EAU Guidelines on

Renal Cell Carcinoma

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European Association of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION

1.1 Aims and scope

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 RCC.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

1.2 Panel composition

The RCC panel is an international group of clinicians consisting of urological surgeons, an oncologist, methodologists, a pathologist and a radiologist, with particular expertise in the field of urological care. Since 2015, the panel has incorporated a patient advocate to provide a consumer perspective for its guidelines.
All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/renal-cell-carcinoma/.

The panel is most grateful for the methodological and scientific support provided by the following individuals in specific parts of the guideline document:

- Prof.Dr. O. Hes, pathologist, Plzen (CZ) (Section - Other renal tumours);
- Dr. M. Lardas, Aberdeen (UK) and Dr. F. Stewart, Aberdeen (UK) (Systematic review - Tumour thrombus);
- Dr. Christina Vogel, Munich (DE) and Prof.Dr. A. Graser, radiologist, Munich (DE) (Systematic review - Diagnostic imaging of RCC).

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the RCC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, as are a number of translations of all versions of the EAU RCC Guidelines [1, 2]. All documents can be assessed on the EAU website: http://uroweb.org/guideline/renal-cell-carcinoma/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU RCC Guidelines were first published in 2000. This 2016 RCC Guidelines document presents an update of the 2015 publication.

*1.4.2 **Summary of changes***

All chapters of the 2016 RCC Guidelines have been updated, based on the 2015 version of the guideline. Conclusions and recommendations have been rephrased and added to, throughout the current document.

Key changes for the 2016 print:

- Chapter 3 - Epidemiology, Aetiology and Pathology: the new Vancouver histological classification has been included.
- Section 7.4.3.1 - Tyrosine kinase inhibitors - A new figure has been included. (Figure 7.1: Recommendations for patients with metastatic clear cell-RCC who have failed one or more lines of VEGF targeted therapy).

New data and recommendations have been included in the following sections.

3.4 Summary of evidence and recommendations for the management of other renal tumours

Recommendations	GR
In AML > 3 cm not requiring surgical intervention, medical treatment with everolimus can be considered.	C
Treat all tumours with the radiologic appearance of RCC in the same way.	C

AML = angiomyolipoma.

7.2.5.1 Summary of evidence and recommendation for adjuvant therapy

Summary of evidence	LE
Adjuvant sunitinib or sorafenib do not improve disease-free and overall survival after nephrectomy.	1b

Recommendation	GR
Adjuvant therapy with sunitinib or sorafenib should not be given.	A

7.3.2.4 Embolisation of metastases

Recommendation	GR
Stereotactic radiotherapy for bone metastases, and stereotactic radiosurgery for brain metastases may be offered for local control and symptom relief.	C

7.4.1.1 Summary of evidence and recommendation for systemic therapy for advanced/metastatic RCC

Summary of evidence	LE
In mRCC, chemotherapy is otherwise not effective.	3

mRCC = metastatic renal cell carcinoma.

7.4.2.5 Summary of evidence and recommendation for immunotherapy in mRCC

Summary of evidence	LE
IFN-α monotherapy is inferior to VEGF-targeted therapy or mTOR inhibition in mRCC.	1b
Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.	1b

Recommendation	GR
Nivolumab is strongly recommended after one or two lines of VEGF-targeted therapy in mRCC.	A

INF = interferon; mRCC = metastatic renal cell carcinoma; mTOR = mammalian target of rapamycin inhibitor; OS = overall survival: VEGF = vascular endothelial growth factor.

7.4.6.3 Summary of evidence and recommendations for systemic therapy in mRCC

Summary of evidence	LE
Nivolumab is superior to everolimus in terms of OS and adverse events in patients failing one or two lines of VEGF-targeted therapy.	1b
Cabozantinib is superior to everolimus in terms of PFS in patients failing one or more lines of VEGF-targeted therapy.	1b

Recommendations	GR
Cabozantinib should be given for ccRCC patients who progressed after one or two lines of VEGF-targeted therapy based on a PFS advantage over everolimus.	A
Nivolumab is strongly recommended for ccRCC patients who progressed after one or two lines of VEGF-targeted therapy based on and OS advantage over everolimus.	A
Axitinib can be given as second-line treatment for mRCC after cytokines or first-line VEGF where other drugs are not safe, tolerable or available.	A
Sunitinib or everolimus can be given as first-line therapy for non-clear cell mRCC.	B

ccRCC = clear-cell renal cell carcinoma; mRCC = metastatic renal cell carcinoma; OS = overall survival: PFS = progression-free survival; VEGF = vascular endothelial growth factor.

2. METHODS

2.1 Data identification

For the 2016 Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature for the majority of chapters in the guideline as listed in Table 2.1.

A broad and comprehensive scoping exercise covering all areas of the entire guideline was performed. The search was limited to studies representing high levels of evidence only (i.e. systematic reviews (SRs) with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published during the period from 1st January 2013 to 30th July 2015. Databases covered by the search included Medline, EMBASE, and the Cochrane Library. A total of 1,602 unique records were identified, retrieved and screened for relevance. The search strategy has been published online: http://uroweb.org/guideline/renal-cell-carcinoma/?type=appendices-publications.

Specific chapters were updated by way of SRs commissioned and undertaken by the panel in conjunction with the EAU Guidelines Office, based on topics or questions prioritised by the guideline panel. These reviews were performed using standard Cochrane SR methodology http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

References used in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: http://uroweb.org/guidelines/.

A list of Associations endorsing the EAU Guidelines can also be viewed online as the above address.

Table 2.1: Description of update and summary of review methodology.

Chapter	Brief description of review methodology
1. Introduction	Not applicable
2. Methods	Not applicable
3. Epidemiology, Aetiology and Pathology	This chapter was updated by a traditional narrative review, based on a structured literature assessment.
4. Staging and grading classification systems	This chapter was updated by a traditional narrative review, based on a structured literature assessment.
5. Diagnostic evaluation	Chapters 5.2 and 5.3 were updated by way of a SR [4]. The remainder of the chapter was updated by a structured literature assessment.
6. Prognosis	This chapter was updated by a traditional narrative review, based on a structured literature assessment.

7. Treatment (Disease management)	Chapters 7.1.2 and 7.2.4 were updated by a SR. The remainder of the chapter was updated using a structured literature assessment. Treatment of localised disease: For 2015 this section was updated by means of a SR mostly based on a literature search from 2000. A new section, 'Management of RCC with venous thrombus' has been added which is based on a SR [5]. Systemic therapy for metastatic disease: For 2015, these sections were updated by a SR.
8. Surveillance following radical or partial nephrectomy or ablative therapies	This chapter was updated by a traditional narrative review, based on a structured literature assessment.

The findings of a number of SR topics have been incorporated in this 2016 update:

- What is the best surgical treatment option for clinical ≥ T2, N0M0 tumours? What is the best way of performing this procedure?
- What is the best treatment for advanced/metastatic non-clear cell RCC?
- Performance of CT for the initial diagnosis of suspected renal masses.

2.2 Review

The following section was peer reviewed prior to publication:

- Chapter 7 – Disease management.

The other sections of the RCC Guidelines were peer-reviewed prior to publication in 2015.

2.3 Future goals

For their future updates, the RCC Panel aim to focus on patient-reported outcomes.

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

- Thorax CT for staging of pulmonary metastasis;
- Proportion of patients with T1aN0M0 tumours undergoing nephron sparing surgery as first treatment;
- The proportion of patients treated within 6 weeks after diagnosis;
- The proportion of patients with metastatic RCC offered treatment with targeting agents;
- Proportion of patients who undergo minimally invasive or operative treatment as first treatment who die within 30 days;
- Panel members have set up a database to capture current practice of follow-up of RCC patients in a number of European Centres. Assessing patterns of recurrence and use of imaging techniques are primary goals for this project.

The results of ongoing and new SRs will be included in the 2017 update of the RCC Guidelines.

Ongoing systematic reviews:

- What is the best treatment option for T1a tumours? (updated).
- What is the best treatment option for T1b-T2b tumours? (updated).
- What are indications for treatment of angiomyolipoma?
- Systematic review and meta-analysis of systemic therapy of renal tumours?
- Imaging following treatment, covering the following subquestions:
  - Post surgical surveillance for either localised disease or locally advance disease;
  - Post-systemic therapy.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Renal cell carcinoma (RCC) represents 2-3% of all cancers [6], with the highest incidence in Western countries. Over the last two decades the incidence of RCC increased by about 2% both worldwide and in Europe, although a continuing decrease has been observed in Denmark and Sweden [7]. In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney cancer-related deaths in the European Union [8]. In Europe, overall mortality rates for RCC increased up to the early 1990s, and stabilised or declined thereafter [9]. Mortality has decreased since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend [9].

Different RCC types have specific histopathological and genetic characteristics [10]. There is a 1.5:1 male predominance, with a peak incidence between 60 and 70 years. Aetiological factors include smoking, obesity [11], hypertension, acetaminophen and non-aspirin nonsteroidal anti-inflammatory drugs [12], and viral hepatitis [13-17]. Having a first-degree relative with kidney cancer also increases the risk of RCC [18]. A number of other factors associated with higher or lower RCC risk include specific dietary habits and occupational exposure to specific carcinogens, however, literature results are inconclusive [19, 20]. Moderate alcohol consumption appears to have a protective effect for unknown reasons [21, 22], as do cruciferous vegetables [23]. Effective prophylaxis includes avoidance of cigarette smoking and obesity.

Due to increased detection of tumours by ultrasound (US) and computed tomography (CT), the number of incidentally diagnosed RCCs has increased. These tumours are usually smaller and of lower stage [24-26].

3.1.1 Summary of evidence and recommendation

Summary of evidence	LE
Several verified risk factors have been identified including smoking, obesity and hypertension. These are considered definite risk factors for RCC.	2a

Recommendation	GR
For the most important primary prevention of for RCC, eliminate cigarette smoking and reduce weight.	B

3.2 Histological diagnosis

Renal cell carcinomas comprise a broad spectrum of histopathological entities described in the 2004 World Health Organization (WHO) classification [27] and modified by the International Society of Urological Pathology (ISUP) Vancouver Classification [28]. There are three main RCC types: clear cell (ccRCC), papillary (pRCC - type I and II) and chromophobe (chRCC). RCC type classification has been confirmed by cytogenetic and genetic analyses [29-31] (LE: 2b). Collecting duct carcinoma and other infrequent renal tumours are discussed in Section 3.3.

Histological diagnosis includes, besides RCC type, evaluation of nuclear grade, sarcomatoid features, vascular invasion, tumour necrosis, and invasion of the collecting system and perirenal fat. Fuhrman nuclear grade has been the most widely accepted grading system [32]. At the ISUP conference, a simplified, nuclear grading system, based only on size and shape of nucleoli, was proposed which will replace the Fuhrman grading system [28].

3.2.1 Clear cell (ccRCC)

Overall, ccRCC is well circumscribed, capsule is usually absent. The cut surface is golden-yellow, often with haemorrhage and necrosis. The Fuhrman nuclear grading system is generally used [32]. Loss of chromosome 3p and mutation of the VHL (von Hippel-Lindau) gene at chromosome 3p25 are frequently found. ccRCC has a worse prognosis compared with pRCC and chRCC [33, 34] even after stratification for stage and grade [35]. The 5-year cancer specific survival (CSS) rate was 91%, 74%, 67% and 32% for TNM stages I, II, III and IV (patients treated 1987-98) [36]. The indolent variant of ccRCC is multilocular cystic and accounts for approximately 4% of all ccRCC [28].

3.2.2 *Papillary (pRCC)*

Macroscopically, pRCC is well circumscribed with pseudocapsule, yellow or brown in colour, and a soft structure. Genetically, pRCC shows trisomies of chromosomes 7 and 17 and the loss of chromosome Y. Papillary RCCs are heterogeneous, with three different subtypes; two basic (1 and 2) and a third oncocytic type. Compared with ccRCC, pRCC has a significantly higher rate of organ confined tumour (pT1-2N0M0) and higher 5-year CSF [37]. Prognosis of pRCC type 2 is worse than for type 1 [38-40]. Exophytic growth, pseudonecrotic changes and pseudocapsule are typical signs of pRCC type 1. Pseudocapsules and extensive necrotic changes cause a spherical tumour in the extrarenal section. Tumours with massive necroses are fragile and vulnerable to spontaneous rupture or rupture resulting from minimal trauma followed by retroperitoneal bleeding. A well-developed pseudocapsule in pRCCs type 1 probably prevents these tumours from rupturing despite necroses. Necroses cohere with a hypodense central area of tumour on post-contrast CT. This area is surrounded by vital tumour tissue, seen as a serpiginous contrast-enhancing margin on CT [41]. Some authors consider type 3; oncocytic pRCC, to have no pseudocapsule or massive necrosis, rare extrarenal growth and low malignant potential [40], although this type is not generally accepted [28].

3.2.3 *Chromophobe (chRCC)*

Overall, chRCC is a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Instead of the Fuhrman grading system, a special histopathological grading system by Paner *et al.* was proposed in 2010 [42, 43]. Loss of chromosomes 2, 10, 13, 17 and 21 are typical genetic changes [44]. The prognosis is relatively good, with high 5-year recurrence-free survival, CSS and 10-year CSS [45].

3.3 Other renal tumours

Other renal tumours constitute the remaining 10-15 % of renal cortical tumours. These include a variety of uncommon, sporadic, and familial carcinomas, some only recently described, and a group of unclassified carcinomas. A summary of these tumours are given in Table 3.1, but some clinically relevant tumours and extremely rare entities are mentioned below.

3.3.1 *Carcinoma associated with end-stage renal disease; acquired cystic disease-associated RCC*

Cystic degenerative changes (acquired cystic kidney disease [ACKD]) and a higher incidence of RCC are typical features of ESKD (end-stage kidney disease). RCCs of native end-stage kidneys are found in about 4% of patients. Their lifetime risk of developing RCCs is at least 10 times higher than in the general population. Compared with sporadic RCCs, ACKDs generally are multicentric and bilateral, found in younger patients (mostly male), and are less aggressive [46, 47]. The relatively indolent outcome of tumours in ESKD is due to the mode of diagnosis and a specific ACKD related molecular pathway still to be determined [47]. Although the histological spectrum of ACKD tumours is similar to that of sporadic RCC, the predominant form is pRCC. The remaining tumours are mostly ccRCC [46-48]. A specific subtype of RCC occurring only in end-stage kidneys has been described as Acquired Cystic Disease-associated RCC (ACD-RCC) [28].

3.3.2 *Papillary adenoma*

These tumours have papillary or tubular architecture of low nuclear grade and are 5 mm in diameter or smaller [27]. They are found incidentally in nephrectomy specimens.

3.3.3 *Hereditary kidney tumours*

Hereditary kidney tumours are found in the following entities: VHL syndrome, hereditary pRCC, Birt-Hogg-Dubé syndrome (see Hybrid oncocytoma-chromophobe carcinoma), hereditary leiomyomatosis and renal cell cancer (HLRCC), tuberous sclerosis complex, germline succinate dehydrogenase (SDH) mutation, non-polyposis colorectal cancer syndrome, hyperparathyroidism-jaw tumour syndrome, phosphatase and tensin homolog (PTEN) harartoma syndrome (PHTS), constitutional chromosome 3 translocation, and familial non-syndromic ccRCC. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [27, 28, 38, 49].

3.3.4 *Angiomyolipoma*

Angiomyolipoma (AML) is a benign mesenchymal tumour, which can occur sporadically, and is four times more likely in women. It also occurs in tuberous sclerosis (TS). It accounts for approximately 1% of surgically removed tumours. Ultrasound, CT, and magnetic resonance imaging (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 smooth muscle cell tumours and epithelial tumours. Angiomyolipoma can be found in TS in lymph nodes (LNs), but is not metastases, and has a multicentric genesis. Angiomyolipoma can be due to angiotrophic-type growth in the renal vein or the IVC. Angiomyolipoma with LN involvement and tumorous thrombus is benign. Only epithelioid AML is potentially malignant [27, 50]. Angiomyolipoma has a slow and consistent growth rate, and minimal morbidity [51]. The main complications of renal AML are retroperitoneal bleeding or bleeding

into the urinary collection system, which can be life-threatening [52]. The bleeding tendency is related to the angiogenic component of the tumour that includes irregular and aneurysmatic blood vessels [52]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of TS [52, 53]. Indications for intervention are pain, bleeding, or suspected malignancy.

3.3.4.1 Treatment

Active surveillance (AS) is the most appropriate option for most AMLs [51, 54] (LE: 3). Risk factors for delayed intervention include tumour size ≥ 4 cm and symptoms at diagnosis [54]. Selective arterial embolisation seems to be the first-line option used for active treatment after AS was discontinued [54] (LE: 3). Selective arterial embolisation (SAE) is an efficient treatment for AML devascularisation but only for volume reduction [55]. And although SAE controls haemorrhage in the acute setting, it has limited value in the longer-term [56, 57]. If surgery is selected, most cases of AML can be managed by conservative nephron-sparing surgery (NSS), although some patients may require complete nephrectomy [53] (LE: 3). Radiofrequency ablation (RFA) can be an option as well [51, 52, 58]. The volume of AML can be reduced by the mTOR inhibitor everolimus [59]. A clinical phase II trial and its open-label extension of medical management with the mTOR inhibitor everolimus in AML, not requiring surgical intervention showed a response rate of 81.6 (64.5%) (≥ 50% or 30% tumour's volume reduction) by week 96, confirming the long-term safety profile of everolimus [59]. Sirolimus can be combined with deferred surgery [60].

Table 3.1: Other renal cortical tumours, and recommendations for treatment (GR: C)

Entity [27, 28]	Clinical relevant notes	Malignant potential	Treatment of localised tumour/metastatic tumour
Sarcomatoid variants of RCC	Sign of high-grade transformation without being a distinct histological entity.	High	Surgery/sunitinib, option of gemcitabine plus doxorubicin [61].
Multilocular clear cell RCC		Low, no metastasis	Surgery, NSS*
Carcinoma of the collecting ducts of Bellini	Rare, often presenting at an advanced stage (N+ 44% and M1 33% at diagnosis). The hazard ratio in CSS in comparison with ccRCC is 4.49 [34].	High, very aggressive. Median survival 30 months [62].	Surgery/Response to targeted therapies was poor [63].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait.	High, very aggressive, median survival is 5 months [62].	Surgery/different chemotherapy regimens, radiosensitive.
Translocation RCC (TRCC) Xp11.2	Rare, mainly younger patients under 40, more common in females. It constitutes with TRCC 6p21 MiT translocation RCCs [64].	High	Surgery/VEGF-targeted therapy.
Translocation RCC t(6;11)		Low/intermediate	Surgery, NSS/VEGF-targeted therapy.
Mucinous tubular and spindle cell carcinoma	Tumour is associated with the loop of Henle.	Intermediate	Surgery, NSS
Acquired cystic disease-associated RCC		Low	Surgery
Clear cell (tubulo) pRCC	It has been reported under the term renal angiomyomatous tumour (RAT) as well.	Low	Surgery, NSS
Tubulocystic RCC	Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS
Hybrid oncocytic chromophobe tumour	Mixture of cells of chRCC and renal oncocytoma. Three clinicopathological situations: sporadic, in association with renal oncocytosis/ oncocytomatosis or in patients with Birt-Hogg-Dubé syndrome.	Low or benign	Surgery, NSS

Metanephric tumours	Divided into metanephric adenoma, adenofibroma, and metanephric stromal tumours.	Benign	Surgery, NSS
Cystic nephroma/mixed epithelial and stromal tumour	Term renal epithelial and stromal tumours (REST) is used as well. Imaging – Bosniak type III or II/IV.	Low/benign	Surgery, NSS
Oncocytoma	3-7% of all renal tumours. Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard [65, 66].	Benign	Observation (when histologically confirmed) [67, 68]/NSS.
Hereditary kidney tumours	Details see above.	High	Surgery, NSS
Angiomyolipoma	Details see above.	Benign	Consider treatment only in very well selected patients.
Carcinoma associated with neuroblastoma	Long-term survivors of childhood neuroblastoma have a 329-fold increased risk of renal carcinoma.	Variable	Surgery, NSS
Thyroid-like follicular carcinoma of the kidney (TLFC)	Succinate Dehydrogenase B Mutation-associated RCC, ALK Translocation RCC (ALK - anaplastic lymphoma kinase).	Low	Surgery, NSS
Unclassified RCC	RCC that cannot be assigned to any other category of RCC-type carcinoma [27].	Variable	Surgery, NSS

CSS = cancer specific survival; NSS = nephron-sparing surgery; VEGF = vascular endothelial growth factor.

3.3.4.2 Summary

A variety of renal tumours exist, and about 15% are benign. All kidney lesions require examination for malignant behaviour.

3.4 Summary of evidence and recommendations for the management of other renal tumours

Summary of evidence	**LE**
Except for AML, most other renal tumours cannot be differentiated from RCC by radiology.	3
Biopsy-proven oncocytomas are benign lesions.	3
In advanced uncommon renal tumours, a standardised oncological treatment approach does not exist.	3

Recommendations	**GR**
Bosniak cysts ≥ type III should be regarded as RCC and treated accordingly. Treat Bosniak type III or IV cysts the same as RCC.	C
Treat most AMLs with active surveillance. Treat with selective arterial embolisation or NSS for: • large tumours (recommended threshold of intervention does not exist, the formerly recommended size of > 4 cm wide is disputed); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate.	C
In AML > 3 cm not requiring surgical intervention, medical treatment with everolimus can be considered.	C
Treat all tumours with the radiologic appearance of RCC in the same way.	C
Offer watchful waiting to patients with biopsy-proven oncocytomas.	C

For advanced uncommon renal tumours, develop individualised oncological treatment plans for each patient.	C

AML = angiomyolipoma; NSS = nephron-sparing surgery.

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Staging

The TNM classification system is recommended for clinical and scientific use [69], but requires continuous improvements [70]. The latest version was published in 2009 with a supplement published in 2012 (Table 4.1), and its prognostic value was confirmed in single and multi-institution studies [71, 72]. Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system (Table 4.1). However, some uncertainties remain:

- The sub-classification of T1 tumours using a cut-off of 4 cm might not be optimal in NSS for localised cancer.
- The value of size stratification of T2 tumours has been questioned [73].
- Since the 2002 version, tumours with renal sinus fat invasion have been classified as pT3a.
- However, renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion but is included in the same pT3a stage group [74-76] (LE: 3).
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [72].
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [77, 78] (LE: 4).

Table 4.1: 2009 TNM classification system [69] **and TNM supplement 2012** [79]

T - Primary tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney		
	T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney	
	T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension	
T2	Tumour > 7 cm in greatest dimension, limited to the kidney		
	T2a	Tumour > 7 cm but ≤ 10 cm in greatest dimension	
	T2b	Tumours > 10 cm limited to the kidney	
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland or beyond Gerota's fascia		
	T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or invades perirenal and/or renal sinus fat (peripelvic), but not beyond Gerota's fascia	
	T3b	Tumour grossly extends into the vena cava (VC) below the diaphragm	
	T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the VC	
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)		
N - Regional LNs			
NX	Regional LNs cannot be assessed		
N0	No regional LN metastasis		
N1	Regional LN metastasis		
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
Stage IV	T1, T2, T3	N1	M0
	T4	Any N	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 Anatomic classification systems

Objective anatomical classification systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the R.E.N.A.L. nephrometry score and the C-index have been proposed, to standardise the description of renal tumours [80-82]. These systems include assessment of tumour size, exophytic/endophytic properties, nearness to the collecting system and renal sinus, and anterior/posterior location.

The use of such a system is helpful as it allows objective prediction of potential morbidity of NSS and tumour ablation techniques. These tools provide information for treatment planning, patient counselling, and comparison of partial nephrectomy (PN) and tumour ablation series. However, when selecting the best treatment option, anatomic scores must always be considered together with patient features and surgeon experience.

5. DIAGNOSTIC EVALUATION

5.1 Symptoms

Many renal masses remain asymptomatic until the late disease stages. More than 50% of RCCs are detected incidentally by non-invasive imaging used to investigate various non-specific symptoms and other abdominal diseases [72, 83] (LE: 3). The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare (6-10%) and correlates with aggressive histology and advanced disease [84, 85] (LE: 3).

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [86] (LE: 3).

*5.1.1 **Physical examination***

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

- Palpable abdominal mass;
- Palpable cervical lymphadenopathy;
- Non-reducing varicocele and bilateral lower extremity oedema, which suggests venous involvement.

*5.1.2 **Laboratory findings***

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 [87, 88], coagulation study, and urinalysis (LE: 4). For central renal masses abutting or invading the collecting system, urinary cytology and possibly endoscopic assessment should be considered in order to exclude urothelial cancer (LE: 4).

Split renal function should be estimated using renal scintigraphy in the following situations [89, 90] (LE: 2b):

- when renal function is compromised, as indicated by increased serum creatinine or significantly decreased GFR;
- when renal function is clinically important - e.g., in patients with a solitary kidney or multiple or bilateral tumours.

Renal scintigraphy is an additional diagnostic option in patients at risk of future renal impairment due to comorbid disorders.

5.2 Imaging investigations

Most renal tumours are diagnosed by abdominal US or CT performed for other medical reasons [83] (LE: 3). Renal masses are classified as solid or cystic based on imaging findings.

*5.2.1 **Presence of enhancement***

With solid renal masses, the most important criterion for differentiating malignant lesions is the presence of enhancement [91] (LE: 3). Traditionally, US, CT and MRI are used for detecting and characterising renal masses. Most renal masses are diagnosed accurately by imaging alone. Contrast-enhanced US can be helpful in specific cases [92-94] (LE: 3).

*5.2.2 **CT or MRI***

Computed tomography or MRI are used to characterise renal masses. Imaging must be performed before and after administration of intravenous contrast material to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield units (HUs) before and after contrast administration. A change of 15 or more HUs demonstrates enhancement [95] (LE: 3). To maximise differential diagnosis and detection, the evaluation should include images from the nephrographic phase for best depiction of renal masses, which do not enhance to the same degree as the renal parenchyma. CT or MRI allow accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free AML from malignant renal neoplasms [65, 96-98] (LE: 3). Abdominal CT provides information on:

- Function and morphology of the contralateral kidney [99] (LE: 3);
- Primary tumour extension;
- Venous involvement;
- Enlargement of locoregional LNs;
- Condition of the adrenal glands and other solid organs (LE: 3).

Abdominal contrast-enhanced biphasic CT angiography is useful in selected cases for detailed information on renal vascular supply [100, 101].

If the results of CT are indeterminate, MRI may provide additional information on:

- Enhancement in renal masses [102];
- Locally advanced malignancy [103-105];
- Venous involvement if the extent of an inferior vena cava (IVC) tumour thrombus is poorly defined on CT [103-106] (LE: 3). Doppler US is less accurate for identifying the extent of a venous tumour thrombus (VTT) [105] (LE: 3).

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [104, 107] (LE: 3). Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored for renal mass assessment [108].

In patients with hereditary RCC who are worried about the radiation exposure of frequent CT scans, MRI may be offered as alternative.

*5.2.3 **Other investigations***

Renal arteriography and inferior venacavography have a limited role in the work-up of selected RCC patients (LE: 3). In patients with any sign of impaired renal function, an isotope renogram and total renal function evaluation should be considered to optimise treatment decision-making [89, 90] (LE: 2a).

The value of positron-emission tomography (PET) in the diagnosis and follow-up of RCC remains to be determined, and PET is not currently recommended [109] (LE: 3).

*5.2.4 **Radiographic investigations for metastatic RCC***

Chest CT is accurate for chest staging [77, 78, 110-112] (LE: 3). However, routine chest radiography must be performed for metastases, but is less accurate than chest CT (LE: 3). There is a consensus that most bone and brain metastases are symptomatic at diagnosis, thus routine bone or brain imaging is not generally indicated [110, 113, 114] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [113, 115, 116] (LE: 3).

*5.2.5 **Bosniak classification of renal cystic masses***

This classification system classifies renal cysts into five categories, based on CT imaging appearance, to predict malignancy risk [117, 118] (LE: 3). This system also advocates treatment for each category (Table 5.1).

Table 5.1: Bosniak classification of renal cysts [117]

Bosniak category	Features	Work-up
I	Simple benign cyst with a hairline-thin wall without septa, calcification, or solid components. Same density as water and does not enhance with contrast medium.	Benign
II	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 without enhancement.	Benign
IIF	These may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall. Minimal thickening of the septa or wall. The cyst may contain calcification, which may be nodular and thick, with no contrast enhancement. No enhancing soft-tissue elements. This category also includes totally intrarenal, non-enhancing, high attenuation renal lesions ≥ 3 cm. Generally well-marginated.	Follow-up. Some are malignant.
III	These are indeterminate cystic masses with thickened irregular walls or septa with enhancement.	Surgery or active surveillance – *see* Chapter 7. Over 50% are malignant
IV	Clearly malignant containing enhancing soft-tissue components.	Surgery. Most are malignant.

5.3 Renal tumour biopsy

Percutaneous renal tumour biopsy can reveal histology of radiologically indeterminate renal masses and should be considered for active surveillance in select patients with small masses, to obtain histology before ablative treatments and to select the most suitable form of medical and surgical treatment strategy in the setting of metastatic disease [119-124] (LE: 3). Due to the high diagnostic accuracy of abdominal imaging, renal tumour biopsy is not necessary in patients with a contrast-enhancing renal mass for whom surgery is planned (LE: 4).

Percutaneous sampling can be performed under local anaesthesia with needle core biopsy and/or fine needle aspiration (FNA). Biopsies can be performed with US or CT guidance, with a similar diagnostic yield [121, 123] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [119-123, 125] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [119-123] (LE: 3).

Core biopsies should be preferred for the characterisation of solid renal masses (LE: 2a). A SR and meta-analysis of the diagnostic performance and complications of renal tumour biopsy (RTB) was recently performed by this Panel. Fifty-seven articles including a total of 5,228 patients were included in the analysis. Needle core biopsies were found to have better accuracy for the diagnosis of malignancy compared with FNA [4]. Other studies showed that solid pattern and larger tumour size are predictors of a diagnostic core biopsy [121, 123] (LE: 2b).

In experienced centres, core biopsies have a high diagnostic yield, specificity, and sensitivity for the diagnosis of malignancy. The above mentioned meta-analysis showed that sensitivity and specificity of diagnostic core biopsies for the diagnosis of malignancy are 99.1% and 99.7%, respectively [4] (LE: 2b). However, 0-22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [119-126] (LE: 2a). If a biopsy is non-diagnostic, and radiologic findings are suspicious for malignancy, a further biopsy or surgical exploration should be considered (LE: 4). Repeat biopsies have been reported to be diagnostic in a high proportion of cases (83-100%) [123, 127-129].

Accuracy of RTBs for the diagnosis of tumour histotype is good. The median concordance rate between tumour histotype on RTBs and on the surgical specimen of the following partial or radical nephrectomy (RN) was 90.3% in the pooled analysis [4].

Assessment of tumour grade on core biopsies is challenging. In the pooled analysis the overall accuracy for nuclear grading was poor (62.5%), but significantly improved (87%) using a simplified two-tier system (high-grade vs. low grade) [4] (LE: 2a).

The ideal number and location of core biopsies are not defined. However, at least two good quality cores should be obtained, and necrotic areas should be avoided to maximise diagnostic yield [121, 123, 130, 131] (LE: 4). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [132] (LE: 2b).

Core biopsies of cystic renal masses have a lower diagnostic yield and accuracy and are not recommended alone, unless areas with a solid pattern are present (Bosniak IV cysts) [4, 121, 123] (LE: 2b).

Combined FNA and core biopsies can provide complementary results, especially for complex cystic lesions [122, 126, 127, 133, 134] (LE: 3).

Overall, percutaneous biopsies have a low morbidity [4]. Tumour seeding along the needle tract is anecdotal. Spontaneously resolving subcapsular/perinephric haematoma are reported in 4.3% of cases in a pooled analysis, but clinically significant bleeding is unusual (0-1.4%; 0.7% in the pooled analysis) and generally self-limiting [4].

5.4 Recommendations for the diagnostic assessment of renal cell carcinoma

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

CT = computed tomography; MRI = magnetic resonance imaging.

6. PROGNOSTIC FACTORS

Prognostic factors can be classified into: anatomical, histological, clinical, and molecular.

6.1 Anatomical factors

Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system [69] (Table 4.1).

6.2 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 grading system [32]. Although affected by intra- and inter-observer discrepancies, Fuhrman nuclear grade is an independent prognostic factor [135]. A simplified two- or three-strata system may be as accurate for prognostication as the classical four-tiered grading scheme [136, 137] (LE: 3). In univariate analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [138, 139]. However, prognostic information provided by the RCC type is lost when stratified to tumour stage [33, 139] (LE: 3).

Differences in tumour stage, grade and cancer specific survival (CSS) between the RCC types are illustrated in Table 6.1.

Table 6.1: Basic characteristics of three main types of RCC [33, 34, 140]

Type	Percentage of RCC (~)	Advanced disease at diagnosis (T3-4, N+, M+)	Fuhrman Grade 3 or 4 [32]	CSS (HR)
ccRCC	80-90%	28%	28.5%	referent
pRCC	6-15%	17.6%	28.8%	0.64 - 0.85
chRCC	2-5%	16.9%	32.7%*	0.24 - 0.56

** The Fuhrman grading system is validated for ccRCC, but is unreliable for chRCC. Data based on the Paner et al. grading system are not available yet [32, 42, 43].*
CSS = cancer-specific survival; HR = hazard ratio.

In all RCC types, prognosis worsens with stage and histopathological grade (Tables 6.2 and 6.3). The 5-year overall survival (OS) for all types of RCC is 49%, which has improved since 2006 probably due to an increase in incidentally detected RCCs and the introduction of tyrosine kinase inhibitor (TKI) [141]. Sarcomatoid changes

can be found in all RCC types and are equivalent to high grade and very aggressive tumours.

Table 6.2: CSS by stage and histopathological grade in RCCs - hazard ratio (95% CI) [34]**).**

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

CI = confidential interval.

Long-term survival in RCC patients treated by radical (RN) or partial nephrectomy (PN) between 1970 and 2003; for unilateral, sporadic ccRCC, pRCC or chRCC in a cohort study [140] (Table 6.3).

Table 6.3: CSS of surgically treated patients by RCC type (estimated survival rate in percentage [95% CI])

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

Two subgroups of pRCC with different outcomes have been identified [142]: 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 propensity for metastases (LE: 3).

RCC with Xp 11.2 translocation has a poor prognosis [143]. Its incidence is low, but should be systematically addressed in young patients.

RCC type classification has been confirmed by cytogenetic and genetic analyses [29-31] (LE: 2b).

6.3 Clinical factors

These include performance status (PS), localised symptoms, cachexia, anaemia, platelet count, neutrophil count, and neutrophil-to-lymphocyte ratio [86, 144-147] (LE: 3).

6.4 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CaIX), vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, p21 [148], PTEN (phosphatase and tensin homolog) (cell cycle), E-cadherin, C-reactive protein (CRP), osteopontin [149] and CD44 (cell adhesion) [150, 151], CXCR4 [152], and other cell cycle and proliferative markers [56, 153] have been investigated (LE: 3). None of these markers have clearly improved the predictive accuracy of current prognostic systems, none have been externally validated, and their use is not recommended in routine practice. Although gene expression profiling seems promising, it has not identified new relevant prognostic factors [154].

6.5 Prognostic systems and nomograms

Post-operative prognostic systems and nomograms combining independent prognostic factors have been developed and externally validated [155-161]. These may be more accurate than TNM stage or Fuhrman grade alone for predicting survival (LE: 3). An advantage of nomograms is their ability to measure predictive accuracy (PA), allowing all new predictive parameters to be objectively evaluated. Before being adopted, new prognostic variables or systems should demonstrate that its PA is superior to conventional post-operative histo-prognostic schemes [162]. Recently, new pre-operative nomograms with excellent PAs have been designed [163, 164]. Table 6.4 summarises the current most relevant prognostic systems.

6.6 Summary of evidence and recommendations for prognostic factors

Summary of evidence	LE
In RCC patients, TNM stage, Fuhrman nuclear grade, and RCC subtype (WHO, 2004; [165]) provide important prognostic information.	2

Recommendations	GR
Use the current TNM classification system.	B
Use grading systems and classify RCC subtype.	B
Use prognostic systems in the metastatic setting.	B
In localised disease, the use of integrated prognostic systems or nomograms is not routinely recommended, although they can provide a rationale for enrolling patients into clinical trials.	C
Molecular prognostic markers are not recommended for routine clinical use.	C

TNM = Tumour, Node, Metastasis (classification); WHO = World Health Organization.

Table 6.4: Anatomical, histological, and clinical variables in the 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	Haemoglobin	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		
	Hang'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.

7. DISEASE MANAGEMENT

7.1 Treatment of localised RCC

*7.1.1 **Introduction***

A SR underpins the findings of Sections 7.1.2 through 7.2.4.2. This review included all relevant published literature comparing surgical management of localised RCC (T1-2N0M0) [166, 167]. 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 the databases of well-defined registries were also included. For this Guidelines version, an updated search was performed (see Methods section 2.1 for details).

*7.1.2 **Surgical treatment***

7.1.2.1 Nephron-sparing surgery versus radical nephrectomy

Based on current available oncological and quality of life (QoL) outcomes, localised renal cancers are better managed by NSS (PN) rather than RN, irrespective of the surgical approach.

The estimated CSS rates at 5 years were comparable using these surgical techniques [168-172]. This was recently confirmed in a study of solitary T1-2 N0M0 renal tumours ≤ 5 cm with normal contralateral kidney function and WHO PS 0-2. At 9.3 years survival follow-up, 198 patients were alive after RN and 173 after PN. The CSS was 98.5 vs 97%, respectively. Local recurrence occurred in one and 6 patients in the RN and PN group, respectively [173].

A number of studies compared PN vs. RN (open or laparoscopic) for renal carcinoma (≤ 4 cm) [173-177]. RN was associated with increased mortality from any cause after adjusting for patient characteristics. In a prematurely closed randomised study of RCC ≤ 5 cm, comparing PN and RN, there was no difference in OS in the targeted population [172]. In studies analysing RCCs of 4-7 cm, no differences in CSS was observed between PN and RN [176, 178-185]. When laparoscopic PN was compared with laparoscopic RN in RCCs > 4 cm, there was no difference in OS, CSS and recurrence-free survival (RFS) rates [186]. Furthermore, a retrospective matched-pair analysis in elderly patients [187] reported a CSS of 98% for PN vs. 95% for RN. Other studies have compared various aspects of QoL and safety in open PN and RN [168, 169, 171, 183, 185, 188-190].

There was no difference in the length of hospital stay [169, 170, 189], blood transfusions [169, 189, 190], or mean blood loss [169, 189]. Complication rates were inconsistently reported and one intervention was not favoured over another [191]. One study found that mean operative time was longer for open PN [191], but other research found no difference [192]. Three studies consistently reported worse renal function after RN compared to PN [168, 171]. More patients had impaired post-operative renal function after RN after adjustment for diabetes, hypertension and age [171].

One database review compared open PN with laparoscopic RN in RCCs 4-7 cm. A significantly lower mean increase in post-operative creatinine levels was found [179]. Another study comparing laparoscopic PN vs. laparoscopic RN found that estimated GFR (eGFR) decreased less in the PN group, while the RN group had significantly more patients with a two-stage increase in ACKD [186]. Another database review [193] compared safety and efficacy of laparoscopic PN in RCCs > 2 cm (2-4 cm vs. > 4 cm). The laparoscopic PN group had a greater post-operative decrease in eGFR compared to the patients with smaller RCCs.

Two studies reported QoL post-surgery for RCC. Patients who underwent PN reported better scores, in many aspects of QoL [188]. Those who underwent RN reported more 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. Those with more complications had lower QoL scores [169].

No prospective comparative studies reporting oncological outcomes for minimally invasive ablative procedures compared with RN were identified. One trial reported on RFA vs. RN or PN for T1a RCC, resulting in CSS of 100% for all three treatments [194].

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

Partial nephrectomy is unsuitable in some patients with localised RCC due to:

- locally advanced tumour growth;
- partial resection is not feasible due to unfavourable tumour location;
- significant deterioration in patient health.

In these situations, the curative therapy is RN, including removal of the tumour-bearing kidney. Complete resection of the primary tumour by open or laparoscopic surgery offers a reasonable chance of cure.

7.1.2.2 Associated procedures

7.1.2.2.1 Adrenalectomy

One prospective NRS compared the outcomes of RN or PN with, or without, ipsilateral adrenalectomy [195]. Multivariate analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at 5 or 10 years was seen, 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.

7.1.2.2.2 Lymph node dissection for clinically negative lymph nodes (cN0)

Lymph node dissection (LND) in RCC is controversial [196]. Clinical assessment of LNs status is based on enlargement of LNs on CT/MRI and intraoperative assessment by direct palpation. Less than 20% of clinically positive (cN+) LNs are confirmed to be metastatic at pathology (pN+) [197]. Computed tomography and MRI do not allow detection of small metastases in normal sized LN [198] and extended LND (e-LND) with histopathological examination is the only way to assess LN status. For clinically positive LNs (cN+) see Section 7.2. on locally advanced RCC.

In patients with clinically negative LN (cN0) six clinical trials have been reported [196], one RCT [197] and five comparative studies [199-203].

Retrospective series support the hypothesis that LND may be beneficial in high-risk patients [198, 204]. However, in the European Organization for Research and Treatment of Cancer (EORTC) study only 4% of cN0 patients had positive LNs at final pathology, suggesting that LND represents over-treatment in the majority of patients [197].

Retrospective studies suggest that eLND should involve the LNs surrounding the ipsilateral great vessel and the interaortocaval region from the crus of the diaphragm to the common iliac artery. Involvement of interaortocaval LNs without regional hilar involvement is reported in up to 35-45% of cases [198, 199, 205]. At least 15 LNs should be removed [206, 207]. Sentinel LND is an investigational technique [208, 209]. Better survival outcomes are seen in patients with a low number of positive LNs (< 4) and no extranodal extension [210, 211]. A pre-operative nomogram to predict pN+ LNs status has been proposed [212].

7.1.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [213, 214]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [215-217]. These indications will be repeated in Sections 7.2 and 7.3 with cross reference to the summary of evidence and recommendations below.

7.1.2.2.4 Summary of evidence and recommendations

Summary of evidence	**LE**
Partial nephrectomy achieves similar oncological outcomes to radical nephrectomy for clinically localised tumours (cT1).	1b
Ipsilateral adrenalectomy, in the absence of clinical evident adrenal involvement during radical nephrectomy or partial nephrectomy, has no survival advantage.	3
In patients with localised disease without evidence of lymph node metastases, there is no survival advantage of lymph node dissection in conjunction with radical nephrectomy.	1b
In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.	3

Recommendations	**GR**
Surgery is recommended to achieve cure in localised RCC.	B
Partial nephrectomy is recommended in patients with T1a tumours.	A
Favour partial nephrectomy over radical nephrectomy in patients with T1b tumour, whenever feasible.	B
Ipsilateral adrenalectomy is not recommended when there is no clinical evidence of invasion of the adrenal gland.	B
Lymph node dissection is not recommended in localised tumour without clinical evidence of lymph node invasion.	A

*7.1.3 **Radical and partial nephrectomy techniques***

7.1.3.1 Radical nephrectomy techniques

No RCTs have assessed oncological outcomes of laparoscopic vs. open RN. A cohort study [218] and retrospective database reviews are available, mostly of low methodological quality [169, 219, 220]. Similar oncological outcomes for laparoscopic vs. open RN were found. Data from one RCT [221] and two NRSs [169, 218] showed a significantly shorter hospital stay and lower analgesic requirement for the laparoscopic RN group compared with the open group. Convalescence time was also significantly shorter [218]. No difference in the number of patients receiving blood transfusions was observed, but peri-operative blood loss was significantly less in the laparoscopic arm in all three studies [169, 218, 221]. Surgical complications were marked by low event rates and very wide confidence intervals. There was no difference in complications, but operation time was significantly shorter in the open nephrectomy arm. Post-operative QoL scores were similar [169].

Some comparative studies focused on the peri-operative outcomes of laparoscopic vs. RN for renal tumours ≥ T2. Overall, patients who underwent laparoscopic RN were shown to have lower estimated blood loss, less post-operative pain, shorter length of stay and convalescence compared to those who underwent open RN [218, 222-224]. Intraoperative and post-operative complications were similar in the two groups [218, 222-225]. No significant differences in CSS, PFS and OS were reported [207, 218, 223, 225, 226] (LE 2b).

The best approach for RN was the retroperitoneal or transperitoneal with similar oncological outcomes in the two RTCs [227, 228] and one quasi-randomised study [229]. Quality of life variables were similar in the two approaches.

Hand-assisted vs. standard laparoscopic RN was compared in one RCT [229] and one database review [191]. Estimated 5-year OS, CSS, and RFS rates were comparable. Duration of surgery was significantly shorter in the hand-assisted approach, while length of hospital stay and time to non-strenuous activities were shorter for the standard laparoscopic RN [191, 229]. However, the sample size was small.

Robot-assisted laparoscopic RN vs. laparoscopic RN was compared in one small study [230]. There were no local recurrences, port-site or distant metastases, but the sample size was small and follow-up was short. Similar results were seen in observational cohort studies comparing ‘portless’ and 3-port laparoscopic RN [231, 232]. Peri-operative outcomes were similar.

7.1.3.2 Partial nephrectomy techniques

Studies comparing laparoscopic PN and open PN found no difference in PFS [233-236] and OS [235, 236] in centres with laparoscopic expertise. The mean estimated blood loss is lower with the laparoscopic approach [233, 235, 237], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events are similar [233, 235]. Operative time is generally longer with the laparoscopic approach [234-236] and warm ischaemia time is shorter with the open approach [233, 235, 237, 238]. In a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [236], but not after a follow-up of 3.6 years. In another comparative study, the surgical approach was not an independent predictor for post-operative chronic kidney disease [238]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [239]. Simple tumour enucleation has similar PFS and CSS rates compared to standard PN and RN in a large study [240, 241].

The feasibility of off-clamp laparoscopic PN and laparoendoscopic single-site PN has been shown in selected patients but larger studies are needed to confirm their safety and clinical role [242, 243].

No studies have compared the oncological outcomes of robot-assisted vs. laparoscopic or open PN. One recent study prospectively compared the peri-operative outcomes of a series of robot-assisted and open PN performed by the same experienced surgeon. Robot-assisted PN was superior to open PN in terms of lower estimated blood loss and shorter hospital stay. Warm ischemia time, operative time, immediate, early, and short-term complications, variation of creatinine levels, and pathologic margins were similar among the groups [12].

A recent meta-analysis including a series of NRS with variable methodological quality compared the peri-operative outcomes of robot-assisted and laparoscopic PN. The robotic group had a significantly lower rate of conversion to open surgery and to radical surgery, shorter warm ischemia time, smaller change of estimated GFR after surgery and shorter length of stay. No significant difference was observed between the two groups regarding complications, change of serum creatinine after surgery, operative time, estimated blood loss and positive surgical margins [13].

7.1.3.3 Summary of evidence and recommendations

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

Recommendations	GR
Laparoscopic radical nephrectomy is recommended for patients with T2 tumours and localised masses not treatable by partial nephrectomy.	B
Radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated.	B

*7.1.4 **Therapeutic approaches as alternatives to surgery***

7.1.4.1 Surgical versus non-surgical treatment

Population-based studies compared the oncological outcomes of surgery (RN or PN) and non-surgical management for tumours < 4 cm. The analyses showed a significantly lower cancer-specific mortality for patients treated with surgery [244, 245]. However, the patients assigned to the surveillance arm were older and likely to be frailer and less suitable candidates for surgery. Other cause mortality rates in the non-surgical group significantly exceeded that of the surgical group [244]. Analyses of older patients (> 75 years) failed to show the same benefit in cancer-specific mortality for surgical treatment [11, 246, 247].

7.1.4.2 Surveillance

Elderly and comorbid patients with incidental small renal masses have a low RCC-specific mortality and significant competing-cause mortality [248, 249]. Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (US, CT, or MRI) with delayed intervention reserved for tumours showing clinical progression during follow-up [250].

In the largest reported series of active surveillance, the growth of renal tumours was low and progression to metastatic disease was reported in a limited number of patients [251, 252].

A single-institutional comparative study evaluating patients aged ≥ 75 years showed decreased OS for those who underwent surveillance and nephrectomy relative to NSS for clinically T1 renal tumours; however, patients selected for surveillance were older with greater comorbidity. At multivariable analysis, management type was not associated with OS after adjusting for age, comorbidity, and other variables [248]. No statistically significant difference in OS and CSS were observed in another study of RN vs. PN vs. active surveillance for T1a renal masses with a follow-up of 34 months [253].

The initial results of the multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry were recently published. This prospective, non-randomised study prospectively enrolled 497 patients with solid renal masses < 4 cm in size who chose active surveillance or primary active intervention. Patients who chose active surveillance were older, had worse ECOG scores, more comorbidities, smaller tumours, and more often multiple and bilateral lesions. Overall survival for primary intervention and active surveillance was 98% and 96% at 2 years, and 92% and 75% at 5 years, respectively (p = 0.06). At 5 years CSS was 99% and 100%, respectively (p = 0.3). Active surveillance was not predictive of overall or CSS in regression modelling with relatively short follow-up [19].

Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, active surveillance is appropriate to initially monitor small renal masses, followed if required, by treatment for progression [250-252, 254-257].

A multicentre study assessed patient QoL undergoing immediate intervention vs. active surveillance. Patients undergoing immediate intervention had higher QoL scores at baseline, specifically for physical health. The perceived benefit in physical health persisted for at least 1 year following intervention. Mental health, which includes domains of depression and anxiety, was not adversely affected while on active surveillance [258].

7.1.4.3 Ablative therapies

7.1.4.3.1 Cryoablation

Cryoablation is performed using either a percutaneous or a laparoscopic-assisted approach. In comparative studies, there was no significant difference in the overall complication rates between laparoscopic and percutaneous cryoablation [259-261]. One comparative study reported similar OS, CSS, and RFS in 172

laparoscopic patients with a longer follow-up compared with 123 percutaneous patients with a shorter follow-up [260]. A shorter average length of hospital stay was found with the percutaneous technique [260, 261]. No studies compared surveillance strategies to cryoablation.

7.1.4.3.2 Cryoablation versus partial nephrectomy

Studies compared open, laparoscopic or robotic PN with percutaneous or laparoscopic cryoablation. Oncological outcomes were mixed, with some studies showing no difference in OS, CSS, RFS, disease-free survival (DFS), local recurrence or progression to metastatic disease [262, 263], and some showing significant benefit for the PN techniques for some or all of these outcomes [264-267]. Not all studies reported all outcomes listed, and some were small and included benign tumours. No study showed oncological benefit for the cryoablation technique over PN.

Peri-operative outcomes, complication rates and other quality of life measures were also mixed. Some studies found the length of hospital stay was shorter and surgical blood loss was less with cryoablation [262-264], while also finding no differences in other peri-operative outcomes, recovery times, complication rates or post-operative serum creatinine levels. Two studies [266, 267] reported specific Clavien rates, with mostly non-significant differences, which were mixed for intra-operative vs. post-operative complications. Estimated GFRs were not significantly different in the two studies, but in favour of cryoablation in a third [265-267]. Estimates of new CKD were also mixed, with one study in favour of cryoablation [265], another strongly in favour of PN [266], and the third showing no difference [267]. One study compared PN with ablation therapy, either cryoablation or RFA [268], and showed significantly improved disease-specific survival at both 5 and 10 years for PN.

7.1.4.3.3 Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Three studies compared patients with T1a tumours treated by laparoscopic or percutaneous RFA [269-271]. Complications occurred in up to 29% of patients but were mostly minor. Complication rates were similar in patients treated laparoscopically or percutaneously. One study with a limited number of patients [271] found a higher rate of incomplete ablation in patients treated by percutaneous RFA. However, no differences in recurrence or CSS were found in the three comparative studies.

7.1.4.3.4 Radiofrequency ablation versus partial nephrectomy

Most publications about RFA are retrospective cohort studies with a low number of patients and limited follow-up. Three studies retrospectively compared RFA to surgery in patients with T1a tumours [194, 272, 273].

One study [272] compared T1a patients who underwent either RFA (percutaneous or laparoscopic) or PN and found no difference in OS and CSS. Another study retrospectively reviewed 105 T1a patients treated by percutaneous RFA or RN. CSS was 100% in both groups. OS was lower in the RFA group but patients treated with surgery were younger [194].

In a monocentric study that compared 34 RFA patients to 16 open PN patients, there was a higher rate of complications and transfusions in the PN group. Although the tumours were larger in PN patients, progression rates were similar (0%) [273].

7.1.4.3.5 Cryoablation versus radiofrequency ablation

Two studies compared RFA and cryoablation [274, 275]. No significant differences were reported for OS, CSS, or RFS in either study. For local RFS at 5 years, one study [274] reported improvement with RFA, while the other [275] reported a benefit with cryoablation. One study [274] reported no differences in Clavien complication rates between the techniques.

7.1.4.3.6 Other ablative techniques

Some studies have shown the feasibility of other ablative techniques, such as microwave ablation, laser ablation, and high-intensity focused US ablation. However, these techniques are considered experimental.

7.1.4.3.7 Summary of evidence and recommendations

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

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

7.2 Treatment of locally advanced RCC

7.2.1 Introduction

In addition to the summary of evidence and recommendations outlined in Section 7.1 for localised RCC certain therapeutic strategies arise in specific situations of locally advanced disease.

7.2.2 Management of clinically positive lymph nodes (cN+)

In the presence of clinically positive LNs (cN+), LND is always justified [36]. However, the extent of LND is controversial [198].

7.2.3 Management of locally advanced unresectable RCC

In patients with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [215-217]. The use of neoadjuvant targeted therapy to downsize tumours is experimental and cannot be recommended outside controlled clinical trials.

7.2.4 Management of RCC with venous thrombus

Tumour thrombus formation in the IVC in RCC patients is a significant adverse prognostic factor. Traditionally, patients with VTT undergo surgery to remove the kidney and tumour thrombus (TT). Aggressive surgical resection is widely accepted as the default management option for patients with VTT [276-284]. However, uncertainties remain over the best approach for surgical treatment of these patients.

7.2.4.1 The evidence base for surgery in patients with VTT

The data on whether patients with VTT should undergo surgery is derived from case series. In one of the largest published studies [281] a higher level of thrombus was not associated with increased tumour dissemination to LNs, perinephric fat or distant metastasis. Thus, all patients with non-metastatic disease and VTT, and an acceptable performance status (PS), should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation (LE: 3). The surgical technique and approach for each case should be selected based on the extent of TT (LE: 3).

7.2.4.2 The evidence base for different surgical strategies

A SR was undertaken which included comparison-only studies on the management of VTT in non-metastatic RCC [5, 285]. Only 5 studies were eligible for final inclusion. There were high risks of bias across all studies.

Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [286, 287]. Pre-operative embolisation [288] was associated with increased operating time, blood loss, hospital stay and peri-operative mortality in patients with T3 RCC.

No significant differences in oncological and process outcomes were observed between cardiopulmonary bypass with deep hypothermic circulatory arrest or partial bypass under normothermia or single caval clamp without circulatory support [289].

No surgical method was shown to be superior for the excision of VTT. The surgical method was dependent on the level of TT, and the grade of occlusion of the IVC [5, 286, 287, 289]. The relative benefits and

harms of other strategies and approaches regarding access to the IVC and the role of IVC filters and bypass procedures remain uncertain.

7.2.4.3 Summary of evidence and recommendations

Summary of evidence	LE
In patients with locally advanced disease due to clinically enlarged lymph nodes, the survival benefit of lymph node dissection is unclear but lymph node dissection can add staging information.	3
Low quality data suggest that tumour thrombus excision in non-metastatic disease may be beneficial.	3
Tumour embolisation or inferior vena cava filter do not appear to offer any benefits.	3

Recommendations	GR
In patients with clinically enlarged lymph nodes, lymph node dissection may be performed for staging purposes or local control.	C
Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic RCC.	C

*7.2.5 **Adjuvant therapy***

There is currently no evidence from randomised phase III trials that adjuvant therapy offers a survival benefit. The impact on OS of adjuvant tumour vaccination in selected patients undergoing nephrectomy for T3 renal carcinomas remains unconfirmed [290-294] (LE: 1b). Heat shock protein-peptide complex-96 (vitespen) [23], may have a benefit in a subgroup of patients but the overall data from phase III trials were negative. A similar observation was made in an adjuvant trial of girentuximab, a monoclonal antibody against carboanhydrase IX (CAIX) (ARISER) [295]. No difference in DFS was observed in the overall trial analysis, but a subgroup evaluation of patients with high CAIX expression suggests a potential benefit of girentuximab in this population. Several RCTs of adjuvant sunitinib, sorafenib, pazopanib, axitinib and everolimus are ongoing. At present, there is no evidence for the use of adjuvant VEGF-R or mammalian target of rapamycin inhibitor (mTOR) inhibitors. One of the largest adjuvant trials of sunitinib vs. sorafenib vs. placebo reported in 2015 (ASSURE) after an interim analysis performed with 62% information. Results demonstrated no significant differences in DFS or OS between the experimental arms and placebo and it was concluded that adjuvant therapy with sunitinib or sorafenib should not be given [144].

7.2.5.1 Summary of evidence and recommendation for adjuvant therapy

Summary of evidence	LE
Adjuvant cytokines do not improve survival after nephrectomy.	1b
Adjuvant sunitinib or sorafenib do not improve disease-free and overall survival after nephrectomy.	1b

Recommendations	GR
Adjuvant therapy with sunitinib or sorafenib should not be given.	A
Do not provide adjuvant therapy following surgery outside of controlled clinical trials.	A

7.3 Advanced/metastatic RCC

*7.3.1 **Local therapy of advanced/metastatic RCC***

7.3.1.1 Cytoreductive nephrectomy

Tumour resection is curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligo-metastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary. In a meta-analysis comparing CN + immunotherapy vs. immunotherapy only, increased long-term survival was found in patients treated with CN [296]. Only retrospective non-comparative data for CN combined with targeting agents, such as sunitinib, sorafenib and others are available. Cytoreductive nephrectomy is currently recommended in mRCC patients with good PS, large primary tumours and low metastatic volume. In patients with poor PS or Metastatic Renal Cancer Database Consortium (IMDC) risk, those with small primaries and high metastatic volume and/or a sarcomatoid tumour, CN is not recommended.

7.3.1.1.1 Embolisation of the primary tumour

In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [215-217] (see recommendation Section 7.1.2.2.4).

7.3.1.1.2 Summary of evidence and recommendation for local therapy of advanced/metastatic RCC

Summary of evidence	LE
Cytoreductive nephrectomy combined with interferon-alpha improves survival in patients with metastatic RCC and good performance status.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3

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

*7.3.2 **Local therapy of metastases in mRCC***

A SR of the local treatment of metastases from RCC in any organ was undertaken [297]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes were OS, CSS and PFS, local symptom control and adverse events. A risk-of-bias assessment was conducted [298]. Of 2,235 studies identified only 16 non-randomised comparative studies were included.

Eight studies reported on local therapies of RCC-metastases in various organs [299-306]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC metastases in bone, including the spine [307-309], two in the brain [310, 311] and one each in the liver [312] lung [313] and pancreas [314]. Three studies [303, 305, 313] were abstracts. Data were too heterogeneous for a meta-analysis. There was considerable variation in the type and distribution of systemic therapies (cytokines and VEGF-inhibitors) and in reporting the results.

7.3.2.1 Complete versus no/incomplete metastasectomy

All eight studies [299-306] on RCC metastases in various organs compared complete vs. no and/or incomplete metastasectomy. However, in one study [302], complete resections were achieved in only 45% of the metastasectomy cohort, which was compared with no metastasectomy. Non-surgical modalities were not applied. Six studies [299, 301-303, 305, 306] reported a significantly longer median OS or CSS following complete metastasectomy (the median value for median OS or CSS was 40.75 months, range 23-122 months) compared with incomplete and/or no metastasectomy (the median value for median OS or CSS was 14.8 months, range 8.4-55.5 months). Of the two remaining studies, one [300] showed no significant difference in CSS between complete and no metastasectomy, and one [304] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases to the lung [313], liver [312], and pancreas [314], respectively. The lung study reported a significantly higher median OS for metastasectomy vs. medical therapy only for both target therapy and immunotherapy. Similarly, the liver and pancreas study reported a significantly higher median OS and 5-year OS for metastasectomy vs. no metastasectomy.

7.3.2.2 Local therapies for RCC bone metastases

Of three studies identified, one [309] compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with RCC bone metastases. Single-dose IGRT (≥ 24 Gray) had a significantly better 3-year actuarial local PFS rate, also shown by Cox regression analysis. Another study [307] compared metastasectomy/curettage and local stabilisation with no surgery of solitary RCC bone metastases in various locations. A significantly higher 5-year CSS rate was observed in the intervention group.

After adjusting for prior nephrectomy, gender and age, multivariate analysis still favoured metastasectomy/curettage and stabilisation. A third study [308] compared the efficacy and durability of pain relief between single-dose stereotactic body radiotherapy (SBRT) and conventional radiotherapy (CRT) in patients with RCC bone metastases to the spine. Pain, objective response rate (ORR), time-to-pain relief and duration of pain relief were similar.

7.3.2.3 Local therapies for RCC brain metastases

Two studies on RCC brain metastases were included. A three-armed study [310] compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS + WBRT. Each group was further subdivided

into recursive partitioning analysis (RPA) classes I to III (I favourable, II moderate and III poor patient status). Two-year OS and intracerebral control were equivalent in patients treated with SRS alone and SRS + WBRT. Both treatments were superior to WBRT alone in the general study population and in the RPA subgroup analyses. A comparison of SRS vs. SRS + WBRT in a subgroup analysis of RPA class I showed significantly better 2-year OS and intracerebral control for SRS + WBRT based on only three participants. The other study [311] compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy (MTS) + CRT or CRT alone. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. 1-, 2- and 3-year survival rates were higher but not significantly so for FSRT than for metastasectomy + CRT or CRT alone. Fractionated stereotactic radiotherapy did not result in a significantly better 2-year local control rate compared with MTS + CRT.

7.3.2.4 Embolisation of metastases

Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss [315]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [316] (see recommendation Section 7.1.2.2.4)

7.3.2.5 Summary of evidence and recommendations for local therapy of metastases in metastatic RCC

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

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

7.4 Systemic therapy for advanced/metastatic RCC

*7.4.1 **Chemotherapy***

Chemotherapy is moderately effective only if 5-fluorouracil (5-FU) is combined with immunotherapeutic agents [317]. However, in one study, interferon-alpha (IFN-α) showed equivalent efficacy to IFN-α + interleukin-2 (IL-2) + 5-FU [318].

7.4.1.1 Summary of evidence and recommendation for systemic therapy for advanced/metastatic RCC

Summary of evidence	LE
In metastatic RCC, 5-FU combined with immunotherapy has equivalent efficacy to IFN-α.	1b
In metastatic RCC, chemotherapy is otherwise not effective.	3

Recommendation	GR
In patients with clear-cell metastatic RCC, chemotherapy should not be offered.	B

5-FU = fluorouracil; INF = interferon.

*7.4.2 **Immunotherapy***

7.4.2.1 IFN-α monotherapy and combined with bevacizumab

Conflicting results exist for IFN-α in clear-cell (cc) mRCC. Several studies showed that IFN-α in mRCC has a survival advantage similar to that of hormonal therapy [319]. IFN-α resulted in a response rate of 6-15%, a 25% decrease in tumour progression risk and a modest survival benefit compared to placebo [87, 320]. However,

patients with intermediate-risk disease, failed to confirm this benefit [321].

Interferon-α may only be effective in some patient subgroups, including patients with ccRCC, favourable-risk criteria, as defined by the Memorial Sloan-Kettering Cancer Center (MSKCC) and lung metastases only [319]. The moderate efficacy of immunotherapy was confirmed in a Cochrane meta-analysis [320]. Bevacizumab + IFN-α increased response rates and PFS in first-line therapy compared with IFN-α monotherapy [322]. All studies comparing targeted drugs to IFN-α monotherapy therapy showed superiority for sunitinib, bevacizumab + IFN-α, and temsirolimus [322-325]. IFN-α has been superseded by targeted therapy in cc-mRCC.

Table 7.1: MSKCC (Motzer) criteria [87]*

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

** The Metastatic Renal Cancer Database Consortium (IMDC) risk model is also widely used in this setting [326].*

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

LDH = lactate dehydrogenase; PS = performance status.

7.4.2.2 Interleukin-2

Interleukin-2 has been used to treat mRCC since 1985, with response rates ranging from 7% to 27% [325, 327, 328]. Complete and durable responses have been achieved with high-dose bolus IL-2 [329]. The toxicity of IL-2 is substantially greater than that of IFN-α [320].

7.4.2.3 Vaccines and targeted immunotherapy

A vaccine trial with tumour antigen 5T4 + first-line standard therapy (i.e. sunitinib, IL-2 or IFN-α) showed no survival benefit compared with placebo and first-line standard therapy [330]. Several vaccination studies are ongoing. Monoclonal antibodies against programmed death-1 (PD-1) or its ligand (PD-1L), which have efficacy and acceptable toxicity in patients with RCC [331], are currently being investigated in phase III trials.

7.4.2.4 Immune checkpoint blockade

Immune checkpoint blockade with monoclonal antibodies target and block the inhibitory T-cell receptor Programmed Death-1 (PD-1) or the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4)-signalling to restore tumour specific T cell immunity [332]. While pembrolizumab and nivolumab target the PD-1 receptor, atezolizumab and durvalumab block the ligand, PD-L1. Ipilumimab targets CTLA-4. A randomised dose ranging phase II trial of nivolumab in metastatic RCC patients revealed a high ORR with rapid and durable responses in heavily pre-treated patients [333]. A phase III trial is currently investigating the combination of nivolumab and ipilumimab vs. sunitinib in first line treatment (CheckMate 214, NCT 02231749) [148]). A phase III trial of nivolumab vs. everolimus after several lines of VEGF-targeted therapy (CheckMate 025, NCT01668784) reported longer OS, better QoL and fewer grade 3 or 4 adverse events with nivolumab than with everolimus [153, 334, 335]. Nivolumab has superior OS to everolimus (Hazard Ratio [HR]: 0.73, 95% CI: 0.57-0.93, $p < 0.002$) in VEGF refractory renal cancer with a median OS of 25 months for nivolumab and 19.6 months for everolimus (LE: 1b). Patients who had failed multiple lines of VEGF targeted therapy were included in this trial making the results broadly applicable. The trial included 15% MSKCC poor-risk patients. There was no PFS advantage with nivolumab despite the OS advantage.

7.4.2.5 Summary of evidence and recommendations for immunotherapy in mRCC

Summary of evidence	LE
IFN-α monotherapy is inferior to VEGF-targeted therapy or mTOR inhibition in metastatic RCC.	1b
IL-2 monotherapy may have an effect in selected cases (good PS, ccRCC, lung metastases only).	2
IL-2 has more side-effects than IFN-α.	2-3
High dose IL-2 is associated with durable complete responses in a limited number of patients. However, no clinical factors or biomarkers exist to accurately predict a durable response in patients treated with HD-IL-2.	1b

Bevacizumab plus IFN-α is more effective than IFN-α treatment-naïve, low-risk and intermediate-risk tumours.	1b
Vaccination therapy with tumour antigen 5T4 showed no survival benefit over first-line standard therapy.	1b
Cytokine combinations, with or without additional chemotherapy, do not improve OS compared with monotherapy.	1b
Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.	1b

Recommendations	**GR**
Nivolumab is strongly recommended after one or two lines of VEGF-targeted therapy in metastatic RCC.	A
Monotherapy with IFN-α or HD bolus IL-2 is not routinely recommended as first-line therapy in metastatic RCC.	A

HD = high-dose; IL = interleukin; INF = interferon; OS = overall survival; PFS = progression-free survival; PS = performance status; VEGF = vascular endothelial growth factor.

*7.4.3 **Targeted therapies***

In sporadic ccRCC, hypoxia-inducible factor (HIF) accumulation due to VHL inactivation results in overexpression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis [336-338]. This process substantially contributes to the development and progression of RCC. There are several targeting drugs approved for treating mRCC in both the USA and Europe:

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

Most published trials have selected for clear-cell carcinoma subtypes, thus no robust evidence-based recommendations can be given for non-ccRCC subtypes.

In major trials leading to registration of the approved targeted agents, patients were stratified according to the MSKCC risk model [319] (Table 7.1). Since the MSKCC (Motzer) criteria were developed during the cytokine era, the IMDC risk model has been established and validated to yield an accurate prognosis for patients treated in the era of targeted therapy. Neutrophilia and thrombocytosis have been added to the list of MSKCC risk factors, while LDH has been removed [326].

The IMDC published data on conditional survival which may be used in patient counselling [339]. The IMDC risk model has been validated and compared with the Cleveland Clinic Foundation (CCF) model, the French model, MSKCC model, and the International Kidney Cancer Working Group (IKCWG) model. The IMDC model did not differ from the other models, indicating that a ceiling has been reached in predicting prognosis based solely on clinical factors [340].

Table 7.2: Median OS and patients surviving 2 years treated in the era of targeted therapy per IMDC risk group (based on references [326, 340]**)**

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

** Based on [340]; ** based on [326]*

CI = confidence interval; IMDC = Metastatic Renal Cancer Database Consortium; OS = overall survival.

7.4.3.1 Tyrosine kinase inhibitors

7.4.3.1.1 Sorafenib

Sorafenib is an oral multikinase inhibitor. A trial compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unfit for immunotherapy. Sorafenib improved PFS [341] (HR: 0.44; 95% CI: 0.35- 0.55; $p < 0.01$). Overall survival improved in patients initially assigned to placebo who were censored at crossover [342]. In patients with previously untreated mRCC sorafenib was not superior to IFN-α (phase II study). A number of studies have used sorafenib as the control arm in sunitinib-refractory disease vs. axitinib, dovitinib and temsirolimus. None showed superior survival for the study drug compared to sorafenib.

7.4.3.1.2 Sunitinib

Sunitinib is an oral tyrosine kinase (TK) inhibitor and has anti-tumour and anti-angiogenic activity. Sunitinib as second-line monotherapy (after cytokines) in patients with mRCC demonstrated a partial response in 34-40% and stable disease at > 3 months in 27-29% of patients [343]). First-line monotherapy with sunitinib demonstrated significantly longer PFS compared with IFN-α. Overall survival was greater in patients treated for 26.4 and 21.8 months with sunitinib despite crossover [344].

In the EFFECT trial, sunitinib 50 mg/day (4 weeks on/2 weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with clear-cell mRCC [345]. Median time to progression (TTP) with sunitinib 50 mg was numerically longer than the 37.5 mg arm (9.9 months vs. 7.1 months). No significant differences in OS were seen (23.1 vs. 23.5 months; $p = 0.615$). Toxicity was comparable in both arms. Because of the non-significant, but numerically longer TTP with the standard 50 mg dosage, the authors recommended using this regimen. Alternate scheduling of sunitinib (2 weeks on/1 week off) is being used to manage toxicity, but robust data to support its use is lacking.

7.4.3.1.3 Pazopanib

Pazopanib is an oral angiogenesis inhibitor. In a trial of pazopanib vs. placebo in treatment-naïve mRCC patients and cytokine-treated patients, a significant improvement in PFS and tumour response was observed [346]. Median PFS with pazopanib compared with placebo was:

- 9.2 vs. 4.2 months in the overall study population;
- 11.1 vs. 2.8 months for the treatment-naïve subpopulation;
- 7.4 vs. 4.2 months for the cytokine-pretreated subpopulation.

A trial comparing pazopanib with sunitinib (COMPARZ) established pazopanib as another first-line option. It showed that pazopanib was not associated with significantly worse PFS or OS compared to sunitinib. The two drugs had different toxicity profiles [347], and QoL was better with pazopanib. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%: $p < 0.05$) due to symptomatic toxicity [348]. Both studies were limited in that intermittent therapy (sunitinib) was compared with continuous therapy (pazopanib).

7.4.3.1.4 Axitinib

Axitinib is an oral selective second-generation inhibitor of VEGFR-1, -2, and -3. Axitinib was first evaluated as second-line treatment. In the AXIS trial, axitinib was compared to sorafenib in patients with previously failed cytokine treatment or targeted agents (mainly sunitinib) [349].

The overall median PFS was greater for axitinib than sorafenib. The difference in PFS was greatest in patients in whom cytokine treatment had failed. For those in whom sunitinib had failed, axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months). Axitinib showed > grade 3 diarrhoea in 11%, hypertension in 16%, and fatigue in 11%. Across all grades, nausea was recorded in 32%, vomiting in 24%, and asthenia in 21%. OS was a secondary end-point of the trial in which crossover was not permitted. Final analysis of OS showed no significant differences between axitinib or sorafenib [350, 351].

Axitinib was investigated in two first-line studies [352, 353]. One investigated the efficacy and safety of axitinib dose titration in previously untreated patients with mRCC. Although the objective response rate (RR) was higher in patients treated to toxicity, median PFS was 14.5 months in the axitinib titration group, 15.7 months in the placebo titration group, and 16.6 months in non-randomised patients [352]. This supports the hypothesis that dose escalation is associated with higher RRs.

In a randomised phase III trial of axitinib vs. sorafenib in first-line treatment-naïve cc-mRCC, a significant difference in median PFS between the treatment groups was not demonstrated [353]. As a result of this study, axitinib is not approved for first-line therapy.

7.4.3.1.5 Cabozantinib

Cabozantinib is an oral inhibitor of tyrosine kinases, including MET, VEGF and AXL. Cabozantinib was investigated in a phase I study in patients resistant to VEGFR and mTOR inhibitors demonstrating objective responses and disease control [152]. Based on these results a randomised phase III trial investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapy (METEOR) [56]. Cabozantinib delayed PFS compared to everolimus in VEGF targeted therapy refractory disease by 42% (HR: 0.58 95% CI: 0.45-0.75) [56] (LE: 1b). The median PFS for cabozantinib was 7.4 (95% CI: 5.6-9.1) months vs. 3.8 (95% CI: 3.7-5.4) months for everolimus. The trial recruited 658 patients although PFS was assessed on the first 375 patients. Interim OS results show a strong trend favouring cabozantinib (HR: 0.67: 95% CI: 0.51-0.89, p = 0.005), however this was not significant at the predefined levels at this interim stage. A final planned mature OS analysis is expected in 2016. Grade 3 or 4 adverse events in 74% were reported with cabozantinib and 65% with everolimus. Adverse events were managed with dose reductions; doses were reduced in 60% of the patients who received cabozantinib. Discontinuation due to toxicity was not significantly different for the 2 drugs. The trial included 16% MSKCC poor-risk patients.

*7.4.4 **Monoclonal antibody against circulating VEGF***

7.4.4.1 Bevacizumab monotherapy and bevacizumab + IFN-α

Bevacizumab is a humanised monoclonal antibody. The AVOREN study compared bevacizumab + IFN-α with INF-α monotherapy in mRCC [322]. Overall response was higher in the bevacizumab + IFN-α group. Median PFS increased from 5.4 months with IFN-α to 10.2 months with bevacizumab + IFN-α. No benefit was seen in MSKCC poor-risk patients. Median OS in this trial, which allowed crossover after progression, was not greater in the bevacizumab/IFN-α group (23.3 vs. 21.3) [354].

A similarly designed trial (CALGB 90206) [355, 356], of bevacizumab + IFN-α vs. Interferon-α showed a higher median PFS for the combination group. Objective response rate was also higher in the combination group. Overall toxicity was greater for bevacizumab + IFN-α, with significantly more grade 3 hypertension, anorexia, fatigue, and proteinuria.

*7.4.5 **mTOR inhibitors***

7.4.5.1 Temsirolimus

Temsirolimus is a specific inhibitor of mTOR [357]. Patients with modified high-risk mRCC in the NCT00065468 trial received first-line temsirolimus or IFN-α monotherapy, or a combination of both [324]. Median OS was higher in the temsirolimus group. However, OS in the temsirolimus + IFN-α group was not significantly superior to IFN-α alone [324]. IFN-α toxicity was marked, partly due to the high doses used. The INTORSECT trial investigated temsirolimus vs. sorafenib in patients who had previously failed sunitinib. Although no benefit in PFS was observed, a significant OS benefit for sorafenib was noted [358]. Based on these results, temsirolimus is not recommended in patients with VEFG TKI refractory disease.

7.4.5.2 Everolimus

Everolimus is an oral mTOR inhibitor, which is established in the treatment of VEGF-refractory disease. The RECORD-1 study compared everolimus + best supportive care (BSC) vs. placebo + BSC in patients with previously failed anti-VEGFR treatment (or previously intolerant of VEGF targeted therapy) [359]. The initial data showed a median PFS of 4.0 months v.s. 1.9 months for everolimus and placebo, respectively [359]. This was extended to 4.9 months in the final analysis (HR: 0.33) [360]. Subset analysis of PFS for patients receiving only 1 previous VEFG TKI was 5.4 months [361]. This included some patients who were intolerant rather than progressed on therapy (PFS was also 5.4 months) [362]. RECORD-1 included patients who failed multiple lines of VEGF-targeted therapy, and received everolimus in a third- and fourth-line setting [359].

The RECORD-3 randomised phase II study of sequential first-line sunitinib and second-line everolimus vs. sequential first-line everolimus and second-line sunitinib in treatment-naïve mRCC reported a higher median PFS for first-line treatment in the sunitinib group [363]. Primary endpoint was to assess PFS non-inferiority of first-line everolimus to first-line sunitinib. A large number of the crossover patients did not receive the planned subsequent therapy making further analysis complex and underpowered.

*7.4.6 **Therapeutic strategies and recommendations***

7.4.6.1 Therapy for treatment-naïve patients with clear-cell mRCC

Key trials have established sunitinib and bevacizumab plus IFN-α as first-line treatment options in treatment-naïve patients with cc-mRCC and a favourable-to-intermediate risk score. The COMPARZ study demonstrated that pazopanib and sunitinib have similar efficacy and different toxicity profiles. This study firmly establishes pazopanib as another first-line option [347].

7.4.6.1.1 Sequencing targeted therapy

7.4.6.1.1.1 Following progression of disease with one or more lines of VEGF-targeted therapy

Several trials investigated therapeutic options for patients who progressed on first-line VEGF-targeted therapy, including studies which investigated options after one or more lines of VEGF-targeted therapy. RECORD-1 established VEGF TKI until disease progression followed by everolimus as one of the treatment options for patients with mRCC [359]. However, both nivolumab and cabozantinib were superior to everolimus following a similar trial design as RECORD-1 [153]. Both of these agents should be considered a new standard of care in patients of all risk categories who have failed one or more VEGF targeted therapies (Figure 7.1).

Nivolumab should be considered for all patients in whom it is not contraindicated in the VEGF refractory setting owing to a significant OS advantage compared to everolimus as well as its attractive tolerability profile. Cabozantinib is the first TKI to have a superior PFS compared to everolimus. Cabozantinib's trend toward an OS advantage at interim analysis (HR: 0.67: 95% CI: 0.51-0.89, p = 0.005), further supports its use in this setting. If this becomes statistically significant in the final analysis the recommendations will match those of nivolumab.

Axitinib is superior to sorafinib in terms of PFS in sunitinib refractory ccRCC [348]. Neither nivolumab nor cabozantinib has been tested directly against axitinib in the second-line setting. However, the OS advantage and tolerability of nivolumab over everolimus in this setting makes it preferable to axitinib, while the impressive PFS of cabozantinib, especially in those who have failed sunitinib, makes it an attractive alternative to axitinib.

Tolerability is an important consideration when recommendations cannot be made of efficacy alone. Both everolimus and sorafenib have been outperformed by other agents in VEGF refractory disease and should not be the standard of care in pure VEGF refractory disease where superior alternatives are available. It is not currently possible to determine therapy based on baseline characteristics or biomarker expression for any of the above drugs.

Direct comparison of RECORD-1, Checkmate-25 and METEOR data with AXIS data is not advised due to differences in patient populations [349-351, 359].

INTORSECT compared temsirolimus vs. sorafenib after disease progression on sunitinib [358]. Median PFS was higher, but not significant, in the temsirolimus group. However, there was a significant difference in OS in favour of sorafenib. Neither of these agents are recommended or widely used in this setting. These data are not necessarily relevant to other mTOR inhibitors such as everolimus.

Based on OS difference, recommendations can currently be made as to the best sequence of targeted therapy (Figure 7.1). Two major trials, testing nivolumab and cabozantinib, have changed treatment paradigms in VEGF-targeted therapy-refractory RCC (LE: 1a). There is a strong rationale for using both drugs in sequence in the 2nd and 3rd line following VEGF-targeted therapy. This creates a new a standard for the majority of patients. Nivolumab was approved in this setting in the United States in 2015. It remains unclear about when these drugs will be approved elsewhere.

7.4.6.1.1.2 Treatment after progression of disease with mTOR inhibition

There are limited data addressing this issue. In view of the efficacy of VEGF-targeted therapy in renal cancer, a switch to VEGF-targeted therapy is advised (expert opinion and [364]).

7.4.6.1.1.3 Treatment after progression of disease with cytokines

Trials have established sorafenib, axitinib and pazopanib as therapeutic options in this setting with a median PFS of 5.5, 12.1 and 7.4 months, respectively. Based on trial data, axitinib is superior to sorafenib in patients previously treated with cytokine therapy [349-351].

7.4.6.1.1.4 Treatment after second-line targeted therapy

7.4.6.1.1.4.1 Treatment after two VEGF-targeted therapies

The RECORD-1 study demonstrated the activity of everolimus in patients who had received more than one line of targeted therapy. Twenty six percent of patients were treated with two or more lines of VEGF-targeted

therapy and significant benefits were seen. However, based on the results of the influential nivolumab and cabozantinib trials, a strong rationale exists for preferring both drugs as third-line treatment upon failure of 2 VEGF-targeted therapies [56, 153] (Figure 7.1).

7.4.6.1.1.4.2 Treatment after VEGFR- and mTOR inhibition

Although the GOLD trial failed to demonstrate superior efficacy of dovitinib over sorafenib in patients with mRCC who experienced disease progression after receiving prior VEGF- and mTOR-targeted therapies, the results suggest efficacy and safety of sorafenib in the third-line setting [364]). This sequence is not recommended where alternative superior drugs are available.

7.4.6.1.1.5 Combination of targeted agents

There have been a number of trials with VEFG targeted therapy and mTOR inhibitors [365-369]. The results have all been negative. No combinations of targeted agents are currently recommended.

7.4.6.2 Non-clear-cell renal cancer

No phase III trials of patients with non-ccRCC have been reported. Expanded access programmes and subset analysis from RCC studies suggest the outcome of these patients with targeted therapy is poorer than for ccRCC. Targeted treatment in non-ccRCC has focused on temsirolimus, everolimus, sorafenib and sunitinib [324, 370-372].

The most common non-clear-cell subtypes are papillary type 1 and non-type 1 pRCCs. There are small single-arm data for sunitinib and everolimus [372-375]. A trial of both types of pRCC treated with everolimus (RAPTOR) [375], showed median PFS of 3.7 months per central review in the intention-to-treat population with a median OS of 21.0 months.

Another trial investigated foretenib (a dual MET/VEGFR2 inhibitor) in patients with pRCC. Toxicity was acceptable with a high RR in patients with germline MET mutations [376]. However, a randomised phase II trial of everolimus vs. sunitinib (ESPN) with crossover design in non-clear-cell mRCC included 73 patients (27 with pRCC) and was stopped after a futility analysis for PFS and OS [377]. The final results presented at the 2014 annual meeting of the American Society of Clinical Oncology showed a non-significant trend favouring sunitinib (6.1 vs. 4.1 months). Based on a SR including subgroup analysis of the ESPN, RECORD-3 and another phase II trial (ASPEN) sunitinib and everolimus remain options in this population, with a preference for sunitinib [126, 378]. Patients with ncc-mRCC should be referred to a clinical trial where appropriate.

Collecting-duct cancers are resistant to systemic therapy. There is a lack of data to support specific therapy in these patients. There is limited data supporting the use of targeted therapy in other histological subtypes such as chromophobe tumours [324, 370].

Figure 7.1: Recommendations for patients with metastatic ccRCC who have failed one or more lines of VEGF targeted therapy

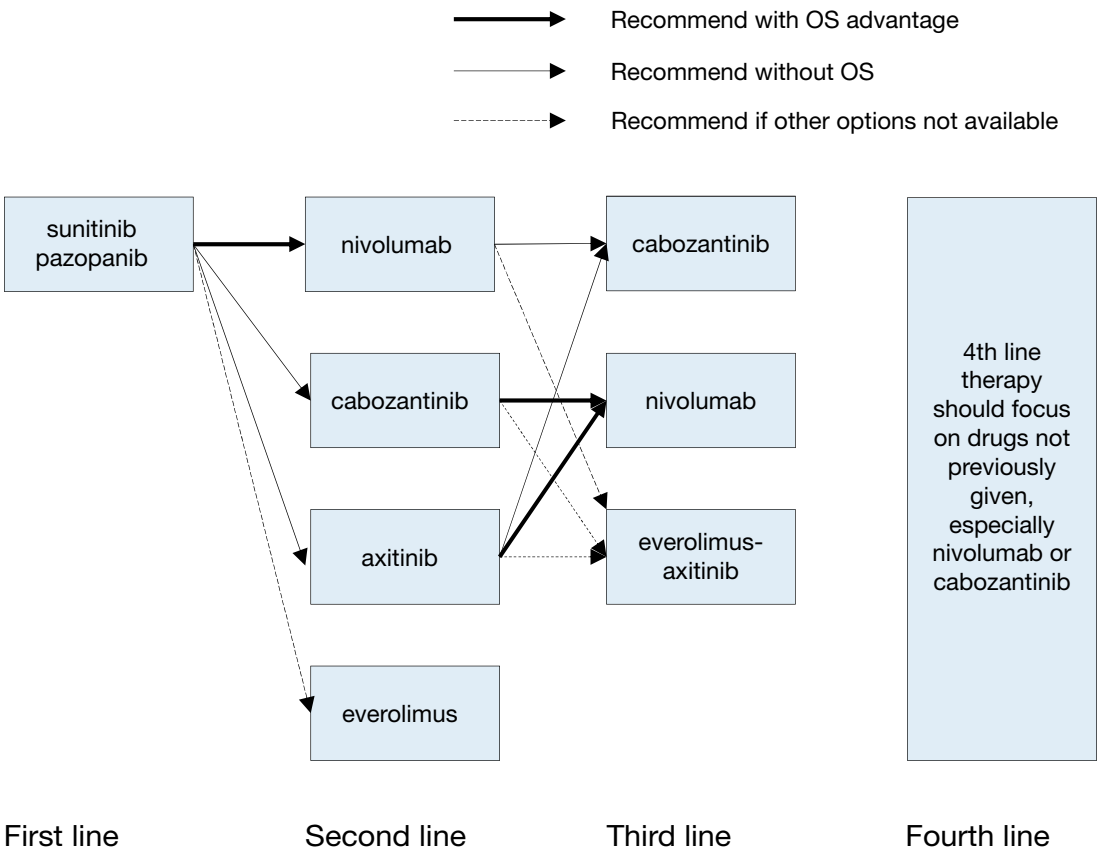

Table 7.3: EAU 2015 evidence-based recommendations for systemic therapy in patients with mRCC

RCC type	MSKCC risk group [319]	First-line	LE^	Second-Line after VEGF therapy*	LE^	Third-line*	LE^	Later lines	LE
Clear cell*	Favourable, intermediate and poor	sunitinib pazopanib bevacizumab + IFN-α (favourable-intermediate only)	1b 1b 1b	based on OS: nivolumab based on PFS: cabozantinib axitinib sorafenib# everolimus&	 2a 2a 2a 2a 2a	**after VEGF therapy**: nivolumab cabozantinib everolimus& **after VEGF and mTOR therapy**: sorafenib **after VEGF and nivolumab**: cabozantinib axitinib everolimus	 2a 2a 2a 1b 4 4 4	any targeted agent	4
Clear cell*	poor¶	temsirolimus	1b	any targeted agent	4				
Non-clear cell §	any	sunitinib everolimus temsirolimus	2a 2b 2b	Any targeted agent	4				

IFN-α = interferon alpha; MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin inhibitor; 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 4 weeks, followed by 2 weeks of rest (37.5 mg continuous dosing did not show significant differences); temsirolimus 25 mg weekly intravenously; pazopanib 800 mg daily orally. Axitinib 5 mg twice daily, to be increased to 7 mg twice daily, unless greater than grade 2 toxicity, blood pressure higher than 150/90 mmHg, or the patient is receiving antihypertensive medication. Everolimus, 10 mg daily orally.*

§ No standard treatment available. Patients should be treated in the framework of clinical trials or a decision can be made in consultation with the patient to perform treatment in line with ccRCC.

¶ Poor risk criteria in the NCT00065468 trial consisted of MSKCC [319] risk plus metastases in multiple organs. Evidence for subsequent therapies unclear, making this option less appealing.

 # Sorafenib was inferior to axitinib in a RCT in terms of PFS but not OS [351].

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

& everolimus was inferior in terms of OS to nivolumab and in terms of PFS to cabozantinib and should not routinely be given where other superior agents are available.

7.4.6.3 Summary of evidence and recommendations for systemic therapy in mRCC

Summary of evidence	LE
VEGF TKIs increase PFS and/or OS as both first-line and second-line treatments for clear-cell mRCC.	1b
Axitinib has proven efficacy and superiority in PFS as a second-line treatment after failure of cytokines and VEGF-targeted therapy in comparison with sorafenib.	1b
Sunitinib is more effective than IFN-α in treatment-naïve patients.	1b
Bevacizumab plus IFN-α is more effective than IFN-α in treatment-naïve low-risk and intermediate-risk patients.	1b
Pazopanib is superior to placebo in both naïve mRCC patients and post-cytokine patients.	1b
Pazopanib is not inferior to sunitinib in clear-cell mRCC patients.	1b
Temsirolimus monotherapy prolongs OS compared to IFN-α in poor-risk mRCC.	1b
Nivolumab is superior to everolimus in terms of OS and adverse events in patients failing one or two lines of VEGF-targeted therapy.	1b
Cabozantinib is superior to everolimus in terms of PFS in patients failing one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS in patients who have previously failed or are intolerant of VEGF-targeted therapy.	1b
Sorafenib has broad activity in a spectrum of settings in clear-cell renal cancer patients previously treated with cytokine or targeted therapies. It is inferior to axitinib in both sunitinib or cytokine pre-treated patients.	4
Both mTOR inhibitors (everolimus and temsirolimus) and VEFG-targeted therapies (sunitinib or sorafenib) can be used in non-clear cell RCC.	3
No combination has proven to be better than single-agent therapy.	1a

Recommendations	GR
Systemic therapy for mRCC should be based on targeted and immune agents.	A
Sunitinib and pazopanib are recommended as first-line therapy for advanced/metastatic ccRCC.	A
Bevacizumab + IFN-α are recommended as first-line therapy for advanced/metastatic RCC in favourable-risk and intermediate-risk ccRCC.	A
Temsirolimus is recommended as first-line treatment in poor-risk RCC patients. Data on subsequent therapies is lacking in this setting.	A
Cabozantinib should be given for ccRCC patients who progressed after one or two lines of VEGF-targeted therapy based on a PFS advantage over everolimus.	A
Nivolumab is strongly recommended for ccRCC patients who progressed after one or two lines of VEGF-targeted therapy based on an OS advantage over everolimus.	A
Axitinib can be given as second-line treatment for mRCC after cytokines or first-line VEGF where other drugs are not safe, tolerable or available.	A
Everolimus can be given for ccRCC patients who failed VEGF-targeted therapy where other drugs are not safe, tolerable or available.	A
Sequencing of targeted agents is strongly recommended.	A
Sunitinib or everolimus can be given as first-line therapy for non-clear cell mRCC.	B

ccRCC = clear-cell renal cell carcinoma; INF = interferon alpha; PFS = progression-free survival; mRCC = metastatic renal cell carcinoma; VEGF = vascular endothelial growth factor.

7.5 Recurrent RCC

*7.5.1 **Introduction***

Locally recurrent disease can occur after RN, PN and thermal ablation. After nephron sparing treatment approaches the recurrence may be intrarenal and/or regional, e.g. venous tumour thrombi or retroperitoneal LN metastases. Both are often summarised as loco-regional recurrences. Recurrence rates for pT1 tumours after PN are observed in 2.2% and are generally managed surgically depending on the extent of the loco-regional recurrence [379]. After thermal ablation loco-regional recurrences (intrarenal and regional) have been described in up to 12% [380]. Repeated ablation has often been recommended for intrarenal recurrences following thermal ablation. For loco-regional recurrences surgical resection is mandatory and has been described for isolated local recurrences following nephrectomy.

After nephrectomy locally recurrent disease is defined as disease recurring in the renal fossa or remnant kidney. However, metastasis in the not removed ipsilateral adrenal or non-resected LNs makes interpretation of the true incidence of isolated recurrence in the renal fossa difficult. Treatment of adrenal

metastases or LN metastases are often described in series of metastasectomy (Section 7.3). Isolated local recurrence however is rare.

The largest series on the treatment of isolated recurrence was published in 2009 [381]. Of 2,945 patients who underwent nephrectomy the authors identified 54 isolated local recurrences in the renal fossa. These however included those to the ipsilateral adrenal and LNs. Exclusively retrospective non-comparative data exist which suggest that aggressive local resection offers durable local tumour control and improves survival. Adverse prognostic factors were a positive surgical margin after resection, the size of the recurrence and sarcomatoid histologic features [381]. In cases where complete surgical removal is not feasible due to advanced tumour growth and pain, palliative treatments including radiation treatment can be considered.

7.5.2 Summary of evidence and recommendation for advanced/metastatic RCC

Summary of evidence	LE
Isolated recurrence in the local renal fossa is rare.	3
Patients who undergo resection of local recurrences in the absence of sarcomatoid features may benefit from durable local control and improved survival.	3

Recommendation	GR
Surgical resection of local recurrent disease may be offered.	C

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

8.1 Introduction

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

- Post-operative complications;
- Renal function;
- Local recurrence;
- Recurrence in the contralateral kidney;
- Development of metastases.

There is no consensus on surveillance after RCC treatment, and there is no evidence that early vs. later diagnosis of recurrences improves survival. However, follow-up is important to increase the available information on RCC, and should be performed by the urologist, who should record the time to recurrence or the development of metastases. Renal function is assessed by the measurement of serum creatinine and eGFR. Repeated long-term monitoring of eGFR is indicated in case of impaired renal function before, or after, surgery. Renal function [382, 383] and non-cancer survival [173-175] can be optimised by performing NSS whenever possible for T1 and T2 tumours [384] (LE: 3). Recurrence after PN is rare, but early diagnosis is useful, as the most effective treatment is redux surgery [385, 386]. Recurrence in the contralateral kidney is also rare and might be related to positive margins, multifocality, and grade [387] (LE: 3). Surveillance can identify local recurrences or metastases at an early stage. In metastatic disease, extended tumour growth can limit the opportunity for surgical resection, considered the standard therapy in cases of resectable and preferably solitary lesions. In addition, early diagnosis of tumour recurrence may enhance the efficacy of systemic treatment if the tumour burden is low.

8.2 Which investigations for which patients, and when?

There is no high level evidence to support any surveillance scheme. However. intensive radiological surveillance for all patients is not necessary. 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 developing recurrence or metastases. Although there is no randomised evidence, large studies have examined prognostic factors with long follow-up periods [33, 388, 389] (LE: 4):

- The sensitivity of chest radiography and US for small metastases is poor.

Surveillance with these imaging modalities should be done with the acknowledgement of these limitations [390]. With low-risk tumours, surveillance intervals should be adapted taking into account radiation exposure and benefit. To reduce radiation exposure, MRI can be used.

- When the risk of relapse is intermediate or high, CT of the chest and abdomen should be performed, although significant morbidity associated with the radiation exposure involved in repeated CT scans should be taken into account [391].
- Surveillance should also include evaluation of renal function and cardiovascular risk factors.
- Positron-emission tomography (PET) and PET-CT as well as bone scintigraphy should not be used in RCC surveillance, due to limited specificity and sensitivity.

There is controversy over the optimal duration of follow-up. Some argue that follow-up with imaging is not cost-effective after five 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 NSS if the tumours are detected early. For tumours < 4 cm, there is no difference between PN and RN with regard to recurrences during follow-up [182] (LE: 3).

Several authors [158, 160, 392, 393], 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 [394] (LE: 2). Using prognostic variables, several stage-based surveillance regimens have been proposed [395, 396], but do not include ablative therapies. A post-operative nomogram is available for estimating the likelihood of freedom from recurrence at 5 years [155]. Recently, a pre-operative prognostic model based on age, symptoms, and TNM staging has been published and validated [164] (LE: 3). A surveillance algorithm for monitoring patients after treatment for RCC is needed, recognising not only the patient risk profile, but also efficacy of the treatment given (Table 8.1). These prognostic systems can be used to adapt the surveillance schedule according to suspected risk of recurrence.

Table 8.1: Proposed surveillance schedule 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 y**	**> 5 y**
Low	RN/PN only	US	CT	US	CT	US	CT	Discharge
Intermediate	RN/PN/ cryo/ RFA	CT	CT	CT	US	CT	CT	CT once every 2 years
High	RN/PN/ cryo/ RFA	CT	CT	CT	CT	CT	CT	CT once every 2 years

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

8.3 Summary of evidence and recommendations for surveillance following RN or PN or ablative therapies in RCC

Summary of evidence	**LE**
Surveillance can detect local recurrence or metastatic disease while the patient is still surgically curable.	4
After NSS, there is an increased risk of recurrence for larger (> 7 cm) tumours, or when there is a positive surgical margin.	3

Recommendations	GR
Follow-up after RCC should be based on the risk of recurrence.	C
For low-risk disease, CT/MRI can be used infrequently.	C
In intermediate-risk patients, intensified follow-up should be performed, including CT/MRI scans at regular intervals in accordance with a risk-stratified nomogram.	C
In high-risk patients, the follow-up examinations should include routine CT/MRI scans.	C
Follow-up should be intensified in patients after NSS for tumours > 7 cm or with a positive surgical margin.	C
Risk stratification can be based on pre-existing classification systems such as the UISS integrated risk assessment score (http://urology.ucla.edu/body.cfm?id=443).	C

CT = computed tomography; MRI = magnetic resonance imaging; NSS = nephron-sparing surgery; UISS = University of California Los Angeles integrated staging system.

8.4 Research priorities

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

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10. 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: http://www.uroweb.org/guidelines/. 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.