Guidelines on Renal Cell Carcinoma

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European Association of Urology

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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 10 clinicians with particular expertise in this field of urological care.

The guideline update methodology is detailed below, but 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.

Without the inspiration and practical assistance provided by Prof. James N'Dow, this would have been unattainable. We owe him and his UCAN team (Urological Cancer Charity, Scotland) a debt of gratitude. In the course of 2012, Dr. Thomas Lam joined our efforts and his support of the review team at his home institution (Aberdeen University Hospital), and in particular of the three young urologists who joined the RCC panel last year (Dr. Saeed Dabestani, Dr. Fabian Hofmann and Dr. Lorenzo Marconi), has been invaluable. Drs. Dabestani, Hofmann and Marconi have taken on the data management of the systematic reviews underpinning this 2013 publication.

For this 2013 update, the Panel did not manage to complete all systematic reviews in a timely fashion. As a result, sections of the document have been updated following a structured literature assessment. The focus for 2014 is to proceed with the systematic review, aiming for the complete guidelines document to be based on a uniformly high level of data work-up.

1.2 Methodology

*1.2.1 **Data identification***

All chapters of the 2013 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.

Table 1: Description of update and summary of review methodology

Chapter	**Brief description of review methodology**
Introduction	Not applicable
Epidemiology and etiology	The chapter has been updated using a structured data assessment
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
Classification and prognostic factors	The chapter has been updated using a structured data assessment
Other renal tumors	The chapter has been updated using a traditional narrative review
Treatment of localised disease	The chapter has been updated using a systematic review
Systemic therapy for metastatic disease	The chapter has been updated using a mixed methods approach. Literature searching, study identification and data abstraction were carried out using systematic review methodology, with 54 studies being deemed eligible for inclusion. Ten of the most important and influential studies, as determined by consensus, were data-abstracted and the review was based on these 10 studies
Surveillance following radical or partial nephrectomy or ablative therapies	The chapter has been updated using a traditional narrative review

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 September 2012. 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. A narrative synthesis of the evidence was produced.

The remaining parts of the guideline have been updated using a traditional narrative review strategy. Structured literature searches using an expert consultant 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. 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).

Most reviewed studies are retrospective analyses that include some larger multicentre studies and well-designed controlled studies. As only a few randomised controlled trials are available, there is a certain lack of data with a strong evidence base. Conversely, in the systemic treatment of metastasised RCC, a number of randomised studies have been performed, resulting in highly evidence-based recommendations.

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), and guideline recommendations have been graded (Table 3) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (3). Grading aims to provide transparency between the underlying evidence and the recommendation given.

Table 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 randomised controlled trials (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. 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 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, and 2010. This current 2013 printing 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 society's web site: http://www.uroweb.org/guidelines/online-guidelines/.

The RCC panel recognises that there is a constant need to reevaluate the published evidence for this particular topic, but the next update, scheduled for 2014, will focus on covering sections with systematic reviews that could not be completed for the current printing.

1.5 Future goals

In addition to the systematic review, a number of other goals need to be taken into account. These include patient-derived needs, as well as recommendations requested by the ordinary urologist. We will be introducing such thoughts in the coming updates.

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 web site: http://www.uroweb.org/guidelines/.

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2. EPIDEMIOLOGY AND ETIOLOGY

Renal cell carcinoma (RCC) represents 2-3% of all cancers with an age-standardised rate incidence of 5.8 and mortality of 1.4 per 100,000, respectively, in more developed areas (1). The highest incidence all over the world is in the Czech Republic, where in 2010 the incidence rate was 14.62 and mortality 5.17 (age-standardised rate/world per 100,000) (2).

Generally, during the last two decades and until recently, there has been an annual increase of about 2% in the incidence both worldwide and in Europe, although in Denmark and Sweden a continuing decrease has been observed (3). In 2008, it was estimated that there were 88,400 new cases of RCC and 39,300 kidney cancer-related deaths in the European Union (4). In Europe, the overall mortality rates for RCC increased up until the early 1990s, with rates generally stabilising in the following years, but increasing again in recent years (5). There has been a decrease in the 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), the mortality rates are still showing an upward trend, with increasing rates (5). The mortality rate in Europe is 14,500 in females and 24,800 in males (both sexes 39,300) (4).

Renal cell carcinoma is the commonest solid lesion in the kidney and accounts for approximately 90% of all kidney malignancies. It includes different types, with specific histopathological and genetic characteristics (6). There is a 1.5:1.0 predominance of men over women, with the peak incidence occurring between the ages of 60 and 70. Etiological factors include lifestyle factors such as smoking, obesity, and hypertension (7-11). Obesity is a controversial issue, as there have been reports showing a better prognosis for obese patients suffering from renal cell cancer (12) Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC (13,14). The most effective prophylaxis is to avoid cigarette smoking and obesity.

As tumours are detected more frequently using imaging techniques such as ultrasound and computed tomography (CT), the numbers of RCCs diagnosed incidentally has increased. These tumours are more often smaller and at a lower stage (15-17).

2.1 Conclusion

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

2.2 Recommendation

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

2.3 References

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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 hematuria, 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 4) (LE: 4). A few symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough (5) (LE: 3).

Table 4. Most common paraneoplastic syndromes

• Hypertension • Cachexia • Weight loss • Pyrexia • Neuromyopathy • Amyloidosis • Elevated erythrocyte sedimentation rate • Anemia • Abnormal liver function • Hypercalcemia • Polycythemia

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;
- Nonreducing varicocele and bilateral lower extremity edema, that 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 ultrasonography (US) or computed tomography (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 4).

Table 4: 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.	Benign
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 (42-111)

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 anesthesia 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 ultrasound 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 hematoma and hematuria are the most frequently reported complications, while clinically significant bleeding is unusual (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 (nonfragmented, > 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 centers, 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% of core biopsies are nondiagnostic (42-50,54,55,57-75) (LE: 2b). If a biopsy is nondiagnostic, 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

The histological diagnosis of RCC is established after surgical removal of renal tumours with radical or partial nephrectomy or after percutaneous biopsy.

According to the World Health Organization (112), there are three major histological subtypes of RCC:

- Clear cell (cRCC, 80-90%)
- Papillary (pRCC, 10-15%)
- Chromophobe (chRCC, 4-5%)

These RCC types can be differentiated on the basis of histological and genetic features (110) (LE: 3) (Table 5). Papillary RCC can be further divided into two different subtypes, type 1 and type 2 (Table 5) (113,114) (LE: 3).

Table 5: Major histological subtypes of RCC

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

3.5 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, hematuria, 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: 1, to establish the diagnosis of radiologically indeterminate renal masses; 2, to obtain histology of incidentally detected renal masses in patients who are candidates for nonsurgical treatment (active surveillance, ablative therapies); and 3, to select the most suitable targeted therapy for metastatic renal tumours.

3.6 Recommendations

	GR
In a patient with one or more suspicious laboratory or physical findings, the possible presence of RCC should be suspected.	B
Contrast-enhanced abdominal CT and MRI are recommended for the work-up of patients with RCC. These are the most appropriate imaging modalities for renal tumour staging prior to surgery.	A
A chest CT is most sensitive for assessment of the lung, but at least a plain chest radiograph should be taken for clinical staging.	A
In patients at risk for bone metastases (raised alkaline phosphatase level or bone pain), further evaluation with a bone scan is needed.	A
Evaluation of renal function is recommended before treatment decision in any patient in whom renal impairment is suspected.	B
Percutaneous biopsy is always required before ablative therapy and systemic therapy without previous pathology.	A
Percutaneous biopsy is recommended in active surveillance strategies in order to stratify the follow-up according to tumour histology.	B
When biopsy is indicated, good-quality needle cores should be obtained with a coaxial technique in order to increase the safety of the procedure and maximise its diagnostic yield.	B

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

Table 6: 2009 TNM classification system (1)

T - Primary tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney		
	T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney	
	T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension	
T2	Tumour > 7 cm in greatest dimension, limited to the kidney		
	T2a	Tumour > 7 cm but ≤ 10 cm in greatest dimension	
	T2b	Tumours > 10 cm limited to the kidney	
T3	Tumour extends into major veins or 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)		
N - Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single regional lymph node		
N2	Metastasis in more than 1 regional lymph node		
M - Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
TNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	N2	M0
	Any T	Any N	M1

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

4.2.2 Histological factors

Histological factors include Fuhrman grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system. Fuhrman nuclear grade is the most widely accepted histological grading system in RCC (12). Although affected by intra- and inter-observer discrepancies, it is an independent prognostic factor (13). 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 (14,15) (LE: 3).

According to the WHO classification (16), 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

(17,18). However, the prognostic information provided by the RCC subtype is lost when stratified to tumour stage (18,19) (LE: 3).

Among papillary RCCs, two subgroups with different outcomes have been identified (20): 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 (21). 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 (22-24) (LE: 2b).

4.2.3 ***Clinical factors***

Clinical factors include patient performance status, localised symptoms, cachexia, anaemia, and platelet count (25-28) (LE: 3).

4.2.4 ***Molecular factors***

Numerous molecular markers being 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 (29) and CD44 (cell adhesion) (30,31) (LE: 3). To date, none of these markers has been shown to improve the predictive accuracy of current prognostic systems and their use is therefore not recommended in routine practice. Finally, even though gene expression profiling seems a promising method, it has not helped so far to identify new relevant prognostic factors (32).

4.2.5 ***Prognostic systems and nomograms***

Postoperative prognostic systems and nomograms that combine independent prognostic factors have been developed and externally validated (33-39). 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 (40). Recently, new preoperative nomograms with excellent PAs have been designed (41,42). Table 7 summarises the current most relevant prognostic systems.

4.3 Conclusions

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

4.4 Recommendations

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

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

Prognostic Models		Variables												
		TNM Stage	ECOG PS	Karnofsky PS	RCC related symptoms	Fuhrman grade	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	X						
	Post operative Karakiewicz's nomogram	X			X	X		X						
Metastatic RCC	MSKCC prognostic system			X					X	X	X	X		
	Heng's model			X					X		X	X	X	X

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status; 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 is expected in 2013. The common clear cell renal carcinoma (cRCC), papillary RCC (pRCC) and chromophobe RCC (chRCC) types account for 85-90% of renal malignancies. The remaining 10-15% of renal tumours includes a variety of uncommon, sporadic, and familial carcinomas, some of which have recently been described, and a group of unclassified carcinomas.

5.1 Bellini duct carcinoma (collecting-duct carcinoma)

Collecting-duct carcinoma is a very rare type of RCC, often presenting at an advanced stage of disease. Up to 40% of patients have metastatic spread at initial presentation and most patients die within 1-3 years from the time of primary diagnosis. The hazard ratio in cancer specific survival is in comparison with cRCC 4.49 (2). 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 (3-5). Median survival was 30 months (6). Response to targeted therapies was poor (7).

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 (3). Renal medullary carcinoma is considered to be a subtype of collecting duct carcinoma (8). 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 (3,9,10). Median survival is 5 months (6). Surgical intervention alone is inadequate (9), 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 (11).

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 (12). The hazard ratio in cancer specific survival is in comparison with cRCC (2). Metastatic sarcomatoid RCC is associated with a poor response to systemic therapy. Sunitinib treatment resulted in a modest response rate (13). The combination of gemcitabine and doxorubicin could also be an option (14). (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

There are no strict histopathological criteria for this subtype. In the WHO 2004 classification (1), multilocular cystic RCC is an independent entity, but it is essentially a well-differentiated clear cell RCC (15). This subtype accounts for up to approximately 3.5% of surgically treated kidney tumours (16). To date, metastases of this tumour have not been described (16,17). According to the Bosniak classification, which is based on imaging criteria, multilocular cystic RCC presents as a Bosniak type II or III cystic 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 (both see section 5.11), or a multilocular cyst, all of which are benign lesions. In many cases, a pre-operative biopsy and intra-operative frozen-section analysis does not lead to a correct diagnosis. Fortunately, all these tumours are treated with the same operative strategy. For this reason, if technically feasible, a nephron-sparing procedure is the technique of choice for a complex multicystic renal mass when enhanced density is observed (LE: 3) (GR: B) (15-17, 19,20).

5.6 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.

5.7 Translocation carcinoma (MITF/TFE family translocation-associated carcinoma)

Renal translocation carcinomas are uncommon tumours, which usually occur in children and young adults. Most translocation carcinomas (about 90%) involve the transcription factor E3 (TFE3) located on Xp11.2 and seem to follow a relatively indolent course, despite often being at an advanced stage at presentation, however, the clinical course is most aggressive in adults (3). Basically, there are 2 well-defined subtypes (ASPL/TFE3 and PRCC/TFE 3). VEGF-targeted agents appear to demonstrate some efficacy (21,22). Another rare group of RCCs that show a translocation [t(6; 11) (p21; q12)] has also been reported (3,23). A case report with a metastatic course and a partial response to sunitinib malate was described (24).

5.8 Mucinous tubular and spindle cell carcinoma

This tumour is associated with the loop of Henle. Most mucinous tubular and spindle-cell carcinomas behave in a low-grade fashion (1,3,25).

5.9 Carcinoma associated with end-stage renal disease

Acquired cystic disease-associated renal cell carcinoma, clear cell papillary 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 (26, 27). 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 (27). 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 (28). Although the histological spectrum of tumours within ACKD is similar to that in sporadic RCC, the most predominant form is pRCC, being found in 41-71% of ACKD-associated RCC versus 10% in sporadic RCC. The remaining tumours are mostly cRCC (3,26,27). Tickoo et al. (29) described two new renal tumours associated with ESKD: 'acquired cystic disease-associated RCC' and 'clear-cell pRCC'. To date, these two entities are under conscientious discussion. Clear cell (tubulo) pRCC has been reported in otherwise normal kidneys as well, and has low potential for malignancy (30, 31). The existence of ACKD-associated RCC is in dispute (27). Patients with ESKD should undergo an annual ultrasound evaluation of the kidneys. Minimally invasive radical nephrectomy can be performed safely in these patients (32).

5.10 Metanephric tumours

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

5.11 Renal epithelial and stromal tumours

Renal epithelial and stromal tumours (REST) is a new concept that brings together two benign mixed mesenchymal and epithelial tumours: cystic nephroma and mixed epithelial and stromal tumours (33). 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 (33).

5.12 Oncocytoma

Renal oncocytomas are benign tumours (1) that comprise about 3-7% of all renal tumours (34).
Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard (35, 36). 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), and 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. (LE: 3) (GR: C) (37,38).

5.13 Hereditary kidney tumours

Hereditary kidney tumours can be found as part of the following entities: Von Hippel-Lindau syndrome, hereditary pRCC, Birt-Hogg-Dubé syndrome (see Hybrid oncocytoma-chromophobe carcinoma), hereditary leiomyomatosis and renal cell cancer (HLRCC), tuberous sclerosis, and constitutional chromosome 3 translocation (1,39).

5.14 Mesenchymal tumours

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

5.14.1 ***Angiomyolipoma***

Angiomyolipoma (AML) is a benign mesenchymal tumour composed of a variable proportion of adipose tissue, spindle and 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), 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, 40). AML is associated with a slow and consistent growth rate (0.088 cm/year), and typically has minimal morbidity (41). The main complications of renal AML are retroperitoneal bleeding or bleeding into the urinary collection system, which can be life-threatening (42). The bleeding tendency is related to the angiogenic component of the tumour that includes irregular and aneurysmatic blood vessels (42). The major risk factors for bleeding are tumour size, grade of the angiogenic component of the tumour, and the presence of tuberous sclerosis (42,43). Primary indications for intervention include symptoms such as pain, bleeding, or suspected malignancy.

Prophylactic intervention is justified for:

- large tumours (the recommended threshold of intervention does not exist, the formerly recommended size of > (3) 4 cm wide is disputed) (41, 42, 44);
- females of childbearing age;
- patients in whom follow-up or access to emergency care may be inadequate (43) (LE: 3) (GR: C).

Most cases of AML can be managed by conservative nephron-sparing approaches, although some cases of AML may require complete nephrectomy (43) (LE: 3). Of the standard surgical interventions, selective arterial embolisation (SAE) and radiofrequency ablation (RFA) can be used (41, 42, 44). Although SAE is effective at controlling haemorrhage in the acute setting, it has limited value in the longer-term management of AML (45). Clinical trials of medical management with m-TOR inhibitors are ongoing (46) and sirolimus can be combined with deferred surgery (47).

5.15 New histological entities

New histological entities have recently been described, for which there currently is very little clinical data. Some of these entities are supposed to be included in a new ongoing histopathological classification. These entities include:

- Hybrid oncocytoma-chromophobe RCC
  Hybrid oncocytic/chromophobe tumours (HOCT) of the kidney have been described for the first time in patients with Birt-Hogg-Dubé syndrome (a rare autosomal dominant syndrome characterised by skin hamartomas and multiple renal tumours) in association with renal oncocytosis. A sporadic variant also exists. The tumours seem to behave indolently as no evidence of malignant behaviour has been documented to date. However, these tumours could have a low malignant potential and patients should be followed-up as chromophobe RCC (48, 49).
- Oncocytic papillary renal cell carcinoma - type 3
  This tumour could be termed a pRCC type 3. In comparison with pRCC type I and II, it has no pseudocapsule, no massive necroses, and extrarenal growth is relatively rare. The malignant potential is low (50).
- 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 (51).
- thyroid-like follicular carcinoma of the kidney (52); rare tumour closely mimicking well-differentiated thyroid follicular neoplasms.
- RCC associated with neuroblastoma (1); extremely rare, morphologically heterogeneous entity.
- Renal angiomyoadenomatous tumour (53); the relation with clear cell pRCC (see above 5.9) is discussed (30,31,54).

Table 8: 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 carcinoma	Intermediate	Surgery, NSS
Mucinous tubular and spindle cell carcinoma	Intermediate	Surgery, NSS
Carcinoma associated with end-stage renal disease	Variable	Surgery
Metanephric tumours	Benign	Surgery, NSS
Renal epithelial and stromal tumours (REST)	Low	Surgery, NSS
Oncocytoma	Benign	Observation/surgery, 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.*

5.16 Summary

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

5.17 Recommendations

	LE	GR
Except for angiomyolipomas, most of these less common renal tumours cannot be differentiated from RCC on the basis of radiology and should therefore be treated in the same way as RCC.	3	C
Bosniak cysts ≥ type III should be treated surgically. When possible, a nephron-sparing procedure should be performed in Bosniak type III.	3	C
In oncocytomas verified on biopsy, follow-up is an option.	3	C
In angiomyolipomas, treatment (surgery, thermal ablation, and selective arterial embolisation) can be considered in only very well selected cases. A nephron-sparing procedure is preferred.	3	C
In advanced uncommon types of renal tumours, a standardised oncological treatment approach does not exist.	4	C

5.18 References

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6. TREATMENT OF LOCALISED RCC AND LOCAL TREATMENT OF METASTATIC RCC

A systematic review underpins the findings of sections 6.1 – 6.2. This review included all relevant published literature comparing surgical management of localised RCC (T1-2N0M0) (1,2). Randomised or quasi-randomised controlled trials (RCTs) were included. However, due to the very limited number of RCTs, non-randomised studies (NRS), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from well-defined registries databases were also included. Studies with no comparator group (for example, 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 sections 6.3 – 6.5, a traditional narrative review was performed (see Chapter 1).
For sections 6.6 – 6.7, a systematic review and narrative synthesis of the evidence was performed (see Chapter 1).

6.1 Main comparisons

6.1.1 ***Surgery versus non-surgical treatment***

One matched pair study (derived from the SEER database) compared surgery for small renal masses (≤ 4 cm) with non-surgical management (3). Included were pT1a patients who were assigned to either observation or active surveillance. The analysis showed that surgical therapy had a significant 5 year cancer-specific mortality benefit over non-surgical intervention. However, even though this study was matched, it is marked by allocation bias; the patients assigned to the surveillance arm were older and likely more frail and less suitable candidates for surgery. There was no comparative study addressing this comparison in terms of perioperative and QoL outcomes.

6.1.2 ***Nephron-sparing surgery versus radical nephrectomy***

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

When open partial nephrectomy was compared to open radical nephrectomy the estimated cancer-specific survival rates (CSS) at 5 years were comparable. (4-7). A number of studies compared partial against radical nephrectomy, either performed by an open or laparoscopic approach for renal carcinoma (≤ 4 cm) (8-11). These studies showed that radical nephrectomy was associated with increased mortality from any cause after adjusting for patient characteristics. In studies analysing RCCs 4-7 cm no differences were shown for CSS between partial nephrectomy and radical nephrectomy (11-16). Also when laparoscopic partial nephrectomy and laparoscopic radical nephrectomy was compared in RCCs > 4 cm there was no difference in overall survival (OS), CSS and recurrence-free survival rates (RFS) (17).

In a number of studies various aspects of QoL and safety were compared for open partial and open radical nephrectomy (4-7,18-20). No difference in length of hospital stay (5,6,20), blood transfusions (5,18,20), or mean blood loss was found (5,20). In general, complication rates are inconsistently reported in NRS, and no clear conclusions in favour of one intervention over another can be drawn (21). The mean operative time was longer for the open partial group (20) but others found no such difference (22). Three studies consistently reported worse renal function after radical nephrectomy compared to partial nephrectomy (4,7,18). A greater proportion of patients had impaired postoperative 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 4-7 cm (13). After partial nephrectomy, the mean increase of post-operative creatinine levels was significantly lower. When laparoscopic partial nephrectomy was compared to laparoscopic radical nephrectomy, the estimated GFR in the nephron-sparing group decreased less as compared to the radical nephrectomy group which showed a significantly greater proportion of patients with a 2-stage increase in the CKD stage (17). Another database review (23) compared laparoscopic partial with laparoscopic radical nephrectomy for RCCs > 4 cm in size. The laparoscopic radical nephrectomy group had a significantly greater decrease in estimated GFR and a greater proportion of patients with a CKD 2 stage.

Two studies reported QoL post-surgery for RCC. Patients who underwent partial nephrectomy reported better scores, in many aspects of quality of life (19). 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 complications rates had lower QoL scores (5).

No comparative studies were identified reporting on oncological outcomes for minimally invasive ablative procedures compared with radical nephrectomy.

Patient and tumour characteristics permitting, the current oncological outcomes evidence base suggests that localised RCCs are best managed by NSS rather than by radical nephrectomy irrespective of 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 localised 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.

6.1.3 ***Associated procedures***

6.1.3.1 Adrenalectomy

One prospective NRS compared the outcomes of radical or partial nephrectomy with, or without, ipsilateral adrenalectomy (24). On multivariate analysis, upper pole location was not predictive of adrenal involvement but tumour size proved significant. 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 2,065 patients underwent concurrent ipsilateral adrenalectomy of which 42 were for benign lesions.

6.1.3.2 Lymph node dissection

An extended or radical lymph node dissection does not appear to improve long-term survival following tumour nephrectomy (25). Thus, for staging purposes, lymph node dissection can be limited to the hilar region. In patients with palpable or CT-detected enlarged lymph nodes, resection of the affected lymph nodes should be performed to obtain adequate staging information.

6.1.3.3 Embolisation

Before a routine nephrectomy, there is no benefit in performing tumour embolisation (26,27). In patients who are unfit for surgery, or who present with non-resectable disease, embolisation can control symptoms such as gross haematuria or flank pain (28-30). Embolisation prior to the resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss (31). In selected patients with painful bone or paravertebral metastases, embolisation can help to relieve symptoms (32).

Conclusions	LE
Radical nephrectomy is no longer the standard treatment for low-stage RCC (T1).	3
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.	3

Recommendations	LE	GR
Surgical therapy remains the mainstay of therapy to achieve a cure in the management of RCC.	C	
Patients with low-stage RCC (T1) should undergo nephron-sparing surgery rather than radical nephrectomy whenever possible.	3	B
Adrenalectomy is not recommended, provided a pre-operative CT scan shows the adrenal gland is normal and the intra-operative findings do not suggest intra-adrenal metastatic spread or a direct invasion of the adrenal gland.	3	C
Extended lymphadenectomy is not recommended since it does not appear to improve survival. It should be restricted to staging purposes with dissection of palpable and/or enlarged lymph nodes.	1b	A
In patients unfit for surgery and suffering from massive haematuria or flank pain, embolisation can be a beneficial palliative approach.		C
For solitary renal tumours up to a diameter of 7 cm, nephron-sparing surgery is the standard procedure, whenever technically feasible.	3	C
A minimal tumour-free surgical margin following partial resection of RCC is sufficient to avoid local recurrence.		B

6.2 Techniques of radical and partial nephrectomy

6.2.1 Techniques of radical nephrectomy

There are no randomised studies assessing oncological outcomes of laparoscopic versus open radical nephrectomy. A prospective cohort study (33) and a retrospective database review (5), both of low methodological quality, found similar oncological outcomes for laparoscopic versus open radical nephrectomy. Data from one RCT (34) and two NRSs (5,33) showed 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 (33). There was no difference in number of patients receiving a blood transfusion between the approaches but the perioperative blood loss was significantly less in the laparoscopic arm in all three studies (5,33,34). 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 arm. Post-operative QoL scores were similar between the two groups (5).

In regard to the approach of performing radical nephrectomy, both retroperitoneal or transperitoneal approaches had similar oncologic outcomes in two RTCs (35,36) and one quasi-randomised study (37). There was no significant difference in quality of life variables between the two approaches.

Hand-assisted laparoscopic radical nephrectomy and standard laparoscopic radical nephrectomy was compared in one RCT (37) and one database review (21). Estimated 5-year overall survival, cancer-specific survival, and recurrence free survival rates were comparable between the approaches. Duration of operation was significantly shorter in the hand-assisted compared to the laparoscopic approach but length of hospital stay and time to non-strenuous activities were shorter for standard laparoscopic radical nephrectomy (21,37). However, the sample size was small.

Robot-assisted laparoscopic radical nephrectomy versus laparoscopic radical nephrectomy was compared in one small prospective cohort study (38). There were no local recurrences, port-site or distant metastases, but 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 (39,40). There was no difference in perioperative outcomes.

6.2.2 Techniques of partial nephrectomy and minimally invasive ablative procedures

Laparoscopic partial nephrectomy compared to open partial nephrectomy showed no difference in overall survival (41-44). Regarding the number of deaths during the study period, a lower risk of all cause death was shown in the laparoscopic group in one study (42) while in other studies no difference in the recurrence patterns between laparoscopic and open partial nephrectomy was reported (41,44). In a matched pair analysis (43) the length of hospital stay was significantly shorter and there was less mean blood loss in the laparoscopic partial group. In one database review more blood transfusion events occurred in the laparoscopic group (41). There were no differences between the groups in postoperative mortality events (41,43), DVT events (43), or pulmonary embolism events but the operative time was significantly longer in the laparoscopic partial group (22,43,44). Decline in GFR was greater in the laparoscopic partial nephrectomy group in the immediate postoperative period (44), but not after a follow-up of 3.6 years.

There is no comparative study that reported on oncological outcomes between robotic assisted partial nephrectomy and laparoscopic partial nephrectomy. One study based on a matched-pair analysis (45) showed no difference in perioperative outcomes (10) or in the estimated GFR.

In regard to partial nephrectomy versus minimally invasive ablative procedures, several studies were identified. For radiofrequency-assisted robotic partial nephrectomy versus laparoscopic partial nephrectomy, a database review (46) found no differences between the groups in terms of positive surgical margins and recurrence rates, but the study was marked by very low event rates, a high number of benign tumours, and short-term survival data.

Data on laparoscopic cryoablation versus laparoscopic partial nephrectomy obtained from one database review (47) 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 (48). It should be noted that the studies also included benign tumours and the data should be treated with caution. In a database review (47) and a matched-pair study (48) there were no differences in perioperative outcomes, recovery times, complication rates or postoperative 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 (47,48). In one matched comparison between laparoscopic cryoablation and open partial nephrectomy (49) 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 duration of operation. However, there were only 20 patients in each arm and the follow-up time was short.

Conclusions	**LE**
Laparoscopic radical nephrectomy appears to have a lower morbidity compared to open surgery.	1a
Tumour control rates appear equivalent for T1-T2 tumours between laparoscopic and open radical nephrectomy.	3
Long-term outcome data indicate that laparoscopic radical nephrectomy has equivalent cancer-free survival rates to those of open radical nephrectomy.	3
Partial nephrectomy by laparoscopic surgery is technically feasible.	3
The data regarding quality of life and perioperative outcomes for laparoscopic nephron-sparing surgery compared with open nephron-sparing surgery remains.	3

Recommendations	**LE**	**GR**
Laparoscopic radical nephrectomy is recommended in T2 renal cell cancer.		C
Laparoscopic radical nephrectomy is the standard of care for patients with T2 tumours and those renal masses not treatable by nephron-sparing surgery.		C
Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated.	3	C
Extended lymphadenectomy is not recommended since it does not appear to improve survival. It should be restricted to staging purposes with dissection of palpable and/or enlarged lymph nodes.	1b	A
Laparoscopic and robot assisted partial nephrectomy is an alternative to open nephron-sparing surgery.		C
Open partial nephrectomy currently remains as a standard of care for partial nephrectomy.		C

6.3 Therapeutic approaches as alternatives to surgery

6.3.1 ***Surveillance***

Elderly and co-morbid patients with incidentally detected small renal masses have a relatively low RCC-specific mortality and a significant competing-cause mortality (50,51).

Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (ultrasound, CT, or MRI) with delayed intervention reserved for those tumors that show clinical progression during follow-up (52).

In the largest reported series of active surveillance the growth of renal tumors is low in the majority of cases and progression to metastatic disease is reported in a limited number of patients (1-2%) (53,54). 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 and if required by treatment for progression (52-58).

6.4 Adjuvant therapy

Current evidence that adjuvant tumour vaccination might improve the duration of the progression-free survival of selected subgroups of patients undergoing nephrectomy for T3 renal carcinomas needs further confirmation regarding the impact on overall survival (LE: 1b) (59-63). Prognostic algorithms might identify patients likely to derive the largest clinical benefit from adjuvant vaccination therapy.

Conclusions	LE
Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (ultrasound, CT, or MRI) with delayed intervention reserved for those tumors that show clinical progression during follow-up.	3
Adjuvant therapy with cytokines does not improve survival after nephrectomy.	1b

Recommendations	GR
Active surveillance is a reasonable option for elderly and/or comorbid patients with small renal masses and limited life expectancy.	C
Patients with small renal tumours and/or significant co-morbidity who are unfit for surgery should be considered for an ablative approach, e.g. cryotherapy and radiofrequency ablation.	C
Pre-treatment biopsy has to be carried out as a standard before ablative therapy and is useful when active surveillance is considered and in order to stratify follow-up based on tumor histology.	C
Other image-guided percutaneous and minimally invasive techniques, such as microwave ablation, laser ablation, and high-intensity focused ultrasound ablation are experimental and are recommended only in studies.	C
Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery.	A

6.5 Surgical treatment of metastatic RCC (tumour nephrectomy or cytoreductive nephrectomy)

Tumour nephrectomy is curative only if surgery can excise all tumour deposits. For the majority of patients with metastatic disease, cytoreductive nephrectomy is palliative and systemic treatments are necessary. In a meta-analysis of two randomized studies, comparing cytoreductive nephrectomy combined with immunotherapy versus immunotherapy only, an increased long-term survival was found in patients subjected to cytoreductive nephrectomy (64). At present, only limited data are available addressing the value of cytoreductive nephrectomy combined with targeting agents such as sunitinib, sorafenib and others. Randomised studies are ongoing.

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

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

6.6 Surgical resection of metastases in metastatic RCC

A systematic review was undertaken (65). No randomised trials were identified comparing metastasectomy with other treatments, but 12 non-randomised comparative studies involving metastasectomy were identified. A number of studies compared complete metastasectomy with partial metastasectomy in patients with metastatic RCC involving multiple organ sites (66-68). The results showed an overall survival advantage for complete resection. When complete metastasectomy was compared with no surgical resection (69-71), complete metastasectomy offered a slight overall survival advantage.

In the treatment of bone metastases, metastasectomy in combination with local stabilization provided a significant survival advantage over that of non-surgical treatment (72).

In visceral metastases affecting the liver and pancreas, metastasectomy showed a significantly prolonged overall survival compared with non-surgical treatment (73,74). For patients with liver metastases, radical resection was associated with significantly better overall survival compared with either partial resection or ablation (75).

For the treatment of brain lesions, one study compared metastasectomy followed by whole brain radiotherapy, against fractionated stereotactic radiotherapy or conventional radiotherapy alone (76). There was no difference in cancer specific survival, although surgery appeared to offer some benefits regarding local tumour control.

6.7 Radiotherapy for metastases in metastatic RCC

A systematic review was undertaken (65). Three non-randomised comparative studies involving different radiotherapy modalities were identified. The results showed there was no significant survival benefit using radiotherapy. However, there was evidence of improved local tumour control with radiotherapy. Two studies (77,78) involving bone metastases showed an improvement in bone pain using different radiotherapy modalities. In a study on brain metastases (79) whole brain radiotherapy alone, stereotactic radiosurgery alone or a combination of the two were compared. The study showed a good local tumour control using either individual modality in patients with 1-3 metastases to the brain.

Conclusions	**LE**
There is a definite role for metastasectomy in patients with RCC in order to improve the clinical prognosis. Its role has to be continuously re-evaluated, especially in combination with targeted systemic therapy.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3

Recommendations	**GR**
In patients with metastatic spread, metastasectomy should be performed where disease is resectable and the patient has a good performance status.	C
Metastasectomy should be performed in patients with residual and resectable metastatic lesions previously responding to immunotherapy and/or other systemic treatment.	C
In individual cases, stereotactic radiotherapy for the treatment of bone and brain metastases can induce 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 therefore 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 randomised study, interferon-alpha (IFN-α) showed equivalent efficacy to a combination of IFN-α + 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-α 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***

Interferon alpha has been shown in randomised studies to be superior in relation to survival to hormonal therapy in patients with mRCC (3). IFN-α 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 in comparison with a placebo equivalent (4,5).

The positive effect of IFN-α is particularly apparent in mRCC patients with clear cell histology, good-risk Motzer criteria, and lung metastases only (5). In a prospective randomised study, IFN-α showed equivalent efficacy to a combination of IFN-α + IL2 + 5-FU (2). The moderate efficacy of immunotherapy was also confirmed in a Cochrane meta-analysis including 42 eligible studies (6).

A combination of bevacizumab + IFN-α was recently shown to be associated with increased response rates and better progression-free survival in first-line therapy in comparison with IFN-α monotherapy (7). All recent randomized studies comparing anti-angiogenic drugs in a first-line setting to IFN-α monotherapy have shown superiority for either sunitinib, bevacizumab + IFN-α, or temsirolimus (7-10).

Table 9: Memorial Sloan-Kettering Cancer Center (Motzer) criteria for predicting survival in patients with advanced RCC treated with interferon alpha, depending on the presence or absence of five distinct risk factors (4)

Risk factors*	Cut-off point used
Karnofsky performance status	< 80
Time from diagnosis to treatment with IFN-α	< 12 months
Hemoglobin	< 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% (10-12). 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 randomised phase III study (13). The toxicity of IL-2 is substantially greater than that of IFN-α. Only clear cell-type RCC responds to immunotherapy. Interleukin-2 has not been validated in controlled randomised studies in comparison with 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 in combination with the first-line standard of care (either sunitinib, interleukin-2, or interferon alpha) failed to demonstrate any survival benefit in comparison with placebo and the first-line standard of care (14). 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 (15), 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 monotherapy is no longer recommended as first-line therapy for mRCC.	1b
Interferon alpha monotherapy still has a role only in selected cases (good performance status, clear cell type, lung metastases only).	2
Interleukin-2 has more side effects than INF-α.	2-3
High-dose IL-2 is associated with durable complete responses in a limited number of patients.	1b
Interleukin-2 can be considered as monotherapy in selected patients with a good prognosis profile.	1b
A combination of bevacizumab and IFN-α is more effective than IFN-α in treatment-naïve, low-risk and intermediate-risk tumours.	1b
Vaccination therapy with tumour antigen 5T4 showed no survival benefit over the first-line standard of care.	1b

7.2.5 ***Recommendations***

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

7.3 Drugs targeting 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 the treatment of mRCC (Table 11).

In sporadic clear cell RCC, hypoxia-inducible factor (HIF) accumulation due to von Hippel-Lindau (VHL) inactivation results in overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), both of which promote neoangiogenesis (16-18). This process substantially contributes to the development and progression of RCC. At present, several targeting drugs have been approved both in the USA and in Europe for the treatment of mRCC:
- Sorafenib (Nexavar®)
- Sunitinib (Sutent®)
- Bevacizumab (Avastin®) combined with IFN-α
- Pazopanib (Votrient®)
- Temsirolimus (Torisel®)
- Everolimus (Afinitor®)
- Axitinib (Inlyta®)

New agents targeting angiogenesis are under investigation, as well as combinations of these new agents with each other or with cytokines. One of the new agents targeting angiogenesis, tivozanib, has been investigated in a phase III trial and is currently not approved. Evidence-based data for this drug are presented below. 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 Memorial Sloan-Kettering Cancer Center (MSKCC) risk model, as published in 2002 (3) (Table 9). Since the MSKCC criteria were established in the era of cytokines, an international database consortium has established and validated a risk model (the Database Consortium Model, DCM) which may yield a more accurate prognosis for patients treated in the era of targeted therapy. In the DCM, neutrophilia and thrombocytosis are added to the MSKCC risk factors. By contrast, lactate dehydrogenase (LDH) is omitted from the factors associated with the prognosis (19). The DCM has recently been used to establish data on conditional survival that can be used to counsel patients (20). 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 for predicting the prognosis based solely on clinical factors. However, the reported versus predicted number of deaths at 2 years was most similar in the DCM in comparison with the other models (21). The DCM has been externally validated for use in the era of targeted therapy (21).

Table 10: 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. (19,21)

Database Consortium Model *'**	Patients**		Median OS* (months)	2-y OS (95% CI) **
	n	%		
Favorable	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 (21); ** based on (19); 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 in favor of sorafenib (22). Survival appears to improve in patients crossed over from placebo to sorafenib treatment (23).

7.3.1.2 Sunitinib

Sunitinib is an oxindol 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 (24).

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

In a recent randomised 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 metastatic clear cell renal carcinoma (26). The median time to progression with sunitinib 50 mg (4/2) (n = 146) was 9.9 months, compared with 7.1 months for 37.5 mg/day continuous dosing (n = 146). The overall response rate was 32% for 50 mg (4/2) versus 28% for 37.5 mg continuous dosing. No significant differences were observed with regard to overall survival (23.1 vs. 23.5 months; $P = 0.615$), commonly reported adverse events, or patient-reported kidney cancer symptoms. Because of the statistically nonsignificant but numerically longer time to progression with the standard 50 mg (4/2) dosage, the authors recommended adherence to 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 and cytokine-treated patients, there was a significant improvement in the progression-free survival and tumour response (9.2 vs 4.2 months) (27). The trial showed significant results that established pazopanib as a first-line option. Since the initial phase III study involved a substantially smaller number of patients than in phase III studies of other targeted agents, the recommendation was to use pazopanib as second option in first-line treatment. Recently, the results of a randomized phase III non-inferiority trial comparing pazopanib with sunitinib (COMPARZ) showed no significant differences in the outcome parameters, with different toxicity profiles for the two drugs. With a very short follow-up period, these data are not yet mature, particularly with regard to remission. One major shortcoming of the COMPARZ trial is the fact that the study recruited almost one-third of its patients in Asia. Given the fact that there are ethnic differences in side effect profiles, the overall assessment of this trial remains unstable and further interpretation of any subgroups is almost impossible. Full publication is expected, but COMPARZ has established pazopanib as a first-line treatment option.

7.3.1.4 Axitinib
Axitinib is an oral selective second-generation inhibitor of VEGFR-1, -2, and -3 that blocks VEGFR receptors at subnanomolar drug concentrations with minimal inhibition of other targets. It has a short half-life. 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 the median progression-free survival PFS from 5 months to 7 months in patients randomly assigned to receive axitinib (28). 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 progression-free survival was 6.7 months for patients in the axitinib group in comparison with 4.7 months for those in the sorafenib group (hazard ratio [HR] 0.67; 95% CI, 0.54 to 0.81). However, the difference in PFS was greatest in the patients in whom cytokine treatment had failed. For those in whom sunitinib had failed (n = 194 axitinib and n = 195 sorafenib), axitinib led to a PFS of 4.8 months (95% CI, 4.5 to 6.4) versus 3.4 months (95% CI, 2.6 to 4.7) for sorafenib.

In the AXIS trial, axitinib showed greater than or equal to grade 3 toxicity for diarrhea 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 (OS) was a secondary end point of the trial, but these data were not mature at the time of publication. However, since crossover was not allowed in this trial comparing two active VEGFR inhibitors, the data have in the meantime been analyzed and showed no significant differences between axitinib and sorafenib in second-line treatment (29).

7.3.1.5 Tivozanib
Tivozanib is an oral selective tyrosine kinase inhibitor targeting all three VEGF receptors. It has a long half-life. Tivozanib showed activity and tolerability in a phase II discontinuation trial. The overall response rate was 24% (95% CI, 19% to 30%), and the median PFS was 11.7 months (95% CI, 8.3 to 14.3 months) in the trial population. The most common grade 3 and 4 treatment-related adverse event was hypertension (12%) (30). The results of a phase III trial of tivozanib versus sorafenib in treatment-naïve mRCC patients or those having received one prior systemic treatment excluding VEGF targeted therapy or mTOR inhibitors were reported at the American Society of Clinical Oncology (ASCO) meeting in 2012, and full publication is pending. For the 70% treatment-naïve patients enrolled, the median PFS was 12.7 months for tivozanib versus 9.1 months for sorafenib (HR 0.756; 95% CI, 0.580 to 0.985). For all patients, the objective response rates were 33% for tivozanib versus 23% for sorafenib. The most common adverse events (AEs) for tivozanib (all grades / ≥ grade 3) were hypertension (46%/26%), diarrhea (22%/2%), fatigue (18%/5%), and neutropenia (10%/2%) (31). Full publication of this study is pending. If approved, tivozanib might be a tyrosine kinase inhibitor with effectiveness not inferior to that of sorafenib, as apparent in the groups of patients tested.

7.3.2 ***Monoclonal antibody against circulating VEGF***
7.3.2.1 Bevacizumab monotherapy and combined with interferon 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 the overall response (10%) and in the progression-free survival in comparison with placebo (27). A double-blind phase III trial (AVOREN) (n = 649) in patients with mRCC compared bevacizumab + IFN-α with IFN-α monotherapy (7). The median overall response was 31% in the bevacizumab + IFN-α group versus 13% in the group receiving only IFN-α ($P < 0.0001$). The median progression-free survival increased significantly from 5.4 months with IFN-α to 10.2 months with bevacizumab + IFN-α ($P < 0.0001$), but only in low-risk and intermediate-risk patients. No benefit was seen in high-risk patients. In a recent update, the median OS in the AVOREN trial, which allowed

crossover after progression, was 23.3 months for bevacizumab-IFN-α versus 21.3 months for IFN-α alone ($P < 0.336$) (32).
A similarly designed trial (CALGB 90206), including 732 patients (33,34), of bevacizumab (10 mg/kg intravenously every 2 weeks) plus IFN (9 million units subcutaneously three times weekly) versus IFN (9 million units subcutaneously three times weekly) showed a median PFS of 8.5 months for the combination versus 5.2 months for IFN-α alone. The median OS with a crossover design was 18.3 months for the combination versus 17.4 months for IFN alpha alone. Bevacizumab plus IFN-α had a higher objective response rate (ORR) in comparison with IFN (25.5%: 95% CI, 20.9% to 30.6%; vs. 13.1%: 95% CI, 9.5% to 17.3%); $P < 0.0001$). The overall toxicity was greater for bevacizumab plus IFN-α, 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) (35). Patients with high-risk mRCC were randomly assigned in a phase III trial (NCT00065468) to receive first-line treatment with temsirolimus or IFN-α monotherapy, or a combination. In the temsirolimus group, the overall survival was 10.9 months versus 7.3 months in the IFN-α group ($P < 0.0069$). However, the overall survival in the temsirolimus + IFN-α group was not significantly improved (9).

7.3.3.2 Everolimus

Everolimus is an oral mTOR inhibitor. A phase III study (RECORD-1) compared everolimus plus best supportive care (BSC) versus placebo plus BSC in patients in whom previous anti-VEGFR treatment had failed. The median progression-free survival was 4 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 to 5.5 months). Comparison with the AXIS data is complicated by the fact that in the RECORD-1 trial, 53% of the patients with progression after previous targeted therapy had at least more than one previous treatment, often cytokines prior to tyrosine kinase inhibitors (TKIs). In addition, the PFS analysis in this trial was not specifically carried out for previous sunitinib treatment (16,36).

7.3.4 ***Sequencing targeted therapy***

Currently, no recommendations can be given as to the best sequence of targeted therapy. 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 7.3.1.3 above. For the subgroup of patients treated previously with sunitinib, the difference in PFS did not reach statistical significance for axitinib versus sorafenib, and no difference in the OS was observed. Randomized phase III trials investigating the safety and efficacy of sorafenib followed by sunitinib versus sunitinib followed by sorafenib (SWITCH-I) and sequential pazopanib and sorafenib versus sorafenib and pazopanib (SWITCH-II) are ongoing.

7.3.5 ***Combination of targeted agents***

No recommendations can be made. At present, there have been no phase III trials reporting on a combination of two targeted agents versus monotherapy with a targeted agent. A previous randomised phase II study reported unacceptable toxicity (37). The TORAVA trial showed that the toxicity of a combination of temsirolimus and bevacizumab was much greater than anticipated and that it limited treatment continuation over time in comparison with either standard treatment with sunitinib or bevacizumab and IFN-α. In addition, clinical activity was low in comparison with the benefit expected from sequential use of each targeted therapy. This combination has not been further recommended or investigated. In a nonrandomized phase II trial, the combination of everolimus with bevacizumab was found to be effective with acceptable toxicity, except for grade 3/4 proteinuria in 25% of the patients (38). A randomised phase II trial of everolimus in combination with bevacizumab and IFN-α versus IFN-α alone is ongoing.

7.3.6 ***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 carcinoma have been reported. A nonrandomized phase II trial in patients with papillary renal cancer who were treated with foretinib, a dual MET/VEGFR2 inhibitor, reported activity and acceptable toxicity with high response rates in patients with germline MET mutations (39). 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.

Table 11: European Association of Urology 2013 evidence-based recommendations for first-line and second-line systemic therapy in patients with mRCC. Levels of evidence are shown in square brackets

RCC type	MSKCC risk group (3)	1st-line therapy*	2nd-line therapy*†	3rd-line therapy
Clear cell	Favorable or intermediate	• Sunitinib [1b] • IFN-α + bevacizumab [1b] Pazopanib ‡ [1b] *In selected patients:* • IFN-α [1b] • High-dose IL-2 [1b]	*After prior TKI:* • Axitinib [1b] • Sorafenib [1b] • Everolimus [1b] *After prior cytokines:* • Sorafenib [1b] • Axitinib [1b] • Pazopanib [1b]	• Everolimus after prior TKI(s) [1b]
	Poor ¶	• Temsirolimus [1b]		
Non-clear cell	Favorable	§		
	Intermediate	§		
	Poor	§		

IFN-α = interferon alpha; MSKCC = Memorial Sloan-Kettering Cancer Center; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor.

* Doses: IFN-α 9 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.

† Listed in the order of data quality.

‡ Initial phase III study; involved a substantially smaller number of patients than in phase III studies of other targeted agents.

§ 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.

7.3.7 Conclusions

	LE
Tyrosine kinase inhibitors (TKIs) increase the progression-free survival and/or overall survival as both first-line and second-line treatments for mRCC.	1b
Sorafenib has proven efficacy as a second-line treatment after failure of cytokine therapy or in patients unfit for cytokines.	1b
Axitinib has proven efficacy and superiority 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 low-risk and intermediate-risk tumours.	1b
Sunitinib at 50 mg (4/2) or 37.5 mg continuous dosing did not show significant differences in relation to overall survival, time to progression, response rate, or safety.	1b
A combination of bevacizumab and IFN-α is more effective than IFN-α in treatment-naïve low-risk and intermediate-risk tumours.	1b
Pazopanib is superior to placebo in both naïve mRCC patients and post-cytokine patients.	1b
Pazopanib is not inferior to sunitinib in good-risk and intermediate-risk clear cell mRCC patients.	1b
Temsirolimus monotherapy in poor-risk mRCC patients is more effective than IFN-α or temsirolimus + IFN-α.	1b
Everolimus prolongs the progression-free survival in patients in whom treatment with one or two TKIs has failed in second-line or later treatments.	1b

The role of the new drugs is still under development and combination studies are ongoing. To date, no data are available indicating whether the new agents have a curative effect. These agents appear promising for stabilizing mRCC for a prolonged period of time. However, this promise has to be balanced against their toxicity profile and the patient's quality of life. Anti-angiogenic monotherapy and its sequences have become the standard of care in mRCC treatment.	4

7.3.8 *Recommendations for systemic therapy for mRCC*

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

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

8.1 Introduction

Surveillance after treatment for renal cell carcinoma (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 information about RCC available, 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 ultrasound has limitations. Surveillance should therefore not be based on these imaging modalities. With low-risk tumours, the surveillance intervals should be adapted relative to radiation exposure and benefit. Magnetic resonance imaging (MRI) can be used to reduce radiation exposure.
- When the risk of relapse is intermediate or high, computed tomography (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 (14).
- 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 (15) (LE: 3).

Several authors - notably Kattan, Liebovich, UCLA, and Karakiewicz (16-19) - have designed scoring systems and nomograms to quantify the likelihood of patients developing tumour recurrences, metastases, and subsequent death. These systems have been compared and validated (20) (LE: 2). Using prognostic variables, several stage-based surveillance regimens have been proposed (21,22), but these do not include ablative therapies. A postoperative nomogram is available for estimating the likelihood of freedom from recurrence at 5 years (23). Most recently, a preoperative prognostic model based on age, symptoms, and TNM staging has been published and validated (24) (LE: 3). There is therefore a need for a surveillance algorithm for monitoring patients after treatment for RCC, recognizing not only the patient risk profile, but also the efficacy of the treatment given (Table 11).

Table 12: Proposed algorithm for surveillance following treatment for RCC, taking into account patient risk profile and treatment efficacy

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

Conclusion
The aim of surveillance is to detect either local recurrence or metastatic disease while the patient is still surgically curable.

Recommendations	**LE**	**GR**
Surveillance after treatment for RCC should be based on a patient's risk factors and the type of treatment delivered.		C
For low-risk disease, CT/MRI can be used infrequently.	4	C
In the intermediate-risk group, intensified follow-up should be performed, including CT/MRI scans at regular intervals in accordance with a risk-stratified nomogram.	4	C
In high-risk patients, the follow-up examinations should include routine CT/MRI scans.	4	C
There is an increased risk of intrarenal recurrences in larger-size (> 7 cm) tumours treated with nephron-sparing surgery, or when there is a positive margin. Follow-up should be intensified in these patients.		C

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9. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

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

Conflict of interest

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.