

# Guidelines on Renal Cell Carcinoma

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# 1. METHODOLOGY

## 1.1 Introduction

The European Association of Urology (EAU) Renal Cell Cancer (RCC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of renal cell cancer. The RCC panel is an international group consisting of clinicians with particular expertise in this field of urological care.

The guideline update methodology is detailed below. For a substantial portion of the text, the evidence base has been upgraded. The aim is to progress this further in the years to come. The Panel adopted Cochrane methodology in undertaking systematic reviews in 2011, with the aim of ensuring that the evidence synthesis can be performed in a robust, standardised, transparent and reproducible manner. For the 2014 update, the Panel has proceeded with the systematic review work in a step-wise fashion. The majority of sections have been updated based on a systematic review; however, it was not possible to replicate this for all sections. As a result, a few sections of the document have been updated following a structured literature assessment, as shown in Table 1.1. The focus for the next two years is to proceed with the systematic review work, aiming for the complete guidelines document to be based on systematic reviews, which represent the highest possible level of data work-up.

The panel is most grateful for the scientific support provided by:

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- Dr. T. Adewuyi, Aberdeen, UK: (systematic review - Systemic therapy for metastatic disease and providing general assistance for various aspects of the systematic review work);
- Dr. H. Bekema, Groningen (NL): (systematic review - Lymph node dissection in localised and locally advanced RCC);
- Dr. F. Stuart, Aberdeen (UK): (systematic review - Tumour thrombus)
- Prof. Dr. A. Graser, radiologist, Munich (DE): (development of a systematic review for the diagnosis and follow-up chapters [in progress]).

## 1.2 Methodology

### 1.2.1 Data identification

All chapters of the 2014 RCC Guidelines publication have been updated. As mentioned above, the consistency of the data work-up will differ between sections. An overview is presented in Table 1.1.

**Table 1.1: Description of update and summary of review methodology for 2014**

Chapter	Brief description of review methodology
1. Introduction	Not applicable
2. Epidemiology and aetiology	The chapter has been updated using a structured data assessment
3. Diagnosis and staging	The chapter has been updated using a systematic review on tumour biopsy and a traditional narrative review for the other aspects of diagnosis and staging
4. Classification and prognostic factors	The chapter has been updated using a structured data assessment
5. Other renal tumours	The chapter has been updated using a traditional narrative review, based on a structured literature search. Of particular note is the inclusion of the new Vancouver Classification in the Histology section (3.4).
6. Treatment of localised disease	The chapter has been updated using a systematic review, in part based on a literature search from 2000. A new section, 'Management of RCC with venous thrombus' has been added which is based on a systematic review.
7. Systemic therapy for metastatic disease	The chapter has been updated using a systematic review.
8. Surveillance following radical or partial nephrectomy or ablative therapies	This chapter was updated based on a traditional narrative review, based on a structured data search.

For the parts of the guideline that have been updated by way of a systematic review, the review methodology is outlined in detail elsewhere (1). In brief, a systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2). Important topics and questions were prioritised by the panel for the present update. Elements for inclusion and exclusion, including patient population, intervention, comparison, outcomes, study design, and search terms and restrictions were developed using an iterative process involving all members of the panel, to achieve consensus. Individual literature searches were conducted separately for each update question, and in most instances the search was conducted up to the end of November 2013. Two independent reviewers screened abstracts and full texts, carried out data abstraction and assessed risk of bias. The results were presented in tables showing baseline characteristics and summaries of findings. Meta-analyses was performed only for randomised controlled trials (RCTs) if consistency and homogeneity of data were demonstrated. When this was not possible, a narrative synthesis of the evidence was provided instead.

The remaining parts of the guideline have been updated using a traditional narrative review strategy. Structured literature searches using an expert information specialist were designed. Searches were carried out in the Cochrane Database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, and 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 (i.e. from 2011 onwards). An update search was carried out before the publication of this document. Other data sources were also consulted, such as the Database of Abstracts of Reviews of Effectiveness (DARE), as well as relevant reference lists from other guidelines producers such as the National Institute for Clinical Excellence (NICE) and the American Urological Association (AUA).

The majority of included studies in this guideline update are retrospective analyses that include some larger multicentre studies and well-designed controlled studies. As only a few RCTs are available, most of the data is not based on high levels of evidence. Conversely, in the systemic treatment of metastatic RCC, a number of randomised studies have been performed, resulting in more reliable recommendations based on higher levels of evidence.

### 1.3 Level of evidence and grade of recommendation

References in the text have been assessed according to their level of scientific evidence (Table 1.2), and guideline recommendations have been graded (Table 1.3) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (3). The purpose of grading is to correlate the underlying evidence with the recommendation given and to provide transparency.

**Table 1.2: 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.

\* Adapted from (3).

It should be noted that when recommendations are graded, the link between the level of evidence (LE) and the grade of recommendation (GR) is not directly linear. The availability of RCTs may not necessarily translate into a grade A recommendation when there are methodological limitations or disparities in the published results.

Conversely, an absence of a high level of evidence does not necessarily preclude a grade A recommendation if there is overwhelming clinical experience and consensus, or a dramatic magnitude of effect based on non-randomised studies. There may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical or other reasons, and in this case unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as “upgraded based on panel consensus.” The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences, and costs when a grade is assigned (4-6).

The EAU Guidelines Office does not perform structured cost assessments, nor can it address local/national preferences in a systematic fashion. But whenever these data are available, the expert panel will include the information.

**Table 1.3: Grade of recommendation\***

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency that addressed the specific recommendations, 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.

\* Adapted from (3).

#### **1.4 Publication history**

The EAU Renal Cell Cancer Guidelines were first published in 2000, with subsequent updates in 2001 (limited update), 2002 (limited update), and 2006 (full update), and partial updates in 2007, 2008, 2009, 2010 and 2013. This current 2014 document presents a full-text update.

A quick reference guide presenting the main findings of the Renal Cell Cancer Guidelines is also available (Pocket Guidelines), as well as a number of scientific publications in the EAU journal, European Urology (7-9). All of the texts can be viewed and downloaded for personal use at the EAU website: <http://www.uroweb.org/guidelines/online-guidelines/>.

The RCC panel recognises that there is a constant need to re-evaluate the published evidence for most topics; as such for the next update, scheduled for 2015, the Panel will focus on performing systematic reviews on topics which were assessed by other means for the current guideline update.

#### **1.5 Future goals**

In addition to further systematic data work-up, the RCC panel intend to focus on patient-reported outcomes, and invite a patient representative to take part in their guidelines development.

The use of clinical quality indicators is an area of interest. A number of key quality indicators for this patient group have been selected:

1. The use of CT thorax for staging of pulmonary metastasis.
2. Proportion of patients with T1aN0M0 tumours undergoing nephron sparing surgery as first treatment.
3. The proportion of patients treated within 6 weeks after diagnosis.
4. The proportion of patients with metastatic RCC that are offered treatment with targeting agents.
5. Proportion of patients who undergo minimally invasive or operative treatment as first treatment who die within 30 days.

#### **1.6 Potential conflict of interest statement**

The members of the expert Panel have submitted potential conflict of interest statements, which can be viewed on the EAU website: <http://www.uroweb.org/guidelines/>.

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## 2. EPIDEMIOLOGY AND AETIOLOGY

Renal cell carcinoma (RCC) 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 2012, there were approximately 84,400 new cases of RCC and 34,700 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 in men over women, with peak incidence occurring between 60 and 70 years of age. Aetiological factors include lifestyle 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). A number of other factors have been suggested to be associated with higher or lower risk of RCC, but these have not been confirmed. These include specific dietary habits and occupational exposure to specific carcinogens, but results in the literature are inconclusive (13,14). Moderate alcohol consumption appears to have a protective effect for reasons not yet known (15,16). The most effective prophylaxis is to avoid cigarette smoking and reduce obesity.

Due to the increased detection of tumours by imaging techniques such as ultrasound (US) and computed tomography (CT), the number of incidentally diagnosed RCCs has increased. These tumours are more often smaller and of lower stage (17-19).

### 2.1 Conclusion and recommendation

Conclusion	LE
Several verified risk factors have been identified including smoking, obesity and hypertension. These factors can be considered as definite risk factors for RCC.	2a

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

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## 3. DIAGNOSIS AND STAGING

### 3.1 Symptoms

Many renal masses remain asymptomatic until the late stages of the disease. Currently, more than 50% of RCCs are detected incidentally when non-invasive imaging is used to investigate a variety of nonspecific symptoms and other abdominal diseases (1,2) (LE: 3). The classic triad of flank pain, gross haematuria, and palpable abdominal mass is now rare (6-10%) and correlates with aggressive histology and advanced disease (3,4) (LE: 3).

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs (Table 3.1) (LE: 4). A few symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough (5) (LE: 3).

**Table 3.1. Most common paraneoplastic syndromes**



#### 3.1.1 Physical examination

Physical examination has only a limited role in the diagnosis of RCC. However, the following findings should prompt radiological examinations:

- Palpable abdominal mass;
- Palpable cervical lymphadenopathy;
- Non-reducing varicocele and 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 (GFR), complete cell blood count, erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium (6,7), coagulation study, and urinalysis (LE: 4).

If there are central renal masses abutting or invading the collecting system, urinary cytology and possibly endoscopic assessment of the upper urinary tract should be considered in order to rule out the presence of urothelial cancer (LE: 4).

Split renal function should be estimated using renal scintigraphy in the following situations (8,9) (LE: 2b):

- when renal function is compromised, as indicated by an increased concentration of serum creatinine or a significantly decreased GFR;
- when renal function is clinically important - e.g., in patients with a solitary kidney or multiple or bilateral tumours (as in the hereditary forms of RCC).

Renal scintigraphy is an additional diagnostic option in patients who are at risk of future renal impairment due to comorbid disorders - e.g. diabetes, severe hypertension, chronic pyelonephritis, renovascular disease, urinary stones, or renal polycystic disease.

### 3.2 Imaging investigations

Most renal tumours are diagnosed when abdominal US or CT are carried out for other medical reasons (LE: 3) (1). Renal masses can be classified as solid or cystic on the basis of the imaging findings.

#### 3.2.1 Presence of enhancement

With solid renal masses, the most important criterion for differentiating malignant lesions is the presence of enhancement (10) (LE: 3). The traditional approach for detecting and characterising renal masses is to use US, CT, or magnetic resonance imaging (MRI). Most renal masses can be diagnosed accurately using

imaging alone. Contrast-enhanced US can be helpful in specific cases (e.g. chronic renal failure with a relative contraindication for iodinated or gadolinium contrast media, complex cystic masses, and differential diagnosis of peripheral vascular disorders such as infarction and cortical necrosis) (11-13) (LE: 3).

### 3.2.2 **CT or MRI**

Computed tomography or MRI are used to characterise a renal mass. Imaging must be performed both before and after administration of intravenous contrast material in order to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield unit (HU) readings before and after contrast administration. A change of 15 Hounsfield units or more is evidence of enhancement (14) (LE: 3). To maximise differential diagnosis and detection, the evaluation should include images from the nephrographic phase, as this phase provides the best depiction of renal masses, which typically do not enhance to the same degree as the renal parenchyma.

CT or MRI allow accurate diagnosis of RCC in most cases. However, CT and MRI features cannot reliably distinguish oncocytoma and fat-free angiomyolipoma from malignant renal neoplasms (15-18) (LE: 3).

Abdominal CT provides information on:

- Function and morphology of the contralateral kidney (19) (LE: 3);
- Primary tumour extension (extrarenal spread);
- Venous involvement;
- Enlargement of locoregional lymph nodes;
- Condition of the adrenal glands and liver (LE: 3).

Abdominal contrast-enhanced biphasic CT angiography is a useful tool in selected cases to obtain detailed information about the renal vascular supply (e.g., for segmental renal artery clamping during partial nephrectomy) (20,21). If the patient is allergic to CT contrast medium, MRI biphasic angiography (MRA) may be indicated, but this is less sensitive and accurate than CT angiography for detecting supernumerary vessels (22).

If the results of CT are indeterminate, MRI may provide additional information in order to:

- Demonstrate enhancement in renal masses (including solid enhancing nodular components in complex cystic masses) (23);
- Investigate locally advanced malignancy (24-26);
- Investigate venous involvement if the extent of an inferior vena cava tumour thrombus is poorly defined on CT scanning (24-27) (LE: 3). Doppler US is less accurate for identification of the extent of a venous tumour thrombus (26) (LE: 3).

MRI is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure (25,28) (LE: 3). Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored in the assessment of renal masses (29).

### 3.2.3 **Other investigations**

Renal arteriography and inferior venacavography only have 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 treatment decision-making - e.g., the need to preserve renal function (8,9) (LE: 2a).

The true value of positron-emission tomography (PET) in the diagnosis and follow-up of RCC remains to be determined, and PET is not currently a standard investigation (30) (LE: 3).

### 3.2.4 **Radiographic investigations for metastatic RCC**

Chest CT is the most accurate investigation for chest staging (31-35) (LE: 3). However, at the very least, routine chest radiography must be performed for metastatic evaluation, as a less accurate alternative to chest CT (LE: 3). There is a consensus that most bone and brain metastases are symptomatic at diagnosis, so that routine bone or brain imaging is not generally indicated (31,36,37) (LE: 3). However, bone scan, brain CT, or MRI may be used in presence of specific clinical or laboratory signs and symptoms (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 their CT imaging appearance, in an attempt to predict the risk of malignancy (40,41) (LE: 3). The Bosniak system also advocates treatment for each category (Table 3.2).

**Table 3.2: The Bosniak classification of renal cysts (40)**

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 has the same density as water and does not enhance with contrast medium.	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 < 3 cm in size, with sharp margins but without enhancement.	
IIF	These cysts may 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, which may 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 ≥ 3 cm in size. 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. Over 50% of the lesions are malignant.
IV	These lesions are clearly malignant cystic lesions that contain enhancing soft-tissue components.	Surgical therapy recommended. Mostly malignant tumour.

### 3.3 Renal tumour biopsy

Percutaneous renal tumour biopsies are increasingly being used: 1, for histological diagnosis of radiologically indeterminate renal masses; 2, to select patients with small renal masses for surveillance approaches; 3, to obtain histology before ablative treatments; 4, to select the most suitable form of targeted pharmacologic therapy in the setting of metastatic disease (42-51) (LE: 3).

Percutaneous sampling of a renal mass can be carried out using needle core biopsy and/or fine-needle aspiration (FNA). The aim is to determine malignancy, histological type, and grade of the renal tumour evaluated.

Due to the high diagnostic accuracy of current abdominal imaging findings, renal tumour biopsy is not necessary before surgical treatment in fit patients with a long life expectancy and a clearly suspicious, contrast-enhancing renal mass at abdominal CT or MRI (LE: 4).

Percutaneous sampling of renal masses can be performed under local anaesthesia in the majority of cases (42-51) (LE: 3). Depending on the tumour's location, its echogenic features, and the patient's physical characteristics, biopsies can be performed with either US or CT guidance, with a similar diagnostic yield (47,50) (LE: 2b).

There is currently agreement that 18-gauge needles are ideal for renal tumour core biopsies, as they are associated with low morbidity and provide sufficient tissue for diagnosis in the majority of cases (42-50,52) (LE: 2b). A coaxial technique that allows multiple biopsies to be performed through a coaxial guide or cannula should always be used, in order to avoid the potential risk of tumour seeding (42-50) (LE: 3). With the use of coaxial techniques, no cases of seeding of renal tumours have been reported in recent years (42-50).

Overall, percutaneous biopsies have low morbidity. Spontaneously resolving subcapsular/perinephric haematoma and haematuria are the most frequently reported complications, while clinically significant bleeding is unusual (0.0-1.4%) and generally self-limiting (42-111).

Needle core biopsies are preferable for solid renal masses, as they have a greater diagnostic yield and better accuracy for diagnosing malignancy and histological type in comparison with FNA (44,47,49,53-55) (LE: 2b). Larger tumour size and solid pattern are predictors of a diagnostic core biopsy (47,50) (LE: 2b).

The ideal number and location of core biopsies have not been defined. However, at least two good

quality cores (non-fragmented, > 10 mm in length) should be obtained, and necrotic areas should be avoided in order to maximize the diagnostic yield (42,44,47,48,50) (LE: 4). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis (56) (LE: 2b).

In recent series from experienced centres, core biopsies of solid renal tumours have shown a diagnostic yield of 78-97%, high specificity (98-100%), and high sensitivity (86-100%) for the diagnosis of malignancy (42-50,54,55,57-75) (LE: 2b). However, it should be noted that 2.5-22.0% of core biopsies are non-diagnostic (42-50,54,55,57-75) (LE: 2b). If a biopsy is non-diagnostic, but there are radiologic findings suspicious for malignancy, a further biopsy or surgical exploration should always be considered (LE: 4).

Assessment of tumour grade on core biopsies is challenging. The accuracy of Fuhrman grading on biopsies is poor (43-75%), but it can be improved using a simplified two-tier system (high-grade vs. low grade) (42-50,54,55,57-75) (LE: 2b).

Core biopsies have a low diagnostic yield for cystic renal masses and should not be recommended alone in these cases, unless areas with a solid pattern are present (Bosniak IV cysts) (47,50) (LE: 2b).

Combined FNA and core biopsies can provide complementary results, especially for complex cystic lesions (49,55,57,58,73,76,77) (LE: 3).

### 3.4 Histological diagnosis

Renal neoplasms comprise a broad spectrum of histopathological entities described in 2004 WHO classification (112) and modified by ISUP Vancouver Classification (113) (for further details see Chapter 5: Other renal tumours). From a clinical point of view, three main types of RCC are important: clear cell (cRCC), papillary (pRCC - type I and II) and chromophobe (chRCC). Differences in tumour stage, grade and cancer specific survival (CSS) between the RCC types is illustrated in table 3.3.

**Table 3.3: Basic characteristics of three main types of RCC (115-117)**

Type	Percentage of RCC (-)	Advanced disease at diagnosis (T3-4, N+, M+)	Fuhrman Grade 3 or 4 (118)	CSS (HR)
cRCC	80-90%	28%	28.5%	referent
pRCC	6-15%	17,6%	28.8%	0.64 - 0.85
chRCC	2-5%	16,9%	32.7%*	0.24 - 0.56

CSS = cancer-specific survival; HR = hazard ratio.

\*The Fuhrman grading system is validated for cRCC, but is unreliable for chRCC. Data based on the Paner et al. grading system are not available just yet (118-120).

Generally, in all RCC types, prognosis worsens with stage and histopathological grade (Tables 3.4 and 3.5). For further details, see Chapter 4.

The 5-year overall survival for all types of RCC is 49%, which has further improved since 2006 probably due to an increase in incidentally detected RCCs as well as by the introduction of TKI inhibitors (114). Sarcomatoid changes can be found in all RCC types and they are equivalent of high grade and very aggressive tumours (see Chapter 5).

**Table 3.4: Cancer specific survival by stage and histopathological grade in RCCs - hazard ratio (95% CI) (Keegan et al, 2012 [117]).**

T1N0M0	Referent
T2N0M0	2.71 (2.17 - 3.39)
T3N0M0	5.20 (4.36 - 6.21)
T4N0M0	16.88 (12.40 - 22.98)
N+M0	16.33 (12.89 - 20.73)
M+	33.23 (28.18 - 39.18)
Grade 1	Referent
Grade 2	1.16 (0.94 - 1.42)
Grade 3	1.97 (1.60 - 2.43)
Grade 4	2.82 (2.08 - 3.31)

CI = confidential interval

The long-term survival in RCC patients treated by radical- or partial nephrectomy between 1970 and 2003; for unilateral, sporadic cRCC, pRCC or chRCC in an American single centre cohort study (116), is shown in table 3.5.

**Table 3.5: Cancer-specific survival of surgically treated patients by histological type of RCC (estimated survival rate in percentage [95% CI])**

Survival time	5 years (%)	10 years (%)	15 years (%)	20 years (%)
cRCC	71 (69-73)	62 (60-64)	56 (53-58)	52 (49-55)
pRCC	91 (88-94)	86 (82-89)	85 (81-89)	83 (78-88)
chRCC	88 (83-94)	86 (80-92)	84 (77-91)	81 (72-90)

CI = confidential interval

#### 3.4.1 Type clear cell (cRCC)

Grossly, cRCC is well circumscribed, capsule is usually absent. Large tumour may show infiltrating growth. The cut surface is golden-yellow, often with haemorrhage and necrosis. The Fuhrman nuclear grading system is generally used (118). Loss of chromosome 3p and mutation of the VHL (von Hippel-Lindau) gene located at chromosome 3p25 are frequently found. Patients with cRCC have a worse prognosis compared with pRCC and chRCC (115,117). Even after stratification for stage and grade (121). The 5-year CSS rate was 91%, 74%, 67% and 32% for TNM stages I, II, III and IV (patient treated 1987-98) (122). The indolent variant of cRCC is multilocular cystic RCC accounts for approximately 4 % of all cRCC (113) (for details see Chapter 5).

#### 3.4.2 Type papillary (pRCC)

Macroscopically pRCC is well circumscribed with pseudocapsule, yellow or brown in colour, with soft structure. Genetically, pRCC shows trisomies of chromosomes 7 and 17 and the loss of chromosome Y. Papillary RCCs are heterogeneous, with three different subtypes; two basic (1 and 2) types of pRCC and a third type, oncocyctic (see Chapter 5: Other renal tumours). In comparison with cRCC, pRCC has significantly higher rate of organ confined tumour (pT1-2N0M0) 74.9% versus 62.9% and higher 5-year CSF (85.1% versus 76.9%) (123). Prognosis of pRCC type 2 is worse with a hazard ratio of 2.16 versus 3.28 for type 1 (124-126). Exophytic growth, pseudonecrotic changes and pseudocapsule (result of a pressure atrophy caused by the slow growth of the tumour) are typical signs of pRCC type 1. Pseudocapsules and extensive necrotic changes cause spherical shape of the tumour in the extrarenal section. Tumours with massive necroses are fragile and vulnerable to spontaneous rupture or rupture resulting from minimal trauma followed by retroperitoneal bleeding. A well-developed pseudocapsule in pRCCs type 1 are probably due to most pRCCs of type 1 not rupturing despite necroses. Necroses cohere with a hypodense central area of tumours on the postcontrast CT. This area is surrounded by a vital tumour tissue, presented as serpiginous contrast-enhancing margin on CT (127).

Some authors consider as a type 3; oncocyctic pRCC, without pseudocapsula, no massive necrosis, with rare extrarenal growth and low malignant potential (126), though this type is not generally accepted (113).

#### 3.4.3 Type chromophobe (chRCC)

The gross picture of chRCC presents as a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Instead of the Fuhrman grading system, a special histopathological grading system by Paner et al. was proposed in 2010 (119,120). Loss of chromosomes 2, 10, 13, 17 and 21 are typical genetic changes (128). The prognosis is relatively good, with 5-year recurrence-free survival and CSS rates of 89.3% and 93.0%, respectively and 10-year CSS of 88.9% (129).

### 3.5 Conclusions

- The incidence of small and incidental renal tumours has significantly increased in recent decades, but a proportion of patients with RCC still present with a palpable mass, haematuria, and paraneoplastic and metastatic symptoms (LE: 3). Appropriate staging of RCC requires abdominal CT or MRI and chest imaging (LE: 3). Chest CT is the most sensitive approach for detecting lung metastases, but at least a chest radiograph should be performed for chest staging. There is no role for routine bone scanning or brain CT or MRI in the standard clinical work-up of asymptomatic patients.
- Percutaneous renal tumour biopsies are increasingly being used:
  - o To establish the diagnosis of radiologically indeterminate renal masses;
  - o To obtain histology of incidentally detected renal masses in patients who are candidates for nonsurgical treatment (active surveillance, ablative therapies); and
  - o To select the most suitable targeted therapy for metastatic renal tumours.

### 3.6 Recommendations

	GR
Contrast-enhanced multi-phasic abdominal CT and MRI are recommended for the work-up of patients with RCC and are considered equal both for staging and diagnosis.	B
Contrast-enhanced multi-phasic abdominal CT and MRI are the most appropriate imaging modalities for renal tumour characterization and staging prior to surgery.	C
A chest CT is recommended for staging assessment of the lungs and mediastinum.	C
Bone scan is not routinely recommended.	C
Renal tumour biopsy is recommended before ablative therapy and systemic therapy without previous pathology.	C
Percutaneous biopsy is recommended in patients in whom active surveillance is pursued.	C
Percutaneous renal tumour biopsy should be obtained with a coaxial technique.	C

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## 4. CLASSIFICATION AND PROGNOSTIC FACTORS

### 4.1 Classification

The TNM classification system is generally recommended for clinical and scientific use (1). However, the system requires continuous improvements (2). The latest version of the TNM classification was published in 2010 (Table 4.1). The prognostic value of the 2010 TNM classification has been confirmed in both single and multi-institution studies (3,4). However, some uncertainties remain:

- The sub-classification of T1 tumours using a cut-off of 4 cm might not be optimal with the widening of nephron-sparing surgery for localised cancer.
- The value of size stratification of T2 tumours has been questioned (5).
- 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).
- Some substages of the classification (pT2b, pT3a, pT3c and pT4) may overlap (4).
- The accuracy of the N1-N2 sub-classification has been questioned (9) (LE: 3). For adequate M staging of patients with RCC, accurate preoperative imaging (currently, chest and abdominal CT) should be performed (10,11) (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 (tumour size, venous invasion, renal capsular invasion, adrenal involvement, and lymph node and distant metastasis) are commonly gathered in the universally used TNM classification system (Table 4.1).

**Table 4.1: 2009 TNM classification system (1)**

<b>T - Primary tumour</b>	
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 directly invades adrenal gland 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)		
<b>N - Regional lymph nodes</b>			
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		
<b>M - Distant metastasis</b>			
M0	No distant metastasis		
M1	Distant metastasis		
<b>TNM stage grouping</b>			
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>.

Objective anatomic classification systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the R.E.N.A.L. nephrometry score and the C-index have been proposed, aiming to standardize the description of renal tumours (12-14). These systems include the assessment of anatomical features such as tumour size, exophytic/endophytic properties, nearness to the collecting system and renal sinus, anterior/posterior location, etc.

The use of an anatomical classification system for renal tumours is helpful since it allows for an objective prediction of potential morbidity of nephron-sparing surgery and tumour ablation techniques. These tools provide information for treatment planning, patient counselling, and proper comparison of partial nephrectomy and tumour ablation series. However, when selecting the best treatment option for each individual patient, anatomic scores must always be considered in conjunction with patient features and surgeon experience.

#### 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 (15). Although affected by intra- and inter-observer discrepancies, it is an independent prognostic factor (16). 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 (17,18) (LE: 3).

According to the WHO classification (19), 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 (20,21). However, the prognostic information provided by the RCC subtype is lost when stratified to tumour stage (21,22) (LE: 3).

Among papillary RCCs, two subgroups with different outcomes have been identified (23): 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).

RCC with Xp 11.2 translocation has been associated with a poor prognosis (24). Its incidence is low but should be systematically addressed in young patients.

The RCC type classification has been confirmed at the molecular level by cytogenetic and genetic analyses (25-27) (LE: 2b).

#### 4.2.3 **Clinical factors**

Clinical factors include patient performance status, localised symptoms, cachexia, anaemia, and platelet count (28-31) (LE: 3).

#### 4.2.4 **Molecular factors**

Numerous molecular markers have been investigated, including: 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, C-reactive protein (CRP), osteopontin (32) 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 yet helped to identify new relevant prognostic factors (35).

#### 4.2.5 **Prognostic systems and nomograms**

Postoperative 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 postoperative histo-prognostic schemes (43). Recently, new preoperative nomograms with excellent PAs have been designed (44,45). Table 4.2 summarises the current most relevant prognostic systems.

For prognostic scores in metastatic RCC see chapter 7.

### 4.3 **Conclusion and recommendations**

	<b>LE</b>
In patients with RCC, TNM stage, nuclear grade according to Fuhrman, and RCC subtype (WHO, 2004; [21]), contribute important prognostic information.	2

<b>Recommendations</b>	<b>GR</b>
The use of the current TNM classification system is recommended.	B
We recommend that grading systems and classification of RCC subtype should be used.	B
We recommend that prognostic systems are used in the metastatic setting.	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.	C
No molecular prognostic marker is currently recommended for routine clinical use.	C



**Table 4.2: 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	Tumour necrosis	Tumour size	Delay between diagnosis and treatment	LDH	Corrected calcium	Hemoglobin	Neutrophil count	Platelet count
Localised RCC	UISS	X	X			X								
	SSIGN	X				X	X							
	Post operative Karakiewicz's nomogram	X			X		X							
Metastatic RCC	MSKCC prognostic system								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; SSIGN = Stage Size Grade Necrosis; 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). A revised histopathological classification was published in 2013 as The International Society of Urological Pathology (ISUP) Vancouver classification of renal neoplasia (2). This classification will probably constitute the basis of the new WHO classification. The common clear cell renal carcinoma (cRCC), papillary RCC (pRCC) and chromophobe RCC (chRCC) types account for 85-90% of renal malignancies. For details see chapter 3.4. 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 Carcinoma of the collecting ducts of Bellini

Carcinoma of the collecting ducts of Bellini is a 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. The hazard ratio in cancer specific survival in comparison with cRCC is 4.49 (3). 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 (4-6). Median survival was 30 months (7). Response to targeted therapies was poor (8).

### 5.2 Renal medullary carcinoma

Renal medullary carcinoma is a devastating malignancy that primarily affects young black men with sickle cell trait. However, case reports in white and Hispanic patients without sickle cell trait have emerged (4). Renal medullary carcinoma is considered to be a subtype of collecting duct carcinoma (9). It is extremely rare; comprising approximately 2% of all primary renal tumours in young people aged 10 to 20 years. Metastatic disease is seen at presentation in 95% of patients (4,10,11). Median survival is 5 months (7). Surgical intervention alone is inadequate (10), systemic therapy is not defined, different regimes of chemotherapy are used, and the tumour is radiosensitive. Due to the rarity of this tumour type, it is unlikely that a randomised trial can be carried out in a timely fashion (12).

### **5.3 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 (13). The hazard ratio in cancer specific survival is in comparison with cRCC (3). Metastatic sarcomatoid RCC is associated with a poor response to systemic therapy. Sunitinib treatment resulted in a modest response rate (14). The combination of gemcitabine and doxorubicin could also be an option (15) (LE: 3) (GR: C).

### **5.4 Unclassified RCC**

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

### **5.5 Multilocular cystic RCC**

It is a well-differentiated clear cell RCC (16). This subtype accounts for up to ~ 4% of surgically treated kidney tumours (2,17). Metastases of this tumour have not been described (2). According to the Bosniak classification, which is based on imaging criteria, multilocular cystic RCC may present as a Bosniak type III cystic lesion (and occasionally as a Bosniak type II lesion) (18-20). However, this type of Bosniak lesion can also be due to a mixed epithelial and stromal tumour of the kidney (MESTK), a cystic nephroma (see section 5.15), or a multilocular cyst, all of which are benign lesions. In many cases, a preoperative biopsy and intra-operative frozen-section analysis does not lead to a correct diagnosis. Fortunately, all these tumours are treated with the same surgical strategy. For this reason, if technically feasible, a nephron-sparing procedure is the technique of choice for a complex multicystic renal mass when enhanced density is observed (16,17,19,20) (LE: 3, GR: B).

### **5.6 Hybrid oncocytoma-chromophobe RCC**

Hybrid oncocytic/chromophobe tumours (HOCTs) are tumours having a mixture of cells of chRCC and renal oncocytoma. HOCTs may occur in three clinicopathological situations: sporadic, in association with renal oncocytosis/oncocytomatosis or in patients with Birt-Hogg-Dubé syndrome (a rare autosomal dominant syndrome, gene locus mapped to 17p11.2, characterised by skin haematomas and multiple renal tumours) (2). The tumours seem to behave indolently as no evidence of malignant behaviour has been documented. However, these tumours could have a low malignant potential and patients should be followed-up as for chRCC (21,22).

### **5.7 MiT Family Translocation RCC (TRCC)**

MiT translocation renal cell carcinomas (TRCC) are rare tumours which predominantly occur in younger patients with only 25% of patients being over 40 years. TRCC contains two main subgroups with translocations involving 6p21 or Xp11.2. Both types have definitive malignant potential (2). VEGF-targeted agents appear to demonstrate in clinical practice some efficacy in both subtypes (23-26).

### **5.8 Tubulocystic renal cell carcinoma (TCRCC)**

This occurs predominantly in men over a wide age range. There is a possible relationship to pRCC. It frequently displays a cystic component which may result in a radiological classification of Bosniak III or IV. TCRCC has definite malignant potential, but the vast majority of reported tubulocystic RCC (90%) have behaved in an indolent manner (2,27).

### **5.9 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 (1,2,4,28).

### **5.10 Carcinoma associated with end-stage renal disease, Acquired cystic disease-associated RCC**

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 that in the general population. Compared with sporadic RCCs, the RCCs associated with ESKD and ACKD are characterised by multicentricity and bilaterality, are found in younger patients (mostly male), and have a less aggressive behaviour (29,30). A relatively indolent outcome of tumours in ESKD is due only to the mode of diagnosis and not to specific ESKD-related molecular pathways still to be determined (30). RCC arising in native kidneys of transplant patients seems to exhibit many favourable clinical, pathological and outcome features compared with those diagnosed in dialysis-only patients. Further research is needed to determine whether this is due

to particular molecular pathways or to biases in relation to mode of diagnosis (31). Although the histological spectrum of tumours within ESKD is similar to that in sporadic RCC, the most predominant form is pRCC, being found in 41-71% of ESKD-associated RCC versus 10% in sporadic RCC. The remaining tumours are mostly cRCC (4,29,30). A specific subtype of RCC occurring in end-stage kidneys only, specifically those with acquired cystic disease, was described under the name Acquired Cystic Disease-associated RCC (ACD-RCC) (2). Patients with ESKD should undergo an annual US evaluation of the kidneys. Minimally invasive radical nephrectomy can be performed safely in these patients (32).

### **5.11 Clear Cell (Tubulo) Papillary RCC, Renal angiomyomatous tumour**

Clear cell (tubulo) papillary RCC was initially reported in patients with end-stage renal disease; however, the majority of cases reported subsequently have been sporadic. The number of cases described in the literature with extended follow-up is small; however published data indicate that these are neoplasms with indolent behaviour. No cases with metastases have been reported (2).

Tumour of similar morphology and immunophenotype but with prominent smooth muscle stroma has been reported under the term renal angiomyomatous tumour (RAT) (2,33).

### **5.12 Carcinoma associated with neuroblastoma**

Very rare tumours arise in long-term survivors of childhood neuroblastoma, who have a 329-fold increased risk of renal carcinoma. This group of tumours is heterogenous and shows oncocytoïd features. It affects children (both sexes) (4).

### **5.13 Papillary adenoma**

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

### **5.14 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).

### **5.15 Cystic nephroma/Mixed Epithelial and Stromal Tumour**

For this group, the term renal epithelial and stromal tumours (REST) is also used. REST is a new concept that brings together two benign mixed mesenchymal and epithelial tumours: cystic nephroma and mixed epithelial and stromal tumours (34). Imaging studies have revealed that most REST cystic lesions are Bosniak type III and less frequently Bosniak type II or IV (18,20). Although aggressive behaviour has been reported in very few cases, both neoplasms are generally considered to be benign and surgical excision is curative (34).

### **5.16 Oncocytoma**

Renal oncocytomas are benign tumours (1) that comprise about 3-7% of all renal tumours (35). Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard (36,37). Although only a percutaneous biopsy can lead to a preoperative diagnosis, it has a low specificity for oncocytoma because oncocytotic cells are also found in cRCC (the granular-cell variant of RCC), in the eosinophilic variant of pRCC (type 2) and the oncocytic variant of pRCC. 'Watchful waiting' can be considered in selected cases of histologically verified oncocytoma. Alternative management includes partial nephrectomy and minimally invasive approaches (38,39).

### **5.17 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 (see Hybrid oncocytoma-chromophobe carcinoma), hereditary leiomyomatosis and renal cell cancer (HLRCC), tuberous sclerosis complex, germline succinate dehydrogenase (SDH) mutation, nonpolyposis colorectal cancer syndrome, hyperparathyroidism-jaw tumour syndrome, PTEN hamartoma syndrome, constitutional chromosome 3 translocation, and familial nonsyndromic clear cell RCC. Renal medullary carcinoma (see above) can be included because of its association with hereditary hemoglobinopathies (1,2,39-41):

- Von Hippel-Lindau - autosomal dominant (AD). Multiple cRCC (seen in up to 65% of affected individuals) and multiple extrarenal manifestation (41).
- Hereditary papillary RCC is AD with incomplete penetrance. Activating mutation in MET protooncogene (7q31) (41).
- Hereditary leiomyomatosis RCC-associated RCC is AD affected gene to chromosome 1q42.3-q43 with germline mutation in the fumarate hydratase. These patients harbour multiple cutaneous and

- uterine leiomyomas. One third have RCC, majority advanced disease (2,41).
- Tuberous sclerosis complex. Mutation in the tumour suppressor genes TSC1 or TSC2. Patients can have 3 types of bilateral renal lesions: multiple AMLs, numerous renal cysts, and, less frequently, RCC (41).

## 5.18 Mesenchymal tumours

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

### 5.18.1 *Angiomyolipoma*

Angiomyolipoma (AML) is a benign mesenchymal tumour composed of a variable proportion of adipose tissue, spindle and epithelioid smooth muscle cells, and abnormal thick-walled blood vessels. It can occur sporadically, and is four times more likely in women. It also occurs in tuberous sclerosis (TS - see above hereditary kidney tumours), 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. AML can be found in TS in lymph nodes, but it is not metastatic disease, but disease with a multicentric genesis. AML can be due to angiotropic-type growth involved in the renal vein even the inferior vena cava. AML with involvement of lymph nodes and tumorous thrombus is benign. Only epithelioid AML is a potentially malignant variant of AML (1,42). AML is associated with a slow and consistent growth rate (0.088 cm/year), and typically has minimal morbidity (43). The main complications of renal AML are retroperitoneal bleeding or bleeding into the urinary collection system, which can be life-threatening (44). The bleeding tendency is related to the angiogenic component of the tumour that includes irregular and aneurysmatic blood vessels (44). The major risk factors for bleeding are tumour size, grade of the angiogenic component of the tumour, and the presence of TS (44,45). Primary indications for intervention include symptoms such as pain, bleeding, or suspected malignancy.

Most cases of AML can be managed by conservative nephron-sparing approaches, although some cases of AML may require complete nephrectomy (45) (LE: 3). Of the standard surgical interventions, selective arterial embolisation (SAE) and radiofrequency ablation (RFA) can be used (43,44,46). Although SAE is effective at controlling haemorrhage in the acute setting, it has limited value in the longer-term management of AML (47). Clinical trials of medical management with m-TOR inhibitors are ongoing (48) and sirolimus can be combined with deferred surgery (49).

## 5.19 Emerging/provisional new tumour entities

Further reports of these entities are required to better understand the nature and behaviour of these highly unusual tumours (2):

- Thyroid-like follicular carcinoma of the kidney; rare tumour closely mimicking well-differentiated thyroid follicular neoplasms. Fewer than 15 cases were reported in the literature (2).
- Succinate Dehydrogenase B Mutation-associated RCC.
- ALK Translocation RCC (ALK - anaplastic lymphoma kinase).

**Table 5.1: Summary of other renal tumours with an indication of malignant potential and recommendation for treatment (GR: C)**

Entity	Malignant potential	Treatment of localised tumour
Sarcomatoid variants of RCC	High	Surgery
Multilocular clear cell RCC	Low, no metastasis	Surgery, NSS*
Carcinoma of the collecting ducts of Bellini	High, very aggressive	Surgery, in M+ discussable
Renal medullary carcinoma	High, very aggressive	Surgery
Translocation RCC Xp11.2	High	Surgery
Translocation RCC t(6;11)	Low	Surgery, NSS
Mucinous tubular and spindle cell carcinoma	Intermediate	Surgery, NSS
Acquired cystic disease-associated RCC	Low	Surgery
Clear cell (tubulo) papillary RCC	Low	Surgery, NSS
Hybrid oncocytic chromophobe tumour	Low	Surgery, NSS
Metanephric tumours	Benign	Surgery, NSS
Cystic nephroma/Mixed Epithelial and Stromal Tumour	Low/benign	Surgery, NSS
Oncocytoma	Benign	Observation (when histologically confirmed)/surgery, NSS
Hereditary kidney tumours	High	Surgery, NSS
Angiomyolipoma	Benign	Consider treatment only in very well selected patients
Unclassified RCC	Variable	Surgery, NSS

\*NSS = *nephron-sparing surgery*.

## 5.20 Summary

A variety of renal tumours exist, 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.

## 5.21 Conclusions and recommendations

Conclusions	LE
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
In biopsy-proven oncocytomas, watchful waiting is an option.	3
In advanced uncommon types of renal tumours, a standardised oncological treatment approach does not exist.	3

Recommendations	GR
Bosniak cysts $\geq$ type III should be regarded as RCC and be treated accordingly.	C
In angiomyolipomas, treatment (surgery, thermal ablation, and selective arterial embolisation) can be considered in: <ul style="list-style-type: none"> <li>• large tumours (the recommended threshold of intervention does not exist, the formerly recommended size of &gt; (3) 4 cm wide is disputed);</li> <li>• females of childbearing age;</li> <li>• patients in whom follow-up or access to emergency care may be inadequate.</li> </ul>	C
A nephron-sparing procedure is preferred.	

## 5.22 References

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## 6. TREATMENT OF LOCALIZED RCC AND LOCAL TREATMENT OF METASTATIC RCC

A systematic review underpins the findings of Sections 6.1-6.3. This review included all relevant published literature comparing surgical management of localized RCC (T1-2N0M0) (1,2). Randomized or quasi-randomized controlled trials (RCTs) were included. However, due to the very limited number of RCTs, non-randomized studies (NRS), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from the databases of well-defined registries were also included. Studies with no comparator group (e.g. case series), unmatched retrospective studies, and chart reviews were excluded due to their inherent risk of selection bias. The systematic review methodology has been reported in detail elsewhere

(1,2). For this Guidelines version, an updated search was performed up to May 31st 2013 (3).

## 6.1 Surgical treatment

### 6.1.1 Nephron-sparing surgery versus radical nephrectomy

Based on the available oncological and QoL outcomes, the current evidence suggests that localized renal cancers are best managed by NSS (partial nephrectomy) rather than by radical nephrectomy, irrespective of the surgical approach.

A study that compared open partial nephrectomy with open radical nephrectomy found that the estimated cancer-specific survival rates (CSS) at 5 years were comparable (4-7). For the first time, this finding has been recently confirmed by a prospective RCT, comparing radical nephrectomy with partial nephrectomy in solitary T1-2 N0M0 renal tumour  $\leq$  5cm with normal contralateral kidney function and WHO PS 0-2. At 9.3 years survival follow-up, 198 patients (72.5 %) were alive after radical nephrectomy and 173 (64.4%) after NSS. The CSS was 98.5 vs 97%, respectively. Local recurrence occurred in one patient in the nephrectomy group and in six in the NSS group (8).

A number of studies compared partial versus radical nephrectomy (open or laparoscopic) for renal carcinoma ( $\leq$  4 cm) (9-13). The results showed that radical nephrectomy was associated with increased mortality from any cause after adjusting for patient characteristics. In studies analyzing RCCs of 4-7 cm, no differences were shown for CSS between partial nephrectomy and radical nephrectomy (12,14-21). In addition, when laparoscopic partial nephrectomy was compared with laparoscopic radical nephrectomy in RCCs  $>$  4 cm, there was no difference in overall survival (OS), CSS and recurrence-free survival rates (RFS) (22). Furthermore, a retrospective matched-pair analysis in elderly patients (23) reported a CSS of 98% for partial nephrectomy versus 95% for radical nephrectomy.

Other studies have compared various aspects of QoL and safety for open partial and open radical nephrectomy (4-7,19,20,24-26). The results showed no difference in the length of hospital stay (5,6,26), blood transfusions (5,24,26), or mean blood loss (5,26). In general, complication rates were inconsistently reported and no clear conclusions could be made in favour of one intervention over another (27). One study found that the mean operative time was longer for the open partial group (27), but other research found no such difference (28). Three studies consistently reported worse renal function after radical nephrectomy compared to partial nephrectomy (4,7). A greater proportion of patients had impaired post-operative renal function after radical nephrectomy after adjustment for diabetes, hypertension and age (7).

One database review compared open partial with laparoscopic radical nephrectomy in RCCs of 4-7 cm. The review found a significantly lower mean increase in post-operative creatinine levels (15). Another study comparing laparoscopic partial versus laparoscopic radical nephrectomy found that estimated GFR decreased less in the NSS group, while the radical nephrectomy group had a significantly greater proportion of patients with a two-stage increase in CKD (22). Another database review (29) compared laparoscopic partial with laparoscopic radical nephrectomy for RCCs  $>$  4 cm in size. The laparoscopic radical nephrectomy group had a significantly greater post-operative decrease in estimated GFR and a greater proportion of patients with a post-operative two-stage increase in CKD 2 stage.

Two studies reported QoL post surgery for RCC. Patients who underwent partial nephrectomy reported better scores, in many aspects of QoL (25). Those who underwent radical nephrectomy reported a higher degree of fear associated with living with only one kidney. Regardless of the intervention, patients with RCCs  $<$  4 cm and a normal contralateral kidney showed the highest QoL scores after treatment, which matched their pre-diagnosis scores. Patients who had higher complication rates had lower QoL scores (5).

No prospective comparative studies were identified reporting on oncological outcomes for minimally invasive ablative procedures compared with radical nephrectomy. One trial reported on radiofrequency ablation versus radical or partial nephrectomy for T1a RCC, resulting in CSS of 100% for each of the three treatment modalities (30).

Patient and tumour characteristics permitting, the current oncological outcomes evidence base suggests that localized RCCs are best managed by NSS rather than by radical nephrectomy, irrespective of the surgical approach. Where open surgery is deemed necessary, the oncological outcomes following open NSS are at least as good as open radical nephrectomy and should be the preferred option when technically feasible.

However, in some patients with localized RCC, NSS 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 curative therapy remains radical nephrectomy, which includes removal of the tumour-

bearing kidney. Complete resection of the primary tumour by either open or laparoscopic surgery offers a reasonable chance of curing the disease.

### 6.1.2 **Associated procedures**

#### 6.1.2.1 *Adrenalectomy*

One prospective NRS compared the outcomes of radical or partial nephrectomy with, or without, ipsilateral adrenalectomy (31). Multivariate analysis showed that upper pole location was not predictive of adrenal involvement but tumour size was predictive. There was no difference in overall survival (OS) at 5 or 10 years, with, or without, adrenalectomy. Adrenalectomy was justified using criteria based on radiographic and intra-operative findings. Only 48 of 2065 patients underwent concurrent ipsilateral adrenalectomy of which 42 were for benign lesions.

#### 6.1.2.2 *Lymph node dissection*

The role of lymph node dissection (LND) in RCC remains controversial (32). Clinical assessment of lymph nodes (LNs) status is based on enlargement of LNs on CT/MRI and on intraoperative assessment by direct palpation. Only less than 20% of clinically positive (cN+) LNs are confirmed to be metastatic at pathology (pN+) (33). CT/MRI do not allow for detection of small metastases in normal sized LNs (34) and extended LND (e-LND) with histopathological examination remains the only modality to properly assess LNs status.

In the presence of clinically positive LNs (cN+), LND seems to be always justified (34). However, the extent of LND remains a matter of controversy (34). Regarding patients with clinically negative LNs (cN0) six clinical trials have been reported (32), one randomised controlled trial (33) and five comparative studies (35-39). Retrospective series support the hypothesis that LND may be beneficial in high-risk patients (tumor size > 10 cm, clinical category T3-T4, high Fuhrman grade, presence of sarcomatoid features, or coagulative tumour necrosis) (34,40). However, in the EORTC randomized study only 4% of cN0 patients had positive lymph nodes at final pathology, suggesting that LND represents overtreatment in the majority of cases (33).

Clinical trials of lower quality suggest that e-LND should involve the LNs surrounding the ipsilateral great vessel and the interaortocaval region from the crus of the diaphragm to the common iliac artery. Involvement of interaortocaval LNs without regional hilar involvement is reported in up to 35-45% of cases (34,35,41). At least 15 LNs should be removed (42,43). Sentinel LND is an investigational technique (44,45). Better survival outcomes have been shown for patients with a low number of positive LNs (< 4) and absence of extranodal extension (46,47). A preoperative nomogram to predict pN+ LNs status has been proposed (48).

#### 6.1.2.3 *Embolization*

Before a routine nephrectomy, there is no benefit in performing tumour embolization (49,50). In patients who are unfit for surgery, or who present with non-resectable disease, embolization can control symptoms, such as gross haematuria or flank pain (51-53). Embolization prior to the resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss (54). In selected patients with painful bone or paravertebral metastases, embolization can help to relieve symptoms (55).

#### 6.1.2.4 *Conclusions and recommendations*

<b>Conclusions</b>	<b>LE</b>
Partial nephrectomy achieves similar oncological outcomes of radical nephrectomy for clinically localized renal tumours (cT1).	1b
Ipsilateral adrenalectomy during radical or partial nephrectomy does not provide a survival advantage.	3
In patients with localized disease and no clinical evidence of lymph-node metastases, no survival advantage of a lymph-node dissection in conjunction with a radical nephrectomy was demonstrated.	1b
In patients with localized disease and clinically enlarged lymph nodes the survival benefit of lymph node dissection is unclear. In these cases lymph node dissection can be performed for staging purposes.	3
In patients unfit for surgery and suffering from massive haematuria or flank pain, embolization can be a beneficial palliative approach.	3

<b>Recommendations</b>	<b>GR</b>
Surgery is recommended to achieve cure in localized RCC.	B
Nephron-sparing surgery is recommended in patients with T1a tumours.	A
Nephron-sparing surgery should be favoured over radical nephrectomy in patients with T1b tumour, whenever technically feasible.	B
Ipsilateral adrenalectomy is not recommended when there is no clinical evidence of invasion of the adrenal gland.	B
Lymph node dissection is not recommended in localized tumour without clinical evidence of lymph node invasion.	A
In patients with clinically enlarged lymph nodes, lymph node dissection can be performed for staging purposes or local control.	C

## 6.2 Techniques of radical and partial nephrectomy

### 6.2.1 *Techniques of radical nephrectomy*

There are no RCTs assessing oncological outcomes of laparoscopic versus open radical nephrectomy. A prospective cohort study (56) and retrospective database reviews are available, mostly of low methodological quality (5,57,58). These studies found similar oncological outcomes for laparoscopic versus open radical nephrectomy. Data from one RCT (59) and two NRSs (5,56) showed a significantly shorter hospital stay and lower analgesic requirement for the laparoscopic radical nephrectomy group compared with the open group. Convalescence time was also significantly shorter (56). There was no difference in the number of patients receiving a blood transfusion between the two surgical approaches, but the peri-operative blood loss was significantly less in the laparoscopic arm in all three studies (5,56,59). Surgical complications were marked by low event rates and very wide confidence intervals. There was no difference in complications but the operation time was significantly shorter in the open nephrectomy arm. The post-operative QoL scores were similar between the two groups (5).

In regard to the best approach for performing radical nephrectomy, both retroperitoneal or transperitoneal approaches had similar oncological outcomes in the two RTCs (60,61) and one quasi-randomized study (62). There was no significant difference in QoL variables between the two approaches.

Hand-assisted versus standard laparoscopic radical nephrectomy was compared in one RCT (62) and one database review (27). Estimated 5-year OS, CSS, and RFS rates were comparable between the two approaches. The duration of surgery was significantly shorter in the hand-assisted approach, while the length of hospital stay and time to non-strenuous activities were shorter for the standard laparoscopic radical nephrectomy (27,62). However, the sample size was small.

Robot-assisted laparoscopic radical nephrectomy versus laparoscopic radical nephrectomy was compared in one small prospective cohort study (63). There were no local recurrences, port-site or distant metastases, but the sample size was small and follow-up was less than 1 year. Similar results were presented in observational cohort studies comparing 'portless' (n = 14) and 3-port (n = 15) laparoscopic radical nephrectomy (64,65). There was no difference in peri-operative outcomes.

### 6.2.2 *Techniques of partial nephrectomy*

Studies comparing laparoscopic partial nephrectomy and open partial nephrectomy found no difference in PFS (66-69) and OS (68,69) between the two techniques in centres with laparoscopic expertise. The mean estimated blood loss was generally found to be lower with the laparoscopic approach (66,68,70). In one database review more blood transfusion events occurred in the laparoscopic group (66). No significant differences were found between the two approaches in post-operative mortality events (66,68), DVT events (68), or pulmonary embolism events. However, the operative time was generally significantly longer in the laparoscopic group (67-69). The warm ischaemia time was found to be shorter with the open approach (66,68,70,71). In a matched-pair comparison, the decline in GFR was greater in the laparoscopic partial nephrectomy group in the immediate post-operative period (69), but not after a follow-up of 3.6 years. In another comparative study, the surgical approach was not identified as an independent predictor for the post-operative development of CKD (71).

Retroperitoneal and transperitoneal laparoscopic partial nephrectomy were found to have similar peri-operative outcomes (72). Simple tumour enucleation was found to harbour similar PFS and CSS rates of standard partial nephrectomy and radical nephrectomy in a large, retrospective, multicentre, comparative dataset and in a single-institutional comparative study, respectively (73,74).

The feasibility of off-clamp laparoscopic partial nephrectomy and laparoendoscopic single-site partial nephrectomy has been shown in selected patients, but larger studies are needed to confirm their safety and clinical role (75,76).

At present, no study has compared the oncological outcomes of robot-assisted versus laparoscopic partial nephrectomy. A prospective comparison of surgical outcomes obtained after robotic or pure laparoscopic partial nephrectomy in moderate-to-complex renal tumours showed a significantly lower estimated blood loss and a shorter warm ischaemia time in the robotic group (77). Two recent meta-analyses of relatively small series showed comparable peri-operative outcomes and a shorter warm ischaemia time for robot-assisted partial nephrectomy (78,79).

### 6.2.3 Conclusions and recommendations

Conclusions	LE
Laparoscopic radical nephrectomy has lower morbidity compared to open surgery.	1b
Oncological outcomes for T1-T2a tumours are equivalent between laparoscopic and open radical nephrectomy.	2a
Partial nephrectomy can be performed, either with an open, pure laparoscopic or robot-assisted approach, based on surgeon's expertise and skills.	2b

Recommendations	GR
Laparoscopic radical nephrectomy is recommended for patients with T2 tumours and localized renal masses not treatable by nephron-sparing surgery.	B
Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated.	A

## 6.3 Therapeutic approaches as alternatives to surgery

### 6.3.1 Surgical versus non-surgical treatment

Population-based studies (derived from the SEER database) compared the oncological outcomes of surgical management (radical nephrectomy or partial nephrectomy) and non-surgical management for < 4 cm renal tumours. The analysis in the overall database consistently showed a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management (80,81). However, although some of these studies were matched, they are limited by allocation bias; the patients assigned to the surveillance arm were older and likely to be more frail and less suitable candidates for surgery. In fact, other-cause mortality rates in the non-surgical management group significantly exceeded that of the nephrectomy group (80). Analyses focusing on the subcategory of older patients (> 75 years old) failed to show the same benefit in cancer-specific mortality for surgical treatment (82-84). In interpreting these studies, it should be taken into account that the non-surgical management group includes patients managed with observation/active surveillance or patients treated with minimally invasive ablation techniques.

### 6.3.2 Surveillance

Elderly and comorbid patients with incidentally detected small renal masses have a relatively low RCC-specific mortality and a significant competing-cause mortality (85,86). Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (US, CT, or MRI) with delayed intervention reserved for those tumours that show clinical progression during follow-up (87).

In the largest reported series of active surveillance the growth of renal tumours is low in most cases and progression to metastatic disease is reported in a limited number of patients (1-2%) (88,89).

A single-institutional comparative study assessed the outcomes of a series of patients aged 75 years old who were managed with surgery or active surveillance for clinically T1 renal tumours. Kaplan-Meier analysis revealed decreased OS for patients who underwent surveillance and nephrectomy relative to nephron-sparing intervention; however, patients selected for surveillance were older and had greater comorbidity. At multivariable analysis, management type was not associated with OS after adjusting for age, comorbidity, and the other variables (85). No statistically significant difference in OS and CSS were observed in another comparative study of radical nephrectomy versus partial nephrectomy versus active surveillance for clinically T1a renal masses with a follow-up of 34 months (90). Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, active surveillance is an appropriate strategy to initially monitor small renal masses, followed if required, by treatment for progression (87-89,91-94).

A multicentre prospective study assessed the QoL of patients undergoing immediate intervention versus active surveillance using the SF12 QoL questionnaire. The authors observed that patients undergoing immediate intervention have higher QoL scores at baseline, specifically in domains that reflect their physical health. The perceived benefit in physical health persists for at least 1 year following intervention. Mental health, which includes domains of depression and anxiety, was not adversely affected while on active surveillance (95).

### 6.3.3 Ablative therapies

#### 6.3.3.1 Cryoablation

Cryoablation can be performed using either a percutaneous or a laparoscopic-assisted approach. In a study comparing laparoscopic with percutaneous cryoablation, there was no significant difference in the overall complication rates (96). Another similar comparison of technique reported no significant differences in OS, CSS, and RFS. However, this study found a non-significant difference in the change in estimated GFR, with an average decrease of 3.7 mL/min in 172 laparoscopic patients with a longer follow-up versus 6.6 mL/min in 123 percutaneous patients with a shorter follow-up ( $p = 0.2$ ). The only significant finding was a shorter average length of hospital stay with the percutaneous technique (2.1 days) versus the laparoscopic technique (3.5 days) ( $p < 0.01$ ) (97). Another study compared open or laparoscopic cryoablation with percutaneous cryoablation. The study did not find any significant differences in survival and recurrence outcomes, but showed a highly significant difference in the average hospital length of stay, with 3.2 days for the combined surgical techniques compared to 0.7 days for the percutaneous technique. This difference may have been influenced by grouping open and laparoscopic techniques together (98).

No studies compared surveillance strategies to ablation procedures. For the comparison of partial nephrectomy versus other minimally invasive ablative procedures, several studies were identified.

#### 6.3.3.2 Cryoablation versus partial nephrectomy

Data on laparoscopic cryoablation versus laparoscopic partial nephrectomy obtained from one database review (99) reported 3 deaths out of 78 patients treated, compared with none out of 153 patients treated with laparoscopic partial nephrectomy. In another matched-pair study, no recurrences were reported in either treatment, but with a follow-up of less than 12 months (100). It should be noted that the studies also included benign tumours and the data should be treated with caution. In a database review (99) and a matched-pair study (100), there were no differences in peri-operative outcomes, recovery times, complication rates or post-operative serum creatinine levels between laparoscopic cryoablation and laparoscopic partial nephrectomy. Blood loss was less and surgical time was quicker in the cryoablation group than the laparoscopic partial nephrectomy group (99,100). In one matched comparison between laparoscopic cryoablation and open partial nephrectomy (101), no local recurrences or metastasis was found in either group. The length of hospital stay was shorter and the mean blood loss was significantly less in the laparoscopic cryoablation group, but there was no difference in number of patients requiring blood transfusions or in the duration of surgery. However, there were only 20 patients in each arm and the follow-up time was short.

In a study comparing laparoscopic partial nephrectomy (48 patients) with laparoscopic cryoablation (30 patients), no difference in OS was found, but significant differences in CSS were seen at 3.5 and 7 years. The CSS was 100% at all times for the laparoscopic partial nephrectomy group, compared with 93%, 88% and 82% for the laparoscopic cryoablation group ( $p = 0.027$ ). Other significant oncological outcomes in favour of laparoscopic partial nephrectomy included RFS, disease-free survival, local recurrence, and metastasis (102).

A study comparing open partial nephrectomy (82 patients) with laparoscopic cryoablation (41 patients) also reported a significant benefit in RFS at 3 years with nephrectomy, but no significant differences in CSS, local recurrence or metastasis. However, a study (103) comparing robotic partial nephrectomy ( $n = 212$ ) with laparoscopic cryoablation ( $n = 234$ ) found significant differences in local recurrence rates (0 vs 11%) and metastasis (0.5 vs 5.6%) in favour of partial nephrectomy compared to cryoablation (104).

For complications and QoL measures, the studies were mixed. Two studies (103,104) reported on specific Clavien rates, with mostly non-significant differences. Differences were mixed as well for the rates of intra-operative versus post-operative complications between different studies. Estimated GFRs were insignificant in two studies but in favour of cryoablation in a third study (102). Estimates of new CKD were also mixed, with one study in favour of cryoablation (102), another strongly in favour of partial nephrectomy (103), and the third showing no difference (104).

There was one study which compared partial nephrectomy with ablation therapy in general, either cryoablation or RFA (105). This study showed significantly improved DSS at both 5 and 10 years for partial nephrectomy.

#### 6.3.3.3 Radiofrequency ablation

RFA can be done laparoscopically or percutaneously. There were three contemporary studies that compared patients with T1a tumours treated by laparoscopic or percutaneous RFA (106-108). Complications occurred in up to 29% of the patients, but were mostly minor. Complication rates were similar in patients treated laparoscopically or percutaneously. One study with a limited number of patients ( $n = 47$ ) (108) found a higher rate of incomplete ablation (defined as persistent enhancement in the ablation zone on the CT or MRI performed at 1 month) in patients treated by percutaneous RFA. However, in the three comparative studies, there was no difference in terms of recurrence or CSS.



#### 6.3.3.4 Radiofrequency ablation versus partial nephrectomy

The quality of evidence regarding RFA for the treatment of localized RCC is low. Most publications are retrospective cohort studies with low number of patients and limited follow-up. Three studies retrospectively compared RFA with surgery in patients with T1a tumours (30,109,110). Two studies comprised 100% of T1a patients (30,109) and one included 47% of T1b in the PN group (110).

One study (109) retrospectively evaluated patients who underwent either RFA (percutaneous or laparoscopic) or partial nephrectomy. With a mean follow-up of 6.3 years, there was no difference in OS and CSS.

A team from Japan retrospectively reviewed 105 patients treated by percutaneous RFA (n = 51) or radical nephrectomy (n = 54). Mean tumour sizes were 2.4 cm in the RFA group and 2.8 cm in the radical nephrectomy group. The CSS was 100% in both groups. The OS was lower in the RFA group (75 vs 100%). However, patients treated with surgery were younger (57.6 vs 70 years old) (30).

In a monocentric study from France comparing 34 RFA patients to 16 open partial nephrectomy patients, there was a higher rate of complications and transfusions in the partial nephrectomy group. Although the tumours were larger in partial nephrectomy patients, progression rates were the same (0%) (110).

#### 6.3.3.5 Cryoablation versus radiofrequency ablation

Two studies were identified which compared the techniques of RFA and cryoablation (111,112). No significant differences were reported for OS, CSS, or RFS in either study. For local RFS at 5 years, one study (111) reported a trend for improvement with RFA (98.1 vs 90.6%, p = 0.09) while the other (112) reported a benefit with cryoablation (85.1 vs 60.4%, p = 0.02). One study (111) also reported no differences in Clavien complication rates between techniques.

#### 6.3.3.6 Other ablative techniques

Some studies have shown the feasibility of other image-guided percutaneous and minimally invasive techniques, such as microwave ablation, laser ablation, and high-intensity focused US ablation. However, at present these techniques should be considered experimental.

#### 6.3.3.7 Conclusions and recommendations

Conclusions	LE
Population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management. However, the same benefit in cancer-specific mortality is not confirmed in analyses focusing on older patients (> 75 years old).	3
In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).	3
The quality of the available data does not allow any definitive conclusions regarding morbidity and oncological outcomes of cryoablation and radiofrequency ablation.	3
Low quality studies suggest a higher local recurrence rate for minimally invasive therapies compared to partial nephrectomy.	3

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

## 6.4 Management of RCC with venous thrombus

A tumour thrombus formation in the inferior vena cava in patients with RCC is a significant adverse prognostic factor (see Chapter 4.2.1). Traditionally, patients with venous tumour thrombus (VTT) usually undergo surgery to remove the kidney and tumour thrombus. Aggressive surgical resection is widely accepted as the default management option for patients with VTT (113-121).

However, uncertainties remain over the surgical treatment of these patients, especially in terms of comparative effectiveness and harms. There is also variation in how the surgery is undertaken, in terms of pre-operative strategies (e.g. use of IVC filter or preoperative embolization), surgical approach to access the IVC, or bypass procedures to achieve vascular control (e.g. venovenous bypass, or cardiopulmonary bypass [CPB] and deep hypothermic circulatory arrest [DHCA]).

#### 6.4.1 **The evidence base for different surgical strategies**

To determine the evidence base for these different strategies, a systematic review of the literature was undertaken, including comparison-only studies reporting on management of VTT in non-metastatic RCC (3).

The literature search returned 564 articles, all of which were assessed for eligibility. Five studies reporting on a total of 463 patients were eligible for final inclusion; all were retrospective non-randomized studies involving small numbers of patients. No comparative studies assessing the benefits or harms of surgical excision of VTT were identified. The following conclusions were made:

- Minimal access techniques compared with traditional median sternotomy (122,123) were associated with a significantly shorter operating time.
- Pre-operative embolization (124) was associated with increases in operating time, blood loss, hospital stay and peri-operative mortality in patients with T3 RCC.
- There was no significant difference in oncological and process outcomes between CPB with DHCA or partial bypass under normothermia or single caval clamp without circulatory support (125).
- IVC filter insertion (126) was associated with a lower incidence of intra-operative pulmonary embolism in patients with RCC and VTT. However, the statistical significance of the results was not reported and hence caution is required in interpreting the findings.
- There were generally high risks of bias across all studies, including a significant risk of confounding, and hence the findings are associated with a large degree of uncertainty
- In summary, there is no distinct surgical method that seems superior for the excision of VTT. The surgical method appears to be dependent on the level of the tumour thrombus, and the grade of occlusion of the IVC (122,123,125). The value of pre-operative embolization is questionable. The relative benefits and harms of other strategies and approaches regarding access to the IVC and the role of IVC filters and bypass procedures remain uncertain.

#### 6.4.2 **The evidence base for performing surgery on patients with VTT**

In terms of whether surgery should be performed on patients with VTT, the data is derived from case series. In one of the largest studies published to date, Moinzadeh et al. (118) found that the higher level of thrombus was not associated with an increase in tumour dissemination to lymph nodes, perinephric fat or distant metastasis. Such data support the notion that all patients with non-metastatic disease and VTT, and an acceptable performance status, should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation (LE: 3). However, the most appropriate or efficacious surgical technique remains unclear.

The traditional surgical approach to the management of VTT is largely based on a combination of retrospective case series, conventional wisdom and expert opinion. It concludes that the surgical technique and approach for each case should be appropriately selected based on the extent of tumour thrombus (LE: 3).

#### 6.4.3 **Conclusions and recommendations**

<b>Conclusions</b>	<b>LE</b>
Low quality data suggests that tumour thrombus in the setting of non-metastatic disease should be excised.	3
Adjunctive procedures such as tumour embolization or IVC filter do not appear to offer any benefits.	3

  

<b>Recommendations</b>	<b>GR</b>
Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic RCC.	C

### 6.5 **Adjuvant therapy**

Current evidence that adjuvant tumour vaccination might improve the duration of the PFS of selected subgroups of patients undergoing nephrectomy for T3 renal carcinomas requires further confirmation regarding the impact on OS (127-131) (LE: 1b). Several phase III RCTs of adjuvant sunitinib, sorafenib, pazopanib, axitinib and everlimus are ongoing. Until these studies report, there is no evidence for the use of adjuvant therapy with inhibitors of VEGF-R or mTOR.

### 6.5.1 Conclusion and recommendation

Conclusions	LE
Adjuvant therapy with cytokines does not improve survival after nephrectomy.	1b

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

## 6.6 Surgical treatment of metastatic RCC (cytoreductive nephrectomy)

Tumour nephrectomy is curative only if surgery can excise all tumour deposits. Retrospective data suggest that this includes patients with the primary tumour in place and single- or oligo-metastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy is palliative and systemic treatments are necessary. In a meta-analysis of two randomized studies, comparing cytoreductive nephrectomy + immunotherapy versus immunotherapy only, there was an increased long-term survival in patients treated with cytoreductive nephrectomy (132). At present, there is only retrospective non-comparative data for cytoreductive nephrectomy combined with targeting agents, such as sunitinib, sorafenib and others. The results of randomized phase III studies are awaited.

### 6.6.1 Conclusions and recommendation

Conclusions	LE
Cytoreductive nephrectomy in combination with interferon-alpha (IFN- $\alpha$ ) improves the survival of patients with mRCC and good performance status.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3

Recommendations	GR
Cytoreductive nephrectomy is recommended in appropriately selected patients with metastatic RCC.	C

## 6.7 Local therapy of metastases in mRCC

A systematic review was undertaken in accordance with Cochrane review methodology, including all types of comparative studies on the local treatment of metastases from RCC in any organ. The databases searched (1st January 2000 to 30th September 2013) included MEDLINE, Embase and the Cochrane Library (3). Relevant interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes were survival (OS, CSS and PFS), local symptom control, and adverse events. A risk-of-bias assessment was conducted for the studies (133). The literature search identified 2,235 studies, none of them randomized trials comparing metastasectomy with other treatments. Eventually, 16 non-randomized comparative studies were included, reporting on a total of 2,350 patients involving metastasectomy. They included studies of the local treatment of metastases to bone and various organs, including the brain, lung, liver and pancreas.

Eight studies reported on local therapies of RCC-metastases in various organs (134-141). Among various organs were metastases to any single organ or multiple organs, such as the lung, bone, liver and brain. Minor sites were the pancreas, adrenal gland, lymph nodes, thyroid gland, spleen, ethmoid sinus and skin. Three studies dealt with local therapies of RCC-metastases in bone, including the spine (142-144), two in the brain (145,146) and one each in the liver (147) lung (148), and pancreas (149). Three studies (138,140,148) were abstracts only. Data were too heterogenous for a meta-analysis. There was considerable variation in the type and distribution of systemic therapies, which consisted of cytokines and VEGF-inhibitors and in the different ways in which results were reported.

### 6.7.1 Complete versus no/incomplete metastasectomy

All of the eight studies (134-141) on RCC metastases in various organs compared complete metastasectomy versus no and/or incomplete metastasectomy. However, in one study (137), complete resections were achieved in only 45% of the metastasectomy cohort, which was compared with no metastasectomy. No non-surgical treatment modalities were applied. Six of the eight studies (134,136-138,140,141) reported a significantly longer median OS or CSS following complete metastasectomy (the median value for median OS or CSS was 40.75 months, range 23-122 months) compared with incomplete and/or no metastasectomy (the median value for median OS or CSS was 14.8 months, range 8.4-55.5 months). Of the two remaining studies, one analysis (135) showed no significant difference in CSS between complete metastasectomy and no metastasectomy (58 vs 50

months,  $p = 0.223$ ), and one study (139) reported a longer median OS for metastasectomy (30 vs 12 months,  $p$  value not provided).

With regard to metastasectomy at specific organs, three studies reported on the treatment of RCC metastases to the lung (148), liver (147), and pancreas (149), respectively. The lung study reported a significantly higher median OS for metastasectomy compared with medical therapy only for both target therapy and immunotherapy (36.3, 30.4, and 18.0 months, respectively,  $p < 0.05$ ). Similarly, the liver study reported a significantly higher median OS for metastasectomy compared with no metastasectomy (142 months vs 24 months,  $p < 0.001$ ). In addition, the pancreas study reported a significantly higher 5-year OS rate compared with no metastasectomy (88% vs 77%,  $p = 0.0263$ ).

### 6.7.2 Local therapies for RCC bone metastases

Of three studies identified, one study (144) compared single-dose image-guided radiotherapy (IGRT) ( $n = 59$ ) with hypofractionated IGRT ( $n = 46$ ) in patients with RCC bone metastases. Single-dose IGRT ( $\geq 24$  Gray) had a significantly better 3-year actuarial local PFS rate (88% vs 17%,  $p = 0.001$ ), which was also shown with a Cox regression analysis ( $p = 0.008$ ). Another study (142) compared metastasectomy/curettage and local stabilization ( $n = 33$ ) with no surgical treatment ( $n = 27$ ) of solitary RCC bone metastases in various locations. A significantly higher 5-year CSS rate was observed in the intervention group (36% vs 8%,  $p = 0.007$ ), even when adjusting for adjuvant local radiotherapy.

After adjusting for prior nephrectomy, gender and age, multivariate analysis still favoured metastasectomy/curettage and stabilization ( $p = 0.018$ ). A third study (143) compared the efficacy and durability of pain relief between single-dose stereotactic body radiotherapy (SBRT) ( $n = 76$ ) and conventional radiotherapy (CRT) ( $n = 34$ ) in patients with RCC bone metastases to the spinal column (C1-sacrum). No significant difference was observed in pain ORR (CRT 68% vs SBRT 62%,  $p = 0.67$ ), time-to-pain relief (CRT 0.6 weeks vs SBRT 1.2 weeks,  $p = 0.29$ ) nor duration of pain relief (CRT 1.7 months vs SBRT 4.8 months,  $p = 0.095$ ).

### 6.7.3 Local therapies for RCC brain metastases

Two studies on RCC brain metastases were found and included in the systematic review. A three-armed study (145) compared stereotactic radiosurgery (SRS) ( $n = 51$ ) versus whole brain radiotherapy (WBRT) ( $n = 20$ ) versus the combination of SRS + WBRT ( $n = 17$ ). Each group was further subdivided into recursive partitioning analysis (RPA) classes I to III (I favourable, II moderate and III poor patient status). Two-year OS and intracerebral control were equivalent for the patient groups treated with SRS alone and SRS + WBRT. Both treatments were superior to WBRT alone ( $p < 0.001$ ) in the general study population and in the RPA subgroup analyses ( $p < 0.001$ ). A comparison of SRS versus SRS + WBRT in a subgroup analysis of RPA class I showed significantly better 2-year OS and intracerebral control for SRS + WBRT based on only three participants. The other study (146) compared fractionated stereotactic radiotherapy (FSRT) ( $n = 10$ ) with metastasectomy + CRT ( $n = 11$ ) or CRT alone ( $n = 12$ ). Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. Survival rates at 1, 2 and 3 years were, respectively: 90%, 54%, and 40.5% for FSRT; 63.6%, 27.3% and 9.1% for metastasectomy + CRT; and 25%, 16.7% and 8.3% for CRT. No  $p$ -value was reported for survival rates. FSRT did not have a significantly better 2-year local control rate compared with MTS + CRT ( $p = 0.61$ ).

### 6.7.4 Conclusions and recommendations

Conclusions	LE
All included studies were retrospective non-randomized comparative studies, resulting in a high risk of bias associated with non-randomization, attrition, and selective reporting.	3
With the exception of brain and possibly bone metastases, metastasectomy remains by default the most appropriate local treatment for most sites.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of overall survival, cancer-specific survival and delay of systemic therapy.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3

Recommendations	GR
No general recommendations can be made. The decision to resect metastases has to be taken for each site, and on a case-by-case basis; performance status, risk profiles, patient preference and alternative techniques to achieve local control, must be considered.	C
In individual cases, stereotactic radiotherapy for bone metastases, and stereotactic radiosurgery for brain metastases can be offered for symptom relief.	C

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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 resistant to most forms of chemotherapy. Chemotherapy appears to be moderately effective only if 5-fluorouracil (5-FU) is combined with immunotherapeutic agents (1). However, in a prospective randomized study, interferon-alpha (IFN- $\alpha$ ) showed equivalent efficacy to a combination of IFN- $\alpha$  + interleukin-2 (IL-2) + 5-FU (2).

#### 7.1.1 Conclusion and recommendation

Conclusion	LE
5-FU in combination with immunotherapy is equivalent in efficacy to monotherapy with IFN- $\alpha$ in patients with mRCC.	1b

Recommendation	GR
In patients with clear-cell mRCC, chemotherapy as monotherapy should not be considered effective in patients with mRCC.	B

### 7.2 Immunotherapy

#### 7.2.1 Interferon-alpha as monotherapy and combined with bevacizumab

Conflicting results exist for IFN- $\alpha$  in clear-cell metastatic renal cancer (mRCC). Several randomized studies have found that IFN- $\alpha$  in mRCC is associated with a survival advantage similar to that of hormonal therapy (3). IFN- $\alpha$  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 to a placebo equivalent (4,5). However, other studies, which focused on patients with intermediate-risk disease, failed to confirm this benefit (6). The positive effect of IFN- $\alpha$  may only occur in some patient subgroups, including patients with clear-cell histology, good-risk criteria, as defined by the Memorial Sloan-Kettering Cancer Center (MSKCC), which are also known as Motzer criteria, and metastases only in the lung (5).

In a prospective randomized study, IFN- $\alpha$  showed equivalent efficacy to a combination of IFN- $\alpha$  + IL2 + 5-FU (2). The moderate efficacy of immunotherapy was confirmed in a Cochrane meta-analysis including 42 eligible studies (7).

A combination of bevacizumab + IFN- $\alpha$  was associated with increased response rates and better progression-free survival in first-line therapy compared with IFN- $\alpha$  monotherapy (8). All recent randomized studies comparing anti-angiogenic drugs to IFN- $\alpha$  monotherapy as first-line therapy have shown superiority for sunitinib, bevacizumab + IFN- $\alpha$ , and temsirolimus (8-11). This includes patients with MSKCC good-risk disease. IFN- $\alpha$  has therefore been superseded by targeted therapy in clear-cell mRCC.

**Table 7.1: Memorial Sloan-Kettering Cancer Center (MSKCC, Motzer) criteria (4)**

Risk factors*	Cut-off point used
Karnofsky performance status	< 80
Time from diagnosis to treatment	< 12 months
Haemoglobin	< Lower limit of laboratory reference range
Lactate dehydrogenase	> 1.5 times the upper limit of laboratory range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)

\* Favourable (low) risk, no risk factors; intermediate risk, one or two risk factors; poor (high) risk, three or more risk factors.

### 7.2.2 Interleukin-2

Interleukin-2 (IL-2) has been used to treat mRCC since 1985, with response rates ranging from 7% to 27% (11-13). The optimal IL-2 regimen is not clear, but long-term (> 10 years) complete responses have been achieved with high-dose bolus IL-2 in a randomized phase III study (14). The toxicity of IL-2 is substantially greater than that of IFN- $\alpha$ . Only clear-cell-type RCC responds to immunotherapy. Interleukin-2 has not been validated in controlled randomized studies compared to best supportive care (5).

### 7.2.3 Vaccines and targeted immunotherapy

No recommendations can be made. An earlier phase III trial of vaccine therapy with tumour antigen 5T4 + first-line standard therapy (i.e. sunitinib, IL-2 or IFN- $\alpha$ ) failed to demonstrate any survival benefit compared with placebo and the first-line standard therapy (15). Several phase III vaccination studies are ongoing. Targeted immunotherapy with programmed death-1 ligand (PD-1L), which has shown efficacy and acceptable toxicity in patients with RCC (16), is currently under investigation in a phase II trial in comparison with everolimus in patients in whom anti-angiogenic therapy previously failed.

### 7.2.4 Conclusions

	LE
Interferon-alpha (IFN- $\alpha$ ) monotherapy is inferior to targeted therapy in mRCC.	1b
Subset analysis suggests IL-2 monotherapy may have a role in selected cases (good performance status, clear-cell type, lung metastases only).	2
Interleukin-2 has more side-effects than IFN- $\alpha$ .	2-3
High dose IL-2 is associated with durable complete responses in a limited number of patients. However, no clinical factors or biomarkers exist to accurately predict a durable response in patients treated with HD-IL2.	1b
A combination of bevacizumab and IFN- $\alpha$ is more effective than IFN- $\alpha$ in treatment-naïve, low-risk and intermediate-risk tumours.	1b
Vaccination therapy with tumour antigen 5T4 showed no survival benefit over the first-line standard therapy.	1b
Cytokine combinations, with or without additional chemotherapy, do not improve the overall survival in comparison with monotherapy.	1b

### 7.2.5 Recommendation

	GR
Monotherapy with IFN- $\alpha$ or high-dose bolus IL-2 should not routinely be recommended as first-line therapy in mRCC.	A

### 7.3 Drugs that target VEGF, including other receptor kinases and mammalian target of rapamycin (mTOR)

Recent advances in molecular biology have led to the development of several novel agents for treating mRCC (Table 7.2). In sporadic clear-cell RCC, hypoxia-inducible factor (HIF) accumulation due to von Hippel-Lindau (VHL) inactivation results in an overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), both of which promote neoangiogenesis (17-19). This process substantially contributes to the development and progression of RCC. At present, there are several targeting drugs approved for treating mRCC in both the USA and Europe:

- sorafenib (Nexavar<sup>®</sup>);
- sunitinib (Sutent<sup>®</sup>);
- bevacizumab (Avastin<sup>®</sup>) combined with IFN- $\alpha$ ;
- pazopanib (Votrient<sup>®</sup>);
- temsirolimus (Torisel<sup>®</sup>);
- everolimus (Afinitor<sup>®</sup>);
- axitinib (Inlyta<sup>®</sup>).

New agents targeting angiogenesis are under investigation, as well as combinations of these new agents with each other or with cytokines. Tivozanib and dovitinib have been investigated in phase III trials and are currently not approved. Most published trials have selected for clear-cell carcinoma subtypes, and consequently no evidence-based recommendations can be given for non-clear-cell subtypes.

In the major phase III trials leading to registration of the approved targeted agents, patients were stratified according to the MSKCC risk model, as published in 2002 (3) (Table 7.1). Since the MSKCC (Motzer) criteria were developed during the cytokine era, an international database consortium has established and validated a risk model that may yield a more accurate prognosis for patients treated in the era of targeted therapy. This model is known as the Database Consortium Model (DCM). Neutrophilia and thrombocytosis have been added to the list of MSKCC risk factors while lactate dehydrogenase (LDH) has been removed as a prognostic factor (20).

The DCM has recently been used to establish data on conditional survival that can be used to counsel patients (21). The DCM has been validated and compared with the risk model of the Cleveland Clinic Foundation (CCF), the French model, MSKCC model, and the International Kidney Cancer Working Group (IKCWG) model. The DCM showed a concordance level of 0.66, which did not differ from the other models, indicating that a ceiling has been reached for clinical risk models to predict prognosis based solely on clinical factors. The reported versus predicted number of deaths at 2 years was most similar in the DCM to the other models (22). The DCM has been externally validated for use in the era of targeted therapy (22).

**Table 7.2: Median overall survival and percentage of patients surviving 2 years treated in the era of targeted therapy per DCM risk group, based on the publications by Heng et al. (20,22)**

Database Consortium Model ***	Patients**		Median OS* (months)	2-y OS (95% CI) **
	n	%		
Favourable	157	18	43.2	75% (65-82%)
Intermediate	440	52	22.5	53% (46-59%)
Poor	252	30	7.8	7% (2-16%)

\* Based on (22); \*\* based on (20); CI = confidence intervals; OS = overall survival.

#### 7.3.1 Tyrosine kinase inhibitors

##### 7.3.1.1 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 prior systemic immunotherapy or in patients unfit for immunotherapy.

The trial reported a 3-month improvement in progression-free survival (PFS) in favour of sorafenib (23). Median PFS was 5.5 months in the sorafenib group and 2.8 months in the placebo group (HR: 0.44; 95% CI: 0.35-0.55;  $p < 0.01$ ). Overall survival (OS) appeared to improve in patients who crossed over from placebo to sorafenib treatment (24). A randomized phase II trial in patients with previously untreated mRCC failed to show superiority of sorafenib compared to IFN- $\alpha$  (25). A number of randomized phase III studies have used sorafenib

as the control arm in sunitinib- refractory disease versus axitinib, dovitinib and temsirolimus. None of these trials showed superior survival compared to sorafenib.

### 7.3.1.2 Sunitinib

Sunitinib is an oral tyrosine kinase (TK) inhibitor. It selectively inhibits PDGFR, VEGFR, c-KIT, and FLT-3 and has antitumour and anti-angiogenic activity. Phase II trials with sunitinib as second-line monotherapy in patients with mRCC demonstrated a partial response in 34-40% of patients and stable disease > 3 months in 27-29% of patients (26).

In a pivotal phase III trial of first-line monotherapy comparing treatment with sunitinib versus IFN- $\alpha$ , sunitinib achieved a longer PFS than IFN- $\alpha$  (11 versus 5 months;  $p < 0.000001$ ). The results suggested that monotherapy with IFN- $\alpha$  was inferior to sunitinib in MSKCC good-risk and intermediate-risk patients with mRCC (27). Overall survival was 26.4 and 21.8 months in the sunitinib and IFN- $\alpha$  arms, respectively ( $p = 0.05$ ) (27). In patients who crossed over from IFN- $\alpha$  to sunitinib ( $n = 25$ ), median OS was 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, median OS reached 28.1 months in the sunitinib group versus 14.1 months in the IFN- $\alpha$  group ( $p = 0.003$ ).

In a randomized phase II trial including 292 patients, sunitinib 50 mg/day (4 weeks on/2 weeks off) was compared with a continuous uninterrupted dosage of sunitinib 37.5 mg/day in patients with clear-cell mRCC (28). The median time to progression (TTP) with sunitinib 50 mg (4 weeks on/2 weeks off) ( $n = 146$ ) was 9.9 months versus 7.1 months for 37.5 mg/day continuous dosing ( $n = 146$ ). The overall response rate (ORR) was 32% for 50 mg (4 weeks on/2 weeks off) versus 28% for 37.5 mg continuous dosing. No significant differences were observed with regard to OS (23.1 vs. 23.5 months;  $p = 0.615$ ), commonly reported adverse events, or patient-reported renal cancer symptoms. Because of the statistically non-significant but numerically longer TTP with the standard 50 mg (4 weeks on/2 weeks off) dosage, the authors recommended using this regimen.

### 7.3.1.3 Pazopanib

Pazopanib is an oral angiogenesis inhibitor that targets VEGFR, PDGFR, and c-KIT.

In a prospective randomized trial of pazopanib versus placebo in treatment-naïve mRCC patients (54%) and cytokine-treated patients (46%), there was a significant improvement in PFS and tumour response (29). The median PFS with pazopanib compared with placebo was:

- 9.2 versus 4.2 months in the overall study population (HR: 0.46; 95% CI: 0.34-0.62;  $p < 0.0001$ );
- 11.1 versus 2.8 months for the treatment-naïve subpopulation (HR: 0.40; 95% CI: 0.27-0.60;  $p < 0.0001$ );
- 7.4 versus 4.2 months for the cytokine-pretreated subpopulation (HR: 0.54; 95% CI: 0.35-0.84;  $p < 0.001$ ).

A randomized phase III non-inferiority trial comparing pazopanib with sunitinib (COMPARZ) established pazopanib as another first-line option. It showed pazopanib was not associated with a significantly worse PFS or OS compared to sunitinib. The two drugs had different toxicity profiles (30), with QoL reported as better with pazopanib. In another patient-preference study (PISCES), patients significantly preferred pazopanib to sunitinib in a double-blind trial due to symptomatic toxicity (31). Both studies are limited by the fact that intermittent therapy (sunitinib) is being compared with continuous therapy (pazopanib).

### 7.3.1.4 Axitinib

Axitinib is an oral selective second-generation inhibitor of VEGFR-1, -2, and -3 with minimal inhibition of other targets and has a short half-life. Axitinib was first evaluated as a second-line treatment. In the AXIS trial (a randomized phase III trial of axitinib versus sorafenib in patients in whom previous cytokine treatment or targeted agents had failed), the sample size calculation was based on a 40% improvement in median PFS from 5 months to 7 months in patients randomly assigned to receive axitinib (32).

Sorafenib was chosen as the comparator because at the time the trial was designed there was no standard for second-line treatment after failure of a previous VEGF- targeted therapy. With 723 patients included, the overall median PFS was 6.7 months for patients in the axitinib group versus 4.7 months for those in the sorafenib group (HR: 0.67; 95% CI: 0.54-0.81). The difference in PFS was greatest in patients in whom cytokine treatment had failed: axitinib 12.1 (10.1-13.9) months versus 6.5 (6.3-8.3) months for sorafenib (HR: 0.464; 95% CI: 0.318-0.676;  $p < 0.0001$ ). For those in whom sunitinib had failed ( $n = 194$  axitinib and  $n = 195$  sorafenib), axitinib was associated with a PFS of 4.8 months (95% CI: 4.5-6.4) versus 3.4 months (95% CI: 2.6-4.7) for sorafenib ( $p < 0.01$ ).

In the AXIS trial, axitinib showed  $\geq$  grade 3 toxicity for diarrhoea in 11%, hypertension in 16%, and fatigue in 11%. Across all grades, nausea was recorded in 32%, vomiting in 24%, and asthenia in 21%. Overall survival



was a secondary end-point of the trial in which crossover was not permitted. Final analysis of OS showed no significant differences between axitinib and sorafenib in second-line treatment (33,34).

Axitinib has been investigated in two published first-line studies (35,36). The first was a double-blind phase II RCT, which investigated the efficacy and safety of axitinib dose titration in previously untreated patients with mRCC.

Although the objective response rate was higher in patients treated to toxicity, the median PFS in the relatively small patient subgroups was 14.5 months (95% CI: 9.2-24.5) in the axitinib titration group, 15.7 months (95% CI: 8.3-19.4) in the placebo titration group, and 16.6 months (94% CI: 11.2-22.5) in non-randomized patients (35). This supports the hypothesis that dose escalation is associated with higher response rates.

In a parallel randomized phase III trial of axitinib versus sorafenib in first-line treatment-naïve clear-cell mRCC, median PFS was much lower for axitinib. In addition, this study failed to demonstrate a significant difference in median PFS between patients treated with axitinib or sorafenib (10.1 months [95% CI: 7.2-12.1] vs. 6.5 months [95% CI: 4.7-8.3]; HR: 0.77; 95% CI: 0.56-1.05) (36). Although PFS was longer with axitinib than sorafenib in patients with ECOG PS 0 (13.7 vs. 6.6 months; HR: 0.64; 95% CI: 0.42-0.99; one-sided  $p = 0.022$ ), no conclusions can be drawn because the subgroup analysis was underpowered. As a result of this study, axitinib is not approved for first-line therapy.

#### 7.3.1.5 Other Tyrosine kinase inhibitors studied in RCC

Tivozanib, an oral selective TKI targeting all three VEGF receptors, and dovitinib, a multi-targeted receptor TKI, have been investigated in phase III trials (37,38). Based on the results of these trials, both drugs are not approved for the treatment of mRCC.

### 7.3.2 Monoclonal antibody against circulating VEGF

#### 7.3.2.1 Bevacizumab monotherapy and bevacizumab + IFN- $\alpha$

Bevacizumab is a humanized monoclonal antibody that binds isoforms of VEGF-A. Bevacizumab, 10 mg/kg every 2 weeks, in patients refractory to immunotherapy was associated with an increase in overall response (OR) of 10% and in PFS in comparison with placebo (29). A double-blind phase III trial (AVOREN) ( $n = 649$ ) in patients with mRCC compared bevacizumab + IFN- $\alpha$  with IFN- $\alpha$  monotherapy (8). Median OR was 31% in the bevacizumab + IFN- $\alpha$  group versus 13% in the group receiving only IFN- $\alpha$  ( $p < 0.0001$ ). Median PFS increased significantly from 5.4 months with IFN- $\alpha$  to 10.2 months with bevacizumab + IFN- $\alpha$  ( $p < 0.0001$ ), but only in good-risk and intermediate-risk patients. No benefit was seen in poor-risk patients. Median OS in the AVOREN trial, which allowed crossover after progression, was 23.3 months for bevacizumab-IFN- $\alpha$  versus 21.3 months for IFN- $\alpha$  alone ( $p = 0.336$ ) (39).

A similarly designed trial (CALGB 90206), including 732 patients (40,41), of bevacizumab (10 mg/kg intravenously every 2 weeks) + IFN- $\alpha$  (9 million units subcutaneously three times weekly) versus IFN- $\alpha$  (9 million units subcutaneously three times weekly) showed a median PFS of 8.5 months for the combination versus 5.2 months for IFN- $\alpha$  alone. Median OS with a crossover design was 18.3 months for the combination versus 17.4 months for IFN- $\alpha$  alone. The combination of bevacizumab + IFN- $\alpha$  had a higher overall response rate of 25% (95% CI: 20.9-30.6%) compared to 13.1% (95% CI: 9.5-17.3%) with IFN- $\alpha$  monotherapy ( $p < 0.0001$ ). The overall toxicity was greater for bevacizumab + IFN- $\alpha$ , with significantly more grade 3 hypertension (9% vs. 0%), anorexia (17% vs. 8%), fatigue (35% vs. 28%), and proteinuria (13% vs. 0%).

### 7.3.3 Mammalian target of rapamycin (mTOR) inhibitors

#### 7.3.3.1 Temsirolimus

Temsirolimus is a specific inhibitor of mammalian target of rapamycin (mTOR) (42). Patients with modified high-risk mRCC were randomly assigned in a phase III trial (NCT00065468) to receive first-line treatment with temsirolimus or IFN- $\alpha$  monotherapy, or a combination of both. In the temsirolimus group, median OS was 10.9 months versus 7.3 months in the IFN- $\alpha$  group ( $p < 0.0069$ ). However, OS in the temsirolimus + IFN- $\alpha$  group was not significantly superior to IFN- $\alpha$  alone (10). Toxicity in the IFN- $\alpha$  group was marked, which may partly be due to the high doses used. A second study investigated temsirolimus versus sorafenib in patients who had previously failed sunitinib. This randomized phase III trial (INTORSECT) failed to demonstrate a benefit in terms of PFS, but showed a significant OS benefit for temsirolimus (43). Based on these results, temsirolimus is not recommended in patients who have VEGF TKI refractory disease.

#### 7.3.3.2 Everolimus

Everolimus is an oral mTOR inhibitor, which is established in the treatment of VEGF- refractory disease. A phase III study (RECORD-1) compared everolimus + best supportive care (BSC) versus placebo + BSC in

patients in whom previous anti-VEGFR treatment had failed (or who were previously intolerant of VEGF-targeted therapy). Median PFS was 4.0 months with everolimus versus 1.9 months with placebo ( $p < 0.001$ ). In the RECORD-1 trial, 124 patients (46%) had received sunitinib as the only previous systemic treatment, with a PFS of 4.0 months (95% CI: 3.7-5.5 months). RECORD-1 included patients who failed multiple lines of VEGF-targeted therapy, supporting its use in third- and fourth-line settings (as well as a second-line setting) (44).

A randomized phase II trial of sunitinib versus everolimus in treatment-naïve mRCC followed by either sunitinib or everolimus upon progression (RECORD-3) was reported at ASCO 2013 (45). The median PFS for the respective drugs in first-line was 7.9 (95% CI: 5.6-8.2) months for everolimus and 10.7 (95% CI: 8.2-11.5) months for sunitinib. These results showed significant PFS benefit for sunitinib compared to everolimus in the first-line setting. A large number of the crossover patients did not receive the planned therapy making further analysis complex and underpowered. A mature analysis of this study is awaited.

## **7.4 Therapeutic strategies and recommendations**

### **7.4.1 Therapy for treatment-naïve patients with clear-cell mRCC**

Pivotal phase III trials have established sunitinib and bevacizumab plus IFN- $\alpha$  as first-line treatment options in treatment-naïve patients with clear-cell mRCC and a good-to-intermediate risk score. The COMPARZ study has demonstrated that pazopanib and sunitinib have similar efficacy at different toxicity profiles. This study therefore firmly establishes pazopanib as another first-line option (30). On the basis of trial results and limitations in study design, axitinib and tivozanib are not approved for therapy of treatment-naïve mRCC.

### **7.4.2 Sequencing targeted therapy**

#### **7.4.2.1 Following progression of disease with VEGF-targeted therapy**

Several phase II and III trials have investigated therapeutic options for patients who have progressed on first-line VEGF-targeted therapy. RECORD-1 established sequential sunitinib until progression of disease followed by everolimus as one of the treatment options for patients with mRCC (44). The AXIS trial is the only recent randomized phase III superiority trial comparing two TKIs after failure of a prior TKI. The results and interpretation are described under 7.3.1.4 above (32-34). Comparison of RECORD-1 data with the AXIS data is not advised due to differences in the patient populations (32-34,44).

INTORSECT is the only randomized phase III superiority trial to compare directly an mTOR inhibitor and TKI (temsirolimus vs. sorafenib) after disease progression on sunitinib (43). Median PFS in the temsirolimus and sorafenib arms were 4.3 and 3.9 months, respectively (HR 0.87; 95% CI: 0.71-1.07). These findings did not reach significance (two-sided  $p = 0.19$ ). However, there was a significant difference in OS in favour of sorafenib (HR 1.31; 95% CI: 1.05-1.63; two-sided  $p = 0.01$ ). However these data are not necessarily relevant to other mTOR inhibitors such as everolimus.

Therefore, no firm recommendations can currently be made as to the best sequence of targeted therapy, beyond the recommendation that VEGF-targeted therapy should be used for patients with good- and intermediate-risk disease.

#### **7.4.2.2 Treatment after progression of disease with mTOR inhibition**

There is very limited data to address this issue. In view of the efficacy of VEGF-targeted therapy in renal cancer, a switch to VEGF-targeted therapy is advised (expert opinion). Only 12 patients (3%) in both arms in AXIS were treated with temsirolimus as first-line therapy, and no recommendations can be made (32-34). The data from RECORD-3 is perhaps the most robust but not mature enough to make recommendations (45). Nevertheless sunitinib in this setting appears to have activity and is therefore an attractive option for treatment.

#### **7.4.2.3 Treatment after progression of disease with cytokines**

Randomized controlled trials established sorafenib, axitinib and pazopanib as therapeutic options in this setting with a median PSF achieved of 5.5, 12.1 and 7.4 months, respectively. Based on the AXIS data, axitinib is superior to sorafenib in patients previously treated with cytokine therapy (32-34).

#### **7.4.2.4 Treatment after second-line targeted therapy**

Subset analysis of the RECORD-1 study demonstrated the activity of everolimus versus placebo in patients who had received more than one line of targeted therapy. In this study 26% of patients were treated with two or more lines of VEGF-targeted therapy and significant benefits were seen (HR 0.28;  $p < 0.0001$ ). Although the GOLD trial failed to demonstrate superior efficacy of dovitinib over sorafenib in patients with mRCC who had experienced disease progression after receiving prior VEGF- and mTOR-targeted therapies, the results suggest efficacy and safety of sorafenib in the third-line setting (OS = 11 months for both arms) (38).

#### 7.4.3 **Combination of targeted agents**

Currently, there are no combinations of targeted agents that can be recommended, based on phase II and III studies demonstrating increased toxicity and no benefit in terms of PFS, OS or response. An early randomized phase II study of bevacizumab + erlotinib was not superior in terms of PFS than bevacizumab + placebo (46). TORAVA, a randomized phase II study (47), showed that toxicity of bevacizumab + temsirolimus was much greater than anticipated. Another randomized phase II trial investigated the combination of bevacizumab + temsirolimus, bevacizumab + sorafenib or sorafenib + temsirolimus versus bevacizumab alone (BeST) and was reported at ASCO 2013 (48). The combinations were not superior to single-agent bevacizumab for the PFS primary end-point. Common severe toxicities were more prevalent with combinations than with bevacizumab single-agent.

Both RECORD-2 and INTORACT studies investigated combinations in treatment-naïve patients. The INTORACT trial investigated the concept of bevacizumab + temsirolimus versus bevacizumab + IFN- $\alpha$  in a phase III study (49). RECORD-2 was presented at ESMO 2012 and used a randomized phase II design to investigate bevacizumab + everolimus versus bevacizumab + IFN- $\alpha$  (50). Both combinations were not superior in terms of PFS or OS.

#### 7.4.4 **Non-clear cell renal cancer**

No recommendations can be made at present. No phase III trials on systemic treatment of patients with non-clear cell RCC have been reported. Expanded access programmes and subset analysis from RCC studies suggest the outcome of these patients with targeted therapy is less good than for clear-cell RCC. Targeted treatment in non-clear cell RCC has focused on temsirolimus, everolimus, sorafenib and sunitinib (10,51-53).

The most common non-clear cell subtypes are papillary type 1 and 2 RCCs, but for this subtype, there is a lack of prospective randomized trials. There are small single-arm data for both sunitinib and everolimus (53-56). Either of these agents can be used but there is no data to compare them. A non-randomized phase II trial for both types of papillary RCC treated with everolimus (RAPTOR), reported at ESMO 2013 (56), showed median PFS of 3.7 months (95% CI: 2.3-5.5) per central review in the intention-to-treat population with a median OS of 21.0 months (95% CI: 15.4-28.0).

Another non-randomized phase II trial investigated foretinib (a dual MET/VEGFR2 inhibitor) in patients with papillary RCC. Toxicity was acceptable with a high response rate in patients with germline MET mutations (57). This is a promising area for further research.

Collecting-duct cancers are resistant to systemic therapy. There is a lack of data to support specific therapy in this subset of patients. There is limited data supporting the use of targeted therapy in other histological subtypes such as chromophobe tumours. These tumours have been included in prospective studies but the numbers are small, and specific subset analysis has not been performed (10,51).

Patients should be treated in the framework of clinical trials. If a trial is not available, a decision can be made in consultation with the patient to perform treatment in line with clear-cell RCC.

**Table 7.3: European Association of Urology 2014 evidence-based recommendations for systemic therapy in patients with mRCC**

RCC type	MSKCC risk group (3)	First-line	LE <sup>^</sup>	Second-line*	LE <sup>^</sup>	Third-line*	LE <sup>^</sup>	Later lines	LE
Clear cell*	Favourable, Intermediate and poor	sunitinib pazopanib bevacizumab + IFN favourable-intermediate only)	1b 1b 1b	after VEGFR: axitinib sorafenib <sup>#</sup> everolimus after cytokines: sorafenib <sup>#</sup> axitinib pazopanib	2a 2a 2a  1b 2a 2a	after VEGFR: everolimus  after mTOR: sorafenib	2a   1b	any targeted agent	4
Clear cell*	poor <sup>¶</sup>	Temsirolimus	1b	any targeted agent					
Non-clear cell <sup>§</sup>	any	sunitinib everolimus temsirolimus	2a 2b 2b	any targeted agent	4				

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

\* Doses: IFN-α9 MU three times per week subcutaneously, bevacizumab 10 mg/kg biweekly intravenously; sunitinib 50 mg daily orally for a period of 4 weeks, followed by 2 weeks of rest (37.5 mg continuous dosing did not show significant differences); temsirolimus 25 mg weekly intravenously; pazopanib 800 mg daily orally. Axitinib 5 mg twice daily, to be increased to 7 mg twice daily, unless greater than grade 2 toxicity, blood pressure higher than 150/90 mmHg, or the patient is receiving antihypertensive medication. Everolimus, 10mg daily orally.

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

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

# Sorafenib was inferior to axitinib in a RCT in terms of PFS but not OS (34).

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

#### 7.4.5 Conclusions

	LE
Tyrosine kinase inhibitors (TKIs) increase the progression-free survival and/or overall survival as both first-line and second-line treatments for clear-cell mRCC.	1b
Axitinib has proven efficacy and superiority in terms of PFS as a second-line treatment after failure of cytokines and VEGF-targeted therapy in comparison with sorafenib.	1b
Sunitinib is more effective than IFN-α in treatment-naïve patients.	1b
A combination of bevacizumab and IFN-α is more effective than IFN-α in treatment-naïve low-risk and intermediate-risk patients.	1b
Pazopanib is superior to placebo in both naïve mRCC patients and post-cytokine patients.	1b
Pazopanib is not inferior to sunitinib in clear-cell mRCC patients.	1b
Temsirolimus monotherapy prolongs overall survival compared to IFN-α in poor-risk mRCC.	1b
Everolimus prolongs the progression-free survival in patients who have previously failed or are intolerant of VEGF-targeted therapy.	1b
Sorafenib appears to have broad activity in a spectrum of settings in clear-cell patients who have been previously treated with cytokine or targeted therapies.	4
Both mTOR inhibitors (everolimus and temsirolimus) and VEGF-targeted therapies (sunitinib or sorafenib) can be used in non-clear cell RCC.	3
No combination has ever proven to be better than single-agent therapy.	1a

#### 7.4.6 Recommendations for systemic therapy for mRCC

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

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## 8. FOLLOW-UP AFTER RADICAL OR PARTIAL NEPHRECTOMY OR ABLATIVE THERAPIES FOR RCC

### 8.1 Introduction

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

- Postoperative complications
- Renal function
- Local recurrence after partial nephrectomy or ablative treatment
- Recurrence in the contralateral or ipsilateral (after partial nephrectomy) kidney
- Development of metastases

The method and timing of examinations have been the subject of many publications. There is no consensus on surveillance after treatment for RCC, and in fact there is no evidence that early versus later diagnosis of recurrences improves survival. However, follow-up is important in order to increase the available information on RCC, and it should be performed by the urologist, who should record the time that has elapsed up to a recurrence or the development of metastases. Postoperative complications and renal function are readily assessed by the patient's 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 postoperative deterioration. Renal function (1,2) and non-cancer survival (3-5) can be optimized by carrying out 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, since 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 carrying out surveillance is to identify local recurrences or metastases at an early stage. This is particularly important with ablative therapies such as cryotherapy and radiofrequency ablation (RFA). Although the local recurrence rate is higher than after conventional surgery, the patient may still be cured using repeat ablative therapy or radical nephrectomy (10) (LE: 3). In metastatic disease, more extended tumour growth can limit the opportunity for surgical resection, which is considered the standard therapy in cases of resectable and preferably solitary lesions. In addition, in 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 the follow-up, taking into account the risk of a recurrence or metastases developing. Although there is no randomized evidence, there have been large studies examining prognostic factors with long follow-up periods, from which some conclusions can be drawn (11-13) (LE: 4):

- The sensitivity of chest radiography for small metastases is poor and US has limitations. Surveillance should therefore not be based on these imaging modalities (14). With low-risk tumours, the surveillance intervals should be adapted relative to radiation exposure and benefit. To reduce radiation exposure MRI can be used.
- When the risk of relapse is intermediate or high, CT of the chest and abdomen is the investigation of choice, although the significant morbidity associated with the radiation exposure involved in repeated CT scans should be taken into account (15). Findings using CT can clearly reveal metastatic lesions from RCC (16).
- Surveillance should also include clinical evaluation of renal function and cardiovascular risk factors.
- Positron-emission tomography (PET) and PET-CT as well as bone scintigraphy are not the standard of care in RCC surveillance, due to their limited specificity and sensitivity.
- Depending on the availability of effective new 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 with 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 the tumours are detected when small. In addition, for tumours < 4 cm in size, there is no difference between partial and radical nephrectomy with regard to recurrences during the follow-up (17) (LE: 3).

Several authors, notably Kattan, Liebovich, UCLA, and Karakiewicz (18-21), have designed scoring systems and nomograms to quantify the likelihood of patients developing tumour recurrences, metastases, and subsequent death. These systems have been compared and validated (22) (LE: 2). Using prognostic variables, several stage-based surveillance regimens have been proposed (23,24), but these do not include ablative therapies. A postoperative nomogram is available for estimating the likelihood of freedom from recurrence at 5 years (25). Most recently, a preoperative prognostic model based on age, symptoms, and TNM staging has been published and validated (26) (LE: 3). There is therefore a need for a surveillance algorithm for monitoring patients after treatment for RCC, recognizing not only the patient risk profile, but also the efficacy of the treatment given (Table 8.1).

**Table 8.1: Proposed algorithm for surveillance following treatment for RCC, taking into account patient risk profile and treatment efficacy**

Risk profile	Treatment	Surveillance						
		6 mo	1 y	2 y	3 y	4 y	5 y	> 5 y
Low	RN/PN only	US	CT	US	CT	US	CT	Discharge
Intermediate	RN/PN/ cryo/RFA	CT	CT	CT	US	CT	CT	CT once every 2 years
High	RN/PN/ cryo/RFA	CT	CT	CT	CT	CT	CT	CT once every 2 years

*Cryo = cryotherapy; CT = computed tomography of chest and abdomen, or MRI = magnetic resonance imaging; PN = partial nephrectomy; RFA = radiofrequency ablation; RN = radical nephrectomy; US = ultrasound of abdomen, kidneys and renal bed.*

### 8.3 Conclusions and recommendations for surveillance following radical or partial nephrectomy or ablative therapies for RCC

Conclusions	LE
The aim of surveillance is to detect either local recurrence or metastatic disease while the patient is still surgically curable. Renal function should be assessed.	4
Risk stratification should be based on preexisting classification systems; like the UISS integrated risk assessment score ( <a href="http://urology.ucla.edu/body.cfm?id=443">http://urology.ucla.edu/body.cfm?id=443</a> [27]).	4

Recommendations	GR
Follow-up after treatment for RCC should be based on a patient's risk factors and the type of treatment delivered.	C
For low-risk disease, CT/MRI can be used infrequently.	C
In the intermediate-risk group, intensified follow-up should be performed, including CT/MRI scans at regular intervals in accordance with a risk-stratified nomogram.	C
In high-risk patients, the follow-up examinations should include routine CT/MRI scans.	C
There is an increased risk of intrarenal recurrences in 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

### 8.4 Research priorities

There is a clear need for future research to determine whether follow-up can optimize the survival of patients. Further information should be sought, at what time point restaging has the highest chance to detect recurrence. Prognostic markers at surgery should be investigated to determine the risk of relapse over time.

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## 9. ABBREVIATIONS USED IN THE TEXT

*This list is not comprehensive for the most common abbreviations*

ACD-RCC	acquired cystic disease-associated RCC
ACKD	acquired cystic kidney disease
CaX	carbonic anhydrase
CCF	Cleveland Clinic Foundation
CKD	cystic kidney disease
c-KIT	a tyrosine-protein kinase encoded by c-kit gene, also called CD117.
CPB	cardiopulmonary bypass
CRP	C-reactive protein
CRT	conventional radiotherapy
CSS	cancer-specific survival rates
DCM	database consortium model
DHCA	deep hypothermic circulatory arrest
DSS	disease-specific survival
eGFR	estimated glomerular filtration rate
e-LND	extended lymph node dissection
FNA	fine-needle aspiration
FSRT	fractionated stereotactic radiotherapy
GFR	glomerular filtration rate
IKCWG	International Kidney Cancer Working Group
LDH	lactate dehydrogenase
LND	lymph node dissection
LN <sub>s</sub>	lymph nodes
MRA	MRI biphasic angiography
MSKCC	Memorial Sloan-Kettering Cancer
MTS	cell proliferation assay
ORR	overall response rate
OS	overall survival
PADUA	Preoperative Aspects and Dimensions Used for an Anatomical
PD-1L	programmed death-1 ligand
PET	positron-emission tomography
PFS	progression-free survival
PN	partial nephrectomy
RFS	recurrence-free survival rates
RN	radical nephrectomy
SRS	stereotactic radiosurgery
TCRCC	Tubulocystic renal cell carcinoma
TKI	tyrosine kinase inhibitors
TRCC	MIT translocation renal cell carcinomas
TTP	time to progression
US	ultrasound
VTT	venous tumour thrombus
WBRT	whole brain radiotherapy

### **Conflict of interest**

All members of the Renal Cell Cancer working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

