);
- tubulocystic carcinoma (34);
- clear cell pRCC (2);
- oncocytic pRCC (2);
- follicular renal carcinoma (2);
- leiomyomatous RCC (2).

Table 8: Summary of other renal tumours with indication of malignant potential and recommendation for treatment (GR: C)

Entity	Malignant potential	Treatment
Sarcomatoid variants of RCC	High	Surgery
Multilocular clear cell RCC	Low, no metastasis	Surgery, NSS*
Papillary adenoma	Benign	Observation
Carcinoma of the collecting ducts of Bellini	High, very aggressive	Surgery, in M+ discussable

Renal medullary carcinoma	High, very aggressive	Surgery
Translocation carcinoma	Intermediate	Surgery, NSS
Mucinous tubular and spindle cell carcinoma	Intermediate	Surgery, NSS
Carcinoma associated with end-stage renal disease	Variable	Surgery
Metanephric tumours	Benign	Surgery, NSS
Renal epithelial and stromal tumours (REST)	Low	Surgery, NSS
Oncocytoma	Benign	Observation/surgery
Hereditary kidney tumours	High	Surgery, NSS
Angiomyolipoma	Benign	Consider treatment when > 4 cm
Unclassified RCC	Variable	Surgery, NSS

**NSS = nephron-sparing surgery*

5.16 Summary

A variety of renal tumours exists, of which about 15% are benign. All kidney lesions have to be examined (e.g. imaging, biopsy, etc.) and judged regarding the likelihood of malignant behaviour.

5.17 Recommendations

	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 surgically treated. 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 when the tumour > 4cm. When possible, a nephron-sparing procedure should be performed.	3	C
In advanced uncommon types of renal tumours, a standardised oncological treatment approach does not exist.	4	C

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6. TREATMENT OF LOCALISED RCC

6.1 Nephron-sparing surgery (partial tumour resection)

Nephron-sparing surgery (partial tumour resection) for localised RCC has a similar oncological outcome to that of radical surgery (1-5). However, in some patients with localised RCC, nephron-sparing surgery is not suitable because of:

- locally advanced tumour growth;
- partial resection is not technically feasible because the tumour is in an unfavourable location;
- significant deterioration of a patient's general health.

In these situations, the gold standard curative therapy remains radical nephrectomy, which includes removal of the tumour-bearing kidney. Complete resection of the primary tumour by either open (6,7) or laparoscopic surgery (8-13) offers a reasonable chance of curing the disease.

*6.1.1 **Associated procedures***

6.1.1.1 Adrenalectomy

Adrenalectomy is not indicated in the following situations (14-22):

- Pre-operative tumour staging (CT, MRI) shows a normal adrenal gland;
- Intra-operative findings do not give any indication of a nodule within the adrenal gland suspicious of metastatic disease;
- There is no evidence of direct invasion of the adrenal gland by a large upper pole tumour.

6.1.1.2 Lymph node dissection

An extended or radical lymph node dissection does not appear to improve long-term survival following tumour nephrectomy (23). Thus, for staging purposes, the lymph node dissection can be limited to the hilar region. In patients with palpable or CT-detected enlarged lymph nodes, resection of the affected lymph nodes should be performed to obtain adequate staging information.

6.1.1.3 Embolisation

There is no benefit in performing tumour embolisation before routine nephrectomy (24-26). In patients who are unfit for surgery, or who present with non-resectable disease, embolisation can control symptoms such as gross haematuria or flank pain (27-31). Embolisation prior to the resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss (32-34). In selected patients with painful bone or paravertebral metastases, embolisation can help to relieve symptoms (35).

6.1.1.4 Conclusions

- Patients with low-stage RCC (T1) should undergo nephron-sparing surgery. Radical nephrectomy is no longer the gold standard treatment in these cases (1-5) (LE: 2b).
- Adrenalectomy is not recommended, provided a pre-operative CT scan shows the adrenal gland is normal and the intra-operative findings do not suggest intra-adrenal metastatic spread or a direct invasion of the adrenal gland by a larger upper pole tumour (14-22) (LE: 3).
- Extended lymphadenectomy does not improve survival in RCC patients and should be restricted to staging purposes with dissection of palpable and enlarged lymph nodes (23) (LE: 1b).
- RCCs with tumour thrombi have a higher stage and grade of disease (LE: 2b). Distant and lymph node metastases are twice as common in these patients (LE: 3). The increase in biological aggressiveness of the disease has a larger influence on clinical prognosis than the cranial extension of an intracaval thrombosis (36-40) (LE: 3).

6.1.1.5 Recommendations

	GR
Surgical therapy is the only curative therapeutic approach for the treatment of RCC. For T1 tumours, nephron-sparing surgery should be performed whenever possible. Extended lymphadenectomy does not improve survival and can be restricted to staging purposes.	A
Adrenalectomy (together with nephrectomy) is not needed in most patients, except when there is a large upper pole tumour and direct invasion of the adrenal gland is likely or when a normal adrenal gland cannot be excluded.	B
Embolisation can be a beneficial palliative approach in patients unfit for surgery and suffering from massive haematuria or flank pain.	C

6.1.2 ***Indications for nephron-sparing surgery***

Standard indications for nephron-sparing surgery are divided into the following categories:

- absolute – anatomical or functional solitary kidney;
- relative – functioning opposite kidney is affected by a condition that might impair renal function in the future;
- elective – localised unilateral RCC with a healthy contralateral kidney.

Relative indications include hereditary forms of RCC, which carry a high risk of developing a tumour in the contralateral kidney.

For elective indications, nephron-sparing surgery for tumours limited in diameter (T1a) provides recurrence-free and long-term survival rates similar to those observed after radical surgery (1-5,41,42) (LE: 2b). For larger tumours (T1b), partial nephrectomy has demonstrated feasibility and oncological safety in carefully selected patients (43-47).

6.1.3 ***Complications***

- The complication rates observed with nephron-sparing surgery are slightly higher but still very tolerable when compared with radical nephrectomy (48) (LE: 1b).
- Nephron-sparing surgery carried out for absolute rather than elective indications carries an increased complication rate and a higher risk of developing locally recurrent disease, probably due to the larger tumour size (49-51) (LE: 3).

6.1.4 ***Prognosis***

- In patients with a sporadic solitary renal tumour of up to 4-5 cm maximum diameter and a normal contralateral kidney, long-term renal function is better preserved with a nephron-sparing approach than with nephrectomy (52).
- There is a strong indication that, due to better preservation of renal function, nephron-sparing surgery

results in an improved overall survival when compared with radical nephrectomy (53-55) (LE: 3).
- If the tumour is completely resected, the thickness of the surgical margin does not impact on the likelihood of local recurrence (56-58) (LE: 3).

*6.1.5 **Conclusions***

- Nephron-sparing surgery has a slightly higher complication rate compared with radical surgery.
- However, nephron-sparing surgery is a safe procedure from the oncological point of view. Whenever technically feasible, nephron-sparing surgery is therefore considered to be the standard of care for T1a/b stage RCC (1-5,41-47).
- In the long term, a nephron-sparing approach results in improved preservation of renal function, decreased overall mortality, and reduced frequency of cardiovascular events (53-55).

*6.1.6 **Recommendations***

	GR
Whenever technically feasible, nephron-sparing surgery is the standard procedure for solitary renal tumours up to a diameter of 7 cm.	A
A minimal tumour-free surgical margin following partial resection of RCC is sufficient to avoid local recurrence.	B
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

6.2 Laparoscopic surgery

Since its introduction, laparoscopic nephrectomy for RCC has become an established surgical procedure worldwide. Whether done retro-peritoneally or trans-peritoneally, the laparoscopic approach must follow established open surgical oncological principles.

*6.2.1 **Laparoscopic radical nephrectomy***

Laparoscopic radical nephrectomy is the standard of care for patients with T2 tumours and smaller renal masses not treatable by nephron-sparing surgery (59-63). Long-term outcome data indicate that laparoscopic radical nephrectomy has equivalent cancer-free survival rates to those of open radical nephrectomy (10,12,13,61,62,64-68).

6.2.1.1 Conclusions

- Laparoscopic radical nephrectomy appears to have a lower morbidity compared to open surgery, though this is based on only a few studies using a standardised quality-of-life evaluation (69) (LE: 3).
- Tumour control rates appear equivalent for T1-T2 tumours (10,12,13,61,62,64-68) (LE: 3).

6.2.1.2 Recommendations

	GR
Laparoscopic radical nephrectomy is recommended in T2 renal cell cancer.	B
Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial resection is indicated.	B

*6.2.2 **Partial laparoscopic nephrectomy***

In experienced hands and selected patients, laparoscopic partial nephrectomy is an alternative to open nephron-sparing surgery. The optimal indication for laparoscopic nephron-sparing surgery is a relatively small and peripheral renal tumour (4).

During laparoscopic partial resection, the intra-operative ischaemia time is longer than with open partial nephrectomy (4,70,71). Long-term renal function depends on the duration of the intra-operative ischaemia time (72).

Laparoscopic nephron-sparing surgery has a higher complication rate compared to open surgery. However, the oncological outcome in available series with limited follow-up appears to be similar to the outcome achieved with open nephron-sparing surgery (4,73,74).

In patients with a solitary kidney, laparoscopic partial nephrectomy results in a prolonged warm ischaemia time and a higher complication rate. Temporary or permanent dialysis is more likely to be necessary (4,72,75).

6.2.2.1 *Robotic-assisted partial nephrectomy*

Robotic-assisted partial nephrectomy is a novel technique that is still undergoing evaluation (76-80).

6.2.2.2 *Conclusion*

Partial nephrectomy by laparoscopic surgery is technically feasible (LE: 2b).

6.2.3 ***Recommendations***

	GR
Open partial nephrectomy currently remains the standard of care.	C
Laparoscopic partial nephrectomy should be performed by experienced surgeons.	C
Open partial resection is recommended for renal masses in a solitary kidney.	C

6.3 Therapeutic approaches as alternative to surgery

6.3.1 ***Surveillance***

In patients presenting with small renal masses, who undergo active surveillance, there appears to be no correlation between local tumour progression and an increased risk of metastatic disease. Both short- and intermediate-term oncological outcomes indicate that it is an appropriate strategy to initially monitor small renal masses followed, if required, by treatment for progression (73,81,82).

6.3.2 ***Percutaneous approaches***

Suggested alternatives to the surgical treatment of RCC have included image-guided percutaneous and minimally invasive techniques, e.g. percutaneous RFA, cryoablation, microwave ablation, laser ablation, and high-intensity focused ultrasound ablation (HIFU) (LE: 2b).

Possible advantages of these and other techniques include reduced morbidity, out-patient therapy, and the ability to treat high-risk surgical candidates (LE: 2b).

Indications for minimally invasive techniques, including RFA, are:

- small, incidentally found, renal cortical lesions in elderly patients;
- patients with a genetic predisposition for developing multiple tumours;
- patients with bilateral tumours;
- patients with a solitary kidney at high risk of complete loss of renal function following surgical tumour resection (LE: 2b).

Contraindications to the above-mentioned procedures include:

- poor life expectancy of < 1 year;
- multiple metastases;
- low possibility of successful treatment due to size or location of tumour. In general, tumours > 3 cm or tumours in the hilum, near the proximal ureter or the central collecting system are not typically recommended for ablative techniques via a percutaneous approach.

Absolute contraindications include:

- irreversible coagulopathies;
- severe medical instability, such as sepsis.

6.3.2.1 *Radiofrequency ablation and cryoablation*

Of all the available ablative techniques, RFA and cryoablation are the most intensively investigated approaches in terms of how practical they are to use, complication rate, and oncological safety.

Before an ablative approach, a pre-treatment biopsy to clarify the histology of the renal mass should be carried out. The available literature indicates that the pathology is unknown in a significantly higher proportion of patients undergoing RFA (40%) versus 25% in patients undergoing cryotherapy.

Compared to RFA, cryoablation is more likely to be performed laparoscopically. The laparoscopic approach is more effective but has a higher complication rate. Repeat ablation is necessary more frequently following RFA. Local tumour progression is significantly higher with RFA. Cancer-specific survival rates for cryotherapy and RFA are poorer than survival rates for surgical procedures (83-86).

6.3.2.2 *Conclusions*

- Radiofrequency and cryoablation are the only minimally invasive approaches for the treatment of small renal tumours with medium follow-up data.

- Although the oncological efficacy is not yet known, currently available data strongly suggest that cryoablation, when performed laparoscopically, results in fewer re-treatments and improved local tumour control compared with RFA (LE: 3).
- For both RFA and cryoablation, recurrence rates are higher than with nephron-sparing surgery (83-86) (LE: 3).

6.3.2.3 Recommendations

	GR
Patients with small tumours and/or significant co-morbidity who are unfit for surgery should be considered for an ablative approach, e.g. cryotherapy and radiofrequency ablation.	A
Pre-treatment biopsy has to be carried out as standard.	C
Other image-guided percutaneous and minimally invasive techniques, such as microwave ablation, laser ablation, and high-intensity focused ultrasound ablation are still experimental in character. The experience obtained with radiofrequency ablation and cryoablation should be considered when using these related techniques.	B

6.4 Adjuvant therapy

Current evidence that adjuvant tumour vaccination might improve the duration of the progression-free survival of selected subgroups of patients undergoing nephrectomy for T3 renal carcinomas needs further confirmation regarding the impact on overall survival (87-91) (LE: 1b). Prognostic algorithms might identify patients likely to derive the largest clinical benefit from adjuvant vaccination therapy.

*6.4.1 **Conclusion***

Adjuvant therapy with cytokines does not improve survival after nephrectomy (LE: 1b).

*6.4.2 **Recommendation***

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

6.5 Surgical treatment of metastatic RCC (tumour nephrectomy)

Tumour nephrectomy is curative only if surgery can excise all tumour deposits. For the majority of patients with metastatic disease, tumour nephrectomy is palliative and other systemic treatments are necessary. In a meta-analysis of two randomised studies, comparing nephrectomy combined with immunotherapy versus immunotherapy only, an increased long-term survival was found in patients subjected to tumour nephrectomy (92). Nephrectomy in patients with metastatic disease is indicated for patients who are both suitable for surgery and have good performance status (93). At present, only limited data are available addressing the value of cytoreductive nephrectomy combined with targeting agents.

*6.5.1 **Conclusion***

Tumour nephrectomy in combination with interferon-alpha (IFN-alpha) improves the survival of patients with metastatic RCC (mRCC) and good performance status (LE: 1b).

*6.5.2 **Recommendation***

	GR
Tumour nephrectomy is recommended for metastatic RCC patients with good performance status when combined with IFN-alpha.	A

6.6 Resection of metastases

Complete removal of metastatic lesions contributes to an improvement of clinical prognosis. Immunotherapy, where there has been complete resection of metastatic lesions or isolated local recurrences, does not contribute to an improvement in clinical prognosis (93-97) (LE: 2b).

*6.6.1 **Conclusion***

There is a definite role for metastasectomy in patients with RCC in order to improve the clinical prognosis

(LE: 3). Therefore; the possibility of metastasectomy has to be continuously re-evaluated, even together with a targeted systemic therapy.

6.6.2 ***Recommendation***

	GR
In patients with synchronous metastatic spread, metastasectomy should be performed where disease is resectable and the patient has a good performance status. The clinical prognosis is worse in patients who have surgery for metachranous metastases.	B
Metastasectomy should be performed in patients with residual and resectable metastatic lesions previously responding to immunotherapy and/or a limited (solitary lesion) number of metachranous metastases in order to improve the patient's prognosis.	B

6.7 Radiotherapy for metastases in RCC

Radiotherapy can be used for selected symptomatic patients with non-resectable brain or osseous lesions who do not respond to systemic treatment approaches (98,99).

6.7.1 ***Conclusion***

Radiotherapy of metastases from RCC can induce a significant relief from symptoms with pain reduction, e.g. a single bony deposit (LE: 2b).

6.7.2 ***Recommendation***

	GR
In individual cases, radiotherapy for the treatment of brain metastases (whole brain irradiation or stereotactic approach) and osseous lesions can induce a relief from symptoms due to mRCC (100,101).	B

6.8 References

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7. SYSTEMIC THERAPY FOR METASTATIC RCC

7.1 Chemotherapy

Since RCCs develop from the proximal tubules, they have high levels of expression of the multiple-drug resistance protein, P-glycoprotein, and are therefore resistant to most chemotherapies. Chemotherapy seems to be moderately effective only if 5-fluorouracil (5FU) is combined with immunotherapeutic agents (1).

*7.1.1 **Conclusion***

Only 5FU in combination with immunotherapy seems to be effective in patients with mRCC (LE: 3).

Recommendation

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

7.2 Immunotherapy

*7.2.1 **Interferon-alpha monotherapy and combined with bevacizumab***

In randomised studies, IFN-alpha has proven superiority for survival over hormonal therapy in patients with mRCC (2). Interferon-alpha provided a response rate of 6-15%, together with a 25% decrease in the risk for tumour progression and a modest survival benefit of 3-5 months compared with a placebo-equivalent (3,4). The positive effect of IFN-alpha is particularly important in mRCC patients with clear-cell histology, good-risk Motzer criteria and lung metastases only (4). In a prospective randomised study, IFN-alpha showed equivalence in efficacy to the combination IFN-alpha + IL2 + 5FU (5).

A combination of bevacizumab + IFN-alpha recently demonstrated increased response rates and progression-free survival in first-line therapy compared to IFN-alpha monotherapy (6). All recent randomised studies comparing anti-angiogenic drugs in a first-line setting to IFN-alpha monotherapy have demonstrated a superiority for either sunitinib, bevacizumab + IFN-alpha or temsirolimus (6-9).

Table 9: MSKCC (Motzer) criteria to predict survival of patients with advanced RCC; depending on the presence or absence of 5 distinct risk factors (3)

Risk factors[1]	Cut Point Used
Karnofsky performance status	< 80
Time from diagnosis to treatment with IFN-alpha	< 12 months
Hemoglobin	< Lower limit of laboratory's reference range
Lactate dehydrogenase	> 1.5 x the upper limit of laboratory's range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)

[1]Favourable (low) risk, 0 risk factor; intermediate, 1-2 risk factors; poor (high) risk ≥ 3 risk factors.

7.2.1.1 Conclusions

- Interferon-alpha monotherapy is no longer recommended as first-line therapy for mRCC (LE: 1b).
- Interferon-alpha monotherapy still has a role only in selected cases (good performance status, clear-cell type, lung metastases only) (LE: 2).

*7.2.2 **Interleukin-2***

Interleukin-2 (IL-2) has been used to treat mRCC since 1985 with response rates ranging from 7-27% (9-11).

The optimal IL-2 regimen is not clear, but long-term (> 10 years) complete responders have been achieved with high-dose bolus IL-2 (12). The toxicity of IL-2 is substantially higher than that of IFN-alpha. Only clear cell type RCC responds to immunotherapy. Interleukin-2 has not been validated in controlled randomised studies compared with best supportive care (4).

7.2.2.1 Conclusions

- Interleukin-2 has more side-effects than INF-alpha.
- High-dose IL-2 gives durable complete responders in a limited number of patients.
- Interleukin-2 can be considered as monotherapy in selected patients with a good prognosis profile.

7.2.2.2 Recommendations

	GR
Monotherapy with IFN-alpha or high-dose bolus IL-2 can only be recommended as a first-line treatment for mRCC in selected cases with clear-cell histology and good prognostic factors.	A
Bevacizumab + IFN-alpha is recommended as first-line therapy in low- and intermediate-risk patients. Only selected patients with mRCC, revealing a good risk profile, and clear-cell subtype histology, show clinical benefit from immunotherapy with IL-2.	B
Cytokine combinations, with or without additional chemotherapy, do not improve overall survival compared with monotherapy.	A

7.3 Angiogenesis inhibitor drugs

Recent advances in molecular biology have led to the development of several novel agents for the treatment of mRCC (Table 9).

In sporadic clear cell RCC, HIF accumulation due to von Hippel Landau (VHL) inactivation, results in overexpression of VEGF and PDGF (platelet-derived growth factor), both of which promote neo-angiogenesis (13-15). This process substantially 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:

- sorafenib (Nexavar®);
- sunitinib (Sutent®);
- bevacizumab (Avastin®) combined with IFN-alpha;
- pazopanib (Votrient®);
- temsirolimus (Torisel®);
- everolimus (Afinitor®).

Several other new agents targeting angiogenesis are under investigation, as well as combinations of these new agents with each other or with cytokines.

*7.3.1 **Sorafenib***

Sorafenib is an oral multikinase inhibitor with activity against Raf-1 serine/threonine kinase, B-Raf, vascular

endothelial growth factor receptor-2 (VEGFR-2), platelet-derived growth factor receptor (PDGFR), FMS-like tyrosine kinase 3 (FLT-3) and c-KIT. A phase III trial compared sorafenib and placebo after failure of a prior systemic immunotherapy or in patients unfit for immunotherapy. The trial reported a 3-month improvement in progression-free survival in favour of sorafenib (16). Survival seems to improve in patients crossed over from placebo to sorafenib treatment (17).

7.3.2 ***Sunitinib***

Sunitinib is an oxindol tyrosine kinase (TK) inhibitor. It selectively inhibits PDGFR, VEGFR, c-KIT and FLT-3 and has anti-tumour and anti-angiogenic activity. Phase II trials with sunitinib as second-line monotherapy in patients with mRCC demonstrated a partial response rate in 34-40% of patients and stable disease > 3 months in 27-29% of patients (18).

In a recent phase III trial of first-line monotherapy comparing treatment with sunitinib versus IFN-alpha, sunitinib achieved a longer progression-free survival than IFN-alpha (11 versus 5 months, $p < 0.000001$). Results suggested monotherapy with IFN-alpha was inferior compared to sunitinib in low- and intermediate-risk patients with mRCC (19). Overall survival was 26.4 and 21.8 months in the sunitinib and IFN-alpha arms, respectively ($p = 0.05$) (19). In patients crossed over from IFN-alpha to sunitinib ($n = 25$), median survival times were 26.4 versus 20.0 months for sunitinib and IFN-alpha, respectively ($p = 0.03$). In patients who did not receive any post-study treatment, the median overall survival reached 28.1 months in the sunitinib group versus 14.1 months in the IFN-alpha group ($p = 0.003$).

7.3.3 ***Bevacizumab monotherapy and combined with interferon-alpha***

Bevacizumab is a humanised monoclonal antibody that binds isoforms of VEGF-A. Bevacizumab, 10 mg/kg every 2 weeks, in patients refractory to immunotherapy showed an increase in overall response (10%) and in progression-free survival versus placebo (20). A recent double-blind phase III trial ($n = 649$) in mRCC compared bevacizumab + IFN-alpha to IFN-alpha monotherapy (6). The median overall response was 31% in the bevacizumab + IFN-alpha group versus 13% in the IFN-alpha-only group ($p < 0.0001$). Median progression-free survival increased significantly from 5.4 months with IFN-alpha to 10.2 months for bevacizumab + IFN-alpha ($p < 0.0001$), but only in low-risk and intermediate-risk patients. No benefit was seen in high-risk patients. No mature data are yet available on overall survival.

7.3.4 ***Pazopanib***

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-KIT. In a prospective randomised trial of pazopanib versus placebo in treatment-naïve mRCC patients and cytokine-treated patients, there was a significant improvement in progression-free survival and tumour response (9.2 vs 4.2 months) (20).

7.3.5 ***Mammalian target of rapamycin (mTOR) inhibitors***

7.3.5.1 Temsirolimus

Temsirolimus is a specific inhibitor of mammalian target of rapamycin (mTOR) (21). Patients with high-risk mRCC were randomised to receive first-line treatment with temsirolimus or IFN-alpha monotherapy or in combination. In the temsirolimus group, overall survival was 10.9 months versus 7.3 months in the IFN-alpha group ($p < 0.0069$). However, overall survival in the temsirolimus + IFN-alpha group was not significantly improved (8).

7.3.5.2 Everolimus

Everolimus is an oral mTOR inhibitor. A recent phase III study compared everolimus plus best supportive care (BSC) versus placebo plus BSC in patients who had failed previous anti-VEGFR treatment. Median progression-free survival was 4 months with everolimus versus 1.9 months with placebo ($p < 0.001$) (13,22).

Table 10: 2010 EAU evidence-based recommendations for first- and second-line systemic therapy in mRCC

Treatment	Risk or prior treatment	Recommended agent
1st-line therapy	Low- or intermediate-risk	Sunitinib
		Bevacizumab + IFN-alpha
		Pazopanib
	High risk	Temsirolimus
2nd-line therapy	Prior cytokine	Sorafenib
		Pazopanib
	Prior VEGFR	Everolimus
	Prior mTOR(-)	Clinical trials

7.3.6 Conclusions

	LE
Tyrosine kinase inhibitors (TKIs) increase progression-free survival and or overall survival as both first- and second-line treatment of mRCC.	1b
Sorafenib has proven efficacy as second-line treatment after failure of cytokine therapy or in patients unfit for cytokines.	1b
Sunitinib is more effective than IFN-alpha in treatment-naïve, low- and intermediate-risk tumours.	1b
The association between bevacizumab and IFN-alpha is more effective than IFN-alpha in treatment-naïve, low- and intermediate-risk tumours.	1b
Pazopanib is superior to placebo in both naïve mRCC patients as post-cytokine patients.	1b
Temsirolimus monotherapy in poor-risk mRCC patients is more effective than IFN-alpha or temsirolimus + IFN-alpha.	1b
Everolimus prolongs progression-free survival in patients who have failed treatment with TKIs.	
The role of the new drugs is still under development and combination studies are ongoing. To date, no data are available indicating the new agents have a curative effect. These agents appear to promise to stabilise mRCC for a prolonged period of time. However, their promise has to be balanced against their toxicity profile and the patient's quality of life.	4

7.3.7 Recommendations for systemic therapy for mRCC

Recommendations	GR
Sunitinib is recommended as first-line therapy in low- and intermediate-risk patients.	A
Bevacizumab + IFN-alpha is recommended as first-line therapy in low- 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 and after cytokine failure.	A
Temsirolimus is recommended as first-line treatment in high-risk patients.	A
Everolimus is recommended as second-line treatment after failure of tyrosine kinase inhibitors.	A

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8. SURVEILLANCE FOLLOWING RADICAL OR PARTIAL NEPHRECTOMY OR ABLATIVE THERAPIES FOR RCC

8.1 Introduction

Surveillance after treatment for RCC allows the urologist to monitor or identify:

- post-operative complications;
- renal function;
- local recurrence after partial nephrectomy or ablative treatment;
- recurrence in the contralateral kidney;
- development of metastases.

The method and timing of investigation has been the subject of many publications. There is no consensus on surveillance after treatment for RCC and in fact no evidence that early versus later diagnosis of recurrence improves survival. However, follow-up is important to increase our knowledge of RCC and should be performed by the urologist, who should record the time elapsed to recurrence or development of metastasis.

Post-operative complications and renal function are readily assessed by history, physical examination and measurement of serum creatinine and estimated glomerular filtration rate (eGFR). Repeated long-term monitoring of eGFR is indicated if there is impaired renal function before surgery or a post-operative deterioration. Renal function (1,2) and non-cancer survival (3-5) can be optimised by performing nephron-sparing surgery whenever possible for T1 and T2 tumours (6) (LE: 3). Tumour-bed recurrence is rare (2.9%), but early diagnosis is useful because the most effective treatment is cytoreductive surgery (7,8). Recurrence in the contralateral kidney is also rare (1.2%) and is related to positive margins, multifocality and grade (9) (LE: 3).

The reason for surveillance is to identify local recurrence or metastases early. This is particularly important with ablative therapies, such as cryotherapy and RFA. Even though the local recurrence rate is higher than conventional surgery, the patient may still be cured by repeat ablative therapy or radical nephrectomy (10) (LE: 3). 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 may enhance the efficacy of a systemic treatment if the tumour burden is low.

8.2 Which investigations for which patients, and when?

Intensive radiological surveillance for all patients is unnecessary. For example, the outcome after surgery for T1a, low-grade, tumours is almost always excellent. It is therefore reasonable to stratify follow-up, taking into account the risk of a recurrence or metastases developing. Although no randomised evidence exists, there are large studies examining prognostic factors with long follow-up from which some conclusions can be drawn (11-13) (LE: 4).

- When the likelihood of relapse is low, chest x-ray and ultrasound may be appropriate. However, the sensitivity of chest x-ray for small metastases is poor and ultrasound has limitations.
- When the risk of relapse is intermediate or high, CT of the chest and abdomen is the investigation of choice, though the significant morbidity of radiation dose with repeated CT scans should be taken into account (14).

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. There is controversy over the optimal duration of follow-up. Some argue that follow-up by imaging is not cost-effective after 5 years; however, late metastases are more likely to be solitary and justify more aggressive therapy with curative intent. In addition, patients with tumours that develop in the contralateral kidney can be treated with nephron-sparing surgery if detected when small. Furthermore, for tumours < 4 cm, there is no difference between partial or radical nephrectomy in recurrence during follow-up (15) (LE: 3).

Several authors, notably Kattan, Liebovich, UCLA, and Karakiewicz (16-19), have designed scoring systems and nomograms to quantify the likelihood of patients developing tumour recurrence, metastases, and subsequent death. These systems have been compared and validated (20) (LE: 2). Using prognostic variables, several stage-based surveillance regimes have been proposed (21,22), but these do not include ablative therapies. A post-operative nomogram is available to give the likelihood of freedom from recurrence at 5 years (23). Most recently, a pre-operative prognostic model based on age, symptoms, and TNM staging has been published and validated (24) (LE: 3). There is therefore a need for a surveillance algorithm to monitor patients

after treatment for RCC, recognising not only the patient risk profile, but also the efficacy of the treatment given (Table 11).

Table 11: Proposed algorithm for surveillance following treatment for RCC taking into account patient risk profile and treatment efficacy

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

RN = radical nephrectomy; PN = partial nephrectomy; CXR = chest x-ray; US = ultrasound of kidneys and renal bed; CT = computed tomography of chest and abdomen; cyro = cryotherapy; RFA = radiofrequency ablation.

8.3 Conclusions

Surveillance after treatment for RCC should be based on a patient's risk factors and the type of treatment delivered. The aim of surveillance is to detect either local recurrence or metastatic disease while the patient is still surgically curable.

- For low-risk disease, the use of CT can be infrequent (LE: 4).
- In the intermediate-risk group, an intensified follow-up that includes CT scans at regular time intervals should be performed according to a risk-stratified nomogram (LE: 4).
- In high-risk patients, the follow-up examinations should include routine CT scans (LE: 4).

8.4 Recommendation

	GR
The intensity of the follow-up programme for an individual patient should be adapted according to the risk of tumour recurrence and the type of treatment.	C

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9. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

ACKD	acquired cystic kidney disease
AML	Angiomyolipoma
5FU	5-fluorouracil
BSC	best supportive care
CaIX	carbonic anhydrase IX
cRCC	clear cell renal carcinoma
chRCC	chromophobe renal cell carcinoma
CT	computed tomography
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
FLT-3	FMS-like tyrosine kinase 3
GR	grade of recommendation
HIF	hypoxia inducible factor
HIFU	high-intensity focused ultrasound
HU	Hounsfield unit
IFN-alpha	interferon-alpha
IL-2	interleukin-2
LDH	lactate dehydrogenase
LE	level of evidence
MESTK	mixed epithelial and stromal tumour of the kidney
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NSS	nephron-sparing surgery
PA	predictive accuracy
pRCC	papillary renal cell carcinoma
RCC	renal cell carcinoma
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PET	positron emission tomography
PTEN	phosphatase and tensin homolog
REST	Renal epithelial and stromal tumours
RFA	radiofrequency ablation
SAE	selective arterial embolisation
TFE3	transcription factor E3
TK	tyrosine kinase
TKI	Tyrosine kinase inhibitors
TNM	Tumour Node Metastasis
US	abdominal ultrasound
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	von Hippel-Lindau
WHO	World Health Organization

Conflict of interest

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