EAU Guidelines on
Renal Cell Carcinoma

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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 and judgement when making treatment decisions for individual patients, but rather help to focus decisions whilst also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition
The RCC Guidelines Panel is an international group of clinicians consisting of urological surgeons, oncologists, methodologists, a pathologist and a radiologist, with particular expertise in the field of renal cancer 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/.

Acknowledgement
The RCC Guidelines Panel is most grateful for the methodological and scientific support provided by Prof. Dr. O. Hes (pathologist, Pilzen, Czech Republic) for two sections of this document: Histological diagnosis and Other renal tumours.

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 accessed 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 2017 RCC Guidelines document presents a limited update of the 2016 publication.

1.4.2 Summary of changes
All chapters of the 2017 RCC Guidelines have been updated, based on the 2016 version of the guideline. References have been added throughout the document.

Key changes in this 2017 print:
- Section 3.3.3 - Hereditary kidney tumours: This section has been expanded
- Section 5.2 - Imaging evaluations: The findings of a systematic review have been incorporated.

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

5.4 Summary of evidence and recommendations for the diagnostic assessment of renal cell cancer

Summary of evidence	**LE**
Contrast enhanced multi-phasic CT has a high sensitivity and specificity for characterisation and detection of RCC, invasion, tumour thrombus and metastatic RCC.	2
MRI has a slightly higher sensitivity and specificity for small renal masses and tumour thrombus as compared to CT.	2
CEUS has a high sensitivity and specificity for characterisation of renal masses.	2
US, Power-Doppler US and PET-CT have a low sensitivity and specificity for detection and characterisation of RCC.	2

Recommendations	grade	
Use multi-phasic contrast-enhanced computed tomography (CT) for general staging and detection of renal cell cancer (RCC).	strong	↑↑
Use axial abdominal imaging and CT of the chest for staging of RCC.	strong	↑↑
Use non-ionising modalities, mainly contrast enhanced ultrasound (CEUS), for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses.	weak	↑
Do not use bone scan and/or positron-emission tomography (PET)-CT for staging of RCC.	weak	↓
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	strong	↑↑
Perform a percutaneous biopsy in select patients who are considered for active surveillance.	weak	↑
When performing a renal tumour biopsy technique, use a coaxial technique.	strong	↑↑
Do not perform a renal tumour biopsy of cystic renal masses.	weak	↓

7.2.5.1 Summary of evidence and recommendations for adjuvant therapy

Summary of evidence	LE
Adjuvant cytokines do not improve survival after nephrectomy.	1b
Adjuvant sunitinib improved disease-free survival in one of the two available studies, but not overall survival, after nephrectomy in selected high-risk patients.	1b

Recommendations	grade	
Do not offer adjuvant therapy with sorafenib.	strong	↓↓
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell cancer.	weak	↓

7.3.2.5 Recommendations for local therapy of metastases in metastatic RCC

Recommendation	grade	
Consider local therapy for metastatic disease (including metastasectomy) in patients with a favourable risk profile in whom complete resection is achievable or when local symptoms need to be controlled.	weak	↑

7.4.1.1 Summary of evidence and recommendation for systemic therapy for advanced/metastatic renal cell cancer

Summary of evidence	LE
In metastatic RCC, 5-FU combined with immunotherapy has equivalent efficacy to INF-α.	1b
In metastatic RCC, chemotherapy is otherwise not effective with the exception of gemcitabine and doxorubicine in sarcomatoid and rapidly progressive disease.	3

Recommendations	grade	
Do not offer chemotherapy as first-line therapy in patients with metastatic clear-cell renal cell cancer (RCC).	strong	↓↓
Consider offering a combination of gemcitabine and doxorubicin to patients with sarcomatoid or rapidly progressive RCC.	weak	↑

7.4.6.3 Summary of evidence and recommendations for systemic therapy in metastatic renal cell cancer

Summary of evidence	LE
First line pazopanib is not inferior to sunitinib in clear-cell mRCC patients.	1b
Cabozantinib is superior to everolimus in terms of PFS and OS 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 when compared to placebo.	1b
No combination has proven to be better than single-agent therapy, with the exception of the combination of lenvatinib plus everolimus.	1a

Recommendations	grade	
Offer sunitinib or pazopanib as first-line therapy for metastatic clear-cell renal cell cancer (ccRCC).	strong	↑↑
Consider offering bevacizumab + Interferon (IFN)-α as first-line therapy for metastatic RCC in favourable-risk and intermediate-risk ccRCC.	weak	↑
Consider offering temsirolimus as first-line treatment in poor-risk RCC patients.	weak	↑
Offer cabozantinib for ccRCC after one or two lines of vascular endothelial growth factor (VEGF)-targeted therapy in metastatic RCC.	strong	↑↑
Sunitinib can be offered as first-line therapy for non-clear cell mRCC.	weak	↑

2. METHODS

2.1 Data identification

For the 2017 Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature for the chapters as listed in Table 2.1.

A broad and comprehensive scoping exercise was performed. The search was limited to studies representing high levels of evidence (i.e. systematic reviews [SRs] with meta-analysis [MA], randomised controlled trials (RCTs), and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published between July 30th 2015 and June 30th 2016. Databases covered included Medline, EMBASE, and the Cochrane Library. A total of 1,602 unique records were identified, retrieved and screened for relevance. A search strategy is published online: https://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 Guidelines Panel. These reviews were performed using standard Cochrane SR methodology http://www.cochranelibrary.com/about/about-cochranesystematic-reviews.html.

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

The EAU Guidelines Office are in the process of introducing modified GRADE methodology accross all 20 guidelines [3, 4]. This will be a phased introduction, with the RCC Guidelines Panel already incorporating these changes in their 2017 Guidelines print.

The Summary of Evidence (SOE) tables provided for each recommendation within the guidelines address a number of key elements:

1. the overall quality of the evidence which exists for the recommendation;
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ and is directional, either ‘do it’ (as represented by arrows pointing upwards) or ‘do not do it’ (arrows pointing downwards) [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The SOE tables will be posted online for consultation.

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	Section 5.2 (Diagnostic imaging) was revised based on a SR [6]. 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 (Treatment of localised and locally advanced disease) were revised based on an updated SR. The remainder of the chapter was updated using a structured literature assessment. Systemic therapy for metastatic disease: this section was 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 2017 update:
- Imaging in Suspected Renal Cell Carcinoma: A Systematic Review [6]
- What is the best surgical treatment option for clinical > T2, N0M0 tumours? What is the best way of performing this procedure? [7];
- A Systematic Review and Meta-analysis Comparing the Effectiveness and Adverse Effects of Different Systemic Treatments for Non-clear Cell Renal Cell Carcinoma [8].

2.2 Review
Chapter 7 'Disease management' was peer reviewed prior to publication. Publications ensuing from SRs have all been peer reviewed. 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 Guideline Panel aims 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 computed tomography (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 six 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 outcomes for this project.

The results of ongoing and new SRs will be included in the 2018 update of the RCC Guidelines.

Topics of ongoing SRs:
- What is the best treatment option for T1-T2 tumours? (updated review);
- What is the best treatment option for T1a tumours?;
- What is the best treatment option for T1b-T2a tumours? (updated review);
- What is the best treatment option for T2b tumours;
- Systematic review and meta-analysis of systemic therapy of renal tumours (Cochrane Review).

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Renal cell cancer represents 2-3% of all cancers [9], 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. In Western European countries this incidence stabilised over the past decade [10]. In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney-cancer-related deaths in the European Union [11]. In Europe, overall mortality rates for RCC increased up to the early 1990s, and stabilised or declined thereafter [12]. 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 [12]. Data from the United States also show increased incidence [13].

There is a 1.5:1 male predominance, with a peak incidence between 60 and 70 years. Aetiological factors include smoking, obesity [14] and hypertension. Having a first-degree relative with RCC also increases the risk of RCC [15]. A number of other factors associated with higher or lower RCC-risk include specific dietary habits, occupational exposure to specific carcinogens, acetaminophen and non-aspirin non-steroidal anti-inflammatory drugs [16], cruciferous vegetables [17], nephrolithiasis [18], and viral hepatitis [19-23]. However, data from the literature are still inconclusive [24, 25]. Moderate alcohol consumption appears to have a protective effect for unknown reasons [26-28]. 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 [29-31].

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	grade	
For the most important primary prevention of RCC, eliminate cigarette smoking and reduce weight.	strong	↑↑

3.2 Histological diagnosis

Renal cell carcinomas comprise a broad spectrum of histopathological entities described in the 2016 World Health Organization (WHO) classification [32, 33]. There are three main RCC types: clear cell (ccRCC), papillary (pRCC - type I and II) and chromophobe (chRCC). Renal cell cancer type classification has been confirmed by cytogenetic and genetic analyses [32, 33] (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 peri-renal fat, pT or even pN categories. The four-tiered WHO/ISUP (International Society of Urological Pathology) grading system has replaced the Fuhrman grading system [32, 33].

3.2.1 ***Clear cell renal cell cancer***

Overall, clear-cell RCC (ccRCC) is well circumscribed and a capsule is usually absent. The cut surface is golden-yellow, often with haemorrhage and necrosis. Loss of chromosome 3p and mutation of the von Hippel-Lindau (VHL) gene at chromosome 3p25 are frequently found, including additional tumour suppressor genes including SETD2, BAP1, and PBRM1; all genes are identified near the VHL gene within a region that is frequently deleted in ccRCC [34]. In general, ccRCC has a worse prognosis compared to pRCC and chRCC [35, 36] even after stratification for stage and grade [37]. The five-year cancer-specific-survival (CSS) rate was 91%, 74%, 67% and 32% for TNM stages I, II, III and IV (patients treated between 1987-1998) [38]. For more details, see Section 6.3 - Histological factors.

3.2.2 *Papillary renal cell cancer*
Papillary RCC (pRCC) is the second most commonly encountered morphotype of RCC. Papillary RCC has traditionally been subdivided into two types [33]. Type 1 and 2 pRCC, which were shown to be clinically and biologically distinct; pRCC type 1 is associated with activating germline mutations of MET and pRCC type 2 is associated with activation of the NRF2-ARE pathway with at least three subtypes [39]. Macroscopically, pRCC is well circumscribed with pseudocapsule, yellow or brown in colour, and a soft structure. Compared to ccRCC, pRCC has a significantly higher rate of organ-confined tumour (pT1-2N0M0) and a higher five-year CSS rate [40]. Papillary RCC type 1 is more common and generally considered to have a better prognosis than pRCC type 2 [33, 41]. Exophytic spherical growth, pseudo-necrotic changes and pseudo-capsule are typical signs of pRCC type 1. Tumours are fragile. On post-contrast CT, a hypodense central area of tumour surrounded by vital tumour tissue is seen, presented as a serpiginous contrast-enhancing margin on CT [42].

3.2.3 *Chromophobe (chRCC)*
Overall, chRCC is a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Chromophobe RCC cannot be graded (by the Fuhrman grading system), because of its innate nuclear atypia. An alternative grading system has been proposed, but has yet to be validated [32, 33]. Loss of chromosomes Y, 1, 2, 6, 10, 13, 17 and 21 are typical genetic changes [32, 33]. The prognosis is relatively good, with high five-year recurrence-free survival (RFS), and ten-year CSS [43]. The new WHO/ISUP Grading system merges former entity hybrid oncocytic chromophobe tumour with chRCC.

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, as well as a group of unclassified carcinomas. A summary of these tumours is provided 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). Renal cell cancers of native end-stage kidneys are found in about 4% of patients. Their lifetime risk of developing RCCs is at least ten times higher than in the general population. Compared with sporadic RCCs, RCCs associated with ESKD are generally multicentric and bilateral, found in younger patients (mostly male), and are less aggressive [44, 45]. The relatively indolent outcome of tumours in ESKD is due to the mode of diagnosis and a specific ACKD-related molecular pathway which has still to be determined [45]. Although the histological spectrum of ESKD tumours is similar to that of sporadic RCC, the predominant form is pRCC. The remaining tumours are mostly ccRCC [44-46]. A specific subtype of RCC occurring only in end-stage kidneys has been described as Acquired Cystic Disease-associated RCC (ACD-RCC) [47] with indolent clinical behaviour, likely due to early detection in patients with ESKD on periodic follow-up [33].

3.3.2 *Papillary adenoma*
These tumours have a papillary or tubular architecture of low nuclear grade and may be up to 15 mm in diameter, or smaller [48], according to the WHO 2016 classification [33].

3.3.3 *Hereditary kidney tumours*
Five to eight percent of RCC is hereditary; to date there are ten hereditary RCC syndromes known, associated with specific germline mutations, RCC histology, and comorbidities. Hereditary RCC syndromes are often suggested by family history, age of onset and presence of other lesions typical for the respective syndromes. Median age for hereditary RCC is 37 years; 70% of hereditary RCC tumours are found in the lowest decile (≤ 46 years old) of all RCC tumours [49]. 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 RCC (HLRCC), tuberous sclerosis (TS), 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 nonsyndromic ccRCC. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [47, 48, 50, 51].

Patients with hereditary kidney cancer syndromes may require repeated surgical interventions [52, 53]. Appropriately timed nephron-sparing approaches are recommended with the exception of Hereditary Leiomyomatosis and RCC (HLRCC) and succinate dehydrogenase (SDH) syndromes, for which surveillance is recommended until the largest solid tumour reaches 3 cm in diameter, to reduce interventions [54]. Active surveillance for VHL, BDH and HPRCC should, in individual patients, follow the growth kinetics, size and location of the tumours rather than apply a standardised fixed follow-up interval. Regular screening for both renal and extra-renal lesions should follow international guidelines for these syndromes. Multi-disciplinary and co-ordinated care should be offered, where appropriate [55].

Although not hereditary, somatic fusion translocations of TFE3 and TFEB may affect 15% of patients with RCC younger than 45 years and 20-45% of children and young adults with RCC [56].

3.3.4 ***Angiomyolipoma***

Angiomyolipoma (AML) is a benign mesenchymal tumour, which can occur sporadically, and is four times more common in females [57]. Angiomyolipoma also occurs in tuberous sclerosis and 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 tuberous sclerosis in lymph nodes (LNs), but it is not metastasis, and has a multicentric genesis. Angiomyolipoma can be due to angiotrophic-type growth extending into the renal vein or the inferior vena cava. Angiomyolipoma with LN involvement and tumorous thrombus is benign. Only epithelioid AML is potentially malignant [48, 58]. Angiomyolipoma has a slow and consistent growth rate, and minimal morbidity [59]. The main complications of renal AML are retroperitoneal bleeding or bleeding into the urinary collection system, which can be life-threatening [60]. The bleeding tendency is related to the angiogenic component of the tumour that includes irregular and aneurysmatic blood vessels [60]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of tuberous sclerosis [60, 61]. 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 [57, 59, 62] (LE: 3). Risk factors for delayed intervention include tumour size > 4 cm and symptoms at diagnosis [62]. Selective arterial embolisation (SAE) seems to be the first-line option used for active treatment after AS is discontinued [62] (LE: 3). Selective arterial embolisation is an efficient treatment for AML devascularisation, but only for volume reduction [63].

Although SAE controls haemorrhage in the acute setting, it has limited value long-term [64, 65]. If surgery is selected, most cases of AML can be managed by conservative nephron-sparing surgery (NSS), although some patients may require complete nephrectomy [61] (LE: 3). Radiofrequency ablation (RFA) can be an option as well [59, 60, 66]. The volume of AML can be reduced by the mammalian target of rapamycin (mTOR) inhibitor everolimus [67]. A clinical phase II trial and its open-label extension of medical management with everolimus in AMLs not requiring surgical intervention, showed a response rate of 81.6 (64.5%) (≥ 50% or 30% tumour volume reduction) by week 96, confirming the long-term safety profile of everolimus [67]. Sirolimus can be combined with deferred surgery [68].

Table 3.1: Other renal cortical tumours, and recommendations for treatment (grade: weak) [32, 33]

Entity	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, gemcitabine plus doxorubicin is also an option [69].
Multilocular cystic renal neoplasm of low malignant potential	Formerly multilocular cystic RCC	Benign	Surgery, nephron-sparing 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 (HR) CSS in comparison with ccRCC is 4.49 [36].	High, very aggressive. Median survival 30 months [70].	Surgery. Response to targeted therapies is poor [71].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait.	High, very aggressive, median survival is five months [70].	Surgery. Different chemotherapy regimes, radiosensitive.
Translocation RCC (TRCC) Xp11.2	Rare, mainly younger patients < 40, more common in females. It constitutes with TRCC 6p21 MiT translocation RCCs [72].	High	Surgery. Vascular endothelial growth factor (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 papillary RCC	Also reported as renal angiomyomatous tumour (RAT).	Low	Surgery, NSS.
Hereditary leiomyomatosis and RCC-associated RCC	Rare, new entity in the 2016 WHO classification, caused by a germline mutation of the fumarate hydratase gene [33].	Aggressive	Surgery. No data about treatment of metastatic disease.
Tubulocystic RCC	Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS.
Succinate dehydrogenase-deficient RCC	Rare.	Low	Surgery.
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 [73, 74].	Benign	Observation (when histologically confirmed) [75-77]. NSS.

Hereditary kidney tumours	Details see above.	High	Surgery, NSS.
Angiomyolipoma	Details see above.	Benign	Consider treatment only in very well selected patients.
Unclassified RCC	RCC that cannot be assigned to any other category of RCC-type carcinoma [48].	Variable	Surgery, NSS.

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

Recommendations	grade	
Treat Bosniak type III or IV cysts the same as RCC.	strong	↑↑
Treat angiomyolipoma (AML) with selective arterial embolisation or nephron-sparing surgery, in: • large tumours (a 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.	weak	↑
Treat AMLs that are not candidates for active treatment with active surveillance.	weak	↑
In AML > 3 cm not requiring surgical intervention, medical treatment with everolimus can be considered.	weak	↑
Offer active surveillance to patients with biopsy-proven oncocytomas.	weak	↑
For advanced uncommon renal tumours, develop individualised oncological treatment plans for each patient.	strong	↑↑

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Staging

The Tumour Node Metastasis (TNM) classification system is recommended for clinical and scientific use [78], but requires continuous re-assessment [79] with the latest version published in 2017. A supplement was published in 2012 (Table 4.1), and the latter's prognostic value was confirmed in single and multi-institution studies [80, 81]. 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 [82].
- Since the 2002 version, tumours with renal sinus fat invasion have been classified as pT3a.
- Renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion but is nevertheless included in the same pT3a stage group [83-85] (LE: 3).
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [81].
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [86, 87] (LE: 4).

Table 4.1: 2017 TNM classification system [78] **and TNM supplement 2012** [88]

T - Primary Tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Tumour ≤ 7 cm or less in greatest dimension, limited to the kidney	
	T1a	Tumour ≤ 4 cm or less
	T1b	Tumour > 4 cm but ≤ 7 cm
T2	Tumour > 7 cm in greatest dimension, limited to the kidney	
	T2a	Tumour > 7 cm but ≤ 10 cm
	T2b	Tumours > 10 cm, limited to the kidney
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia	
	T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia
	T3b	Tumour grossly extends into the vena cava below diaphragm
	T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)	
N - Regional Lymph Nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in regional lymph node(s)	
M - Distant Metastasis		
M0	No distant metastasis	
M1	Distant metastasis	

TNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	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, the C-index, an Arterial Based Complexity (ABC) Scoring System and Zonal NePhRO scoring system, have been proposed to standardise the description of renal tumours [89-91]. These systems include assessment of tumour size, exophytic/endophytic properties, proximity to the collecting system and renal sinus, and anterior/posterior or lower/upper pole 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 most optimal 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 investigating various non-specific symptoms and other abdominal diseases [81, 92] (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 [93, 94] (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 [95] (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 [96], 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 [97, 98] (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 [92] (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 [99] (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 [100-102] (LE: 3).

5.2.2 ***Computed tomography or magnetic resonance imaging***

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 fifteen, or more, HUs demonstrates enhancement [103] (LE: 3). Computed tomography or MRI allow accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free AML from malignant renal neoplasms [73, 104-106] (LE: 3). Abdominal CT provides information on [107]:

- function and morphology of the contralateral kidney [108] (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 CT angiography is useful in selected cases for detailed information on renal vascular supply [109, 110].

If the results of CT are indeterminate, contrast enhanced ultrasound (CEUS) is a valuable alternative to further characterise renal lesions [6] (LE: 1b).

Magnetic resonance imaging may provide additional information on venous involvement if the extent of an inferior vena cava (IVC) tumour thrombus is poorly defined on CT [111-114] (LE: 3).

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [112, 115] (LE: 3). Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored for renal mass assessment [116].

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 [97, 98] (LE: 2a).

Positron-emission tomography (PET) is not recommended [6, 117] (LE: 1b).

*5.2.4 **Radiographic investigations to evaluate RCC metastases***
Chest CT is accurate for chest staging [86, 87, 118-120] (LE: 3). There is a consensus that most bone metastases are symptomatic at diagnosis; thus, routine bone imaging is not generally indicated [118, 121, 122] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [121, 123, 124] (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 [125, 126] (LE: 3). This system also advocates treatment for each category (Table 5.1).

Table 5.1: Bosniak classification of renal cysts [125]

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, up to five years. 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 can be considered in patients who are candidates for AS of 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 [127-132] (LE: 3).

Renal biopsy is not indicated for comorbid and frail patients who can be considered only for conservative management (watchful waiting) regardless of biopsy results. 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 [130, 133] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [127-131, 134] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [127-131] (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 [135]. Other studies showed that solid pattern, larger tumour size and exophytic location are predictors of a diagnostic core biopsy [127, 130, 133] (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 [135] (LE: 2b). However, 0-22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [128-134, 136] (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%) [127, 137-139].

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 PN or radical nephrectomy (RN) was 90.3% in the pooled analysis [135].

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) [135] (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 [127, 130, 140, 141] (LE: 4). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [142] (LE: 2b). In cT2 or greater renal masses multiple core biopsies taken from at least four separate solid enhancing areas in the tumour were shown to achieve a higher diagnostic yield and a higher accuracy to identify sarcomatoid features without increasing the complication rate [143].

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) [127, 130, 135] (LE: 2b). Combined FNA and core biopsies can provide complementary results, especially for complex cystic lesions [131, 136, 137, 144, 145] (LE: 3).

Overall, percutaneous biopsies have a low morbidity [135]. Tumour seeding along the needle tract is anecdotal. Spontaneously resolving subcapsular/perinephric haematomas 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 [135].

5.4 Summary of evidence and recommendations for the diagnostic assessment of renal cell cancer

Summary of evidence	LE
Contrast enhanced multi-phasic CT has a high sensitivity and specificity for characterisation and detection of RCC, invasion, tumour thrombus and metastatic RCC.	2
MRI has a slightly higher sensitivity and specificity for small renal masses and tumour thrombus as compared to CT.	2
CEUS has a high sensitivity and specificity for characterisation of renal masses.	2
US, Power-Doppler US and PET-CT have a low sensitivity and specificity for detection and characterisation of RCC.	2

Recommendations	grade	
Use multi-phasic contrast-enhanced computed tomography (CT) for general staging and detection of RCC.	strong	↑↑
Use axial abdominal imaging and CT of the chest for staging of RCC.	strong	↑↑
Use non-ionising modalities, mainly contrast enhanced ultrasound (CEUS), for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses.	weak	↑
Do not use bone scan and/or positron-emission tomography (PET)-CT for staging of RCC.	weak	↓
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	strong	↑↑
Perform a percutaneous biopsy in select patients who are considered for active surveillance.	weak	↑
Use a coaxial technique when performing a renal tumour biopsy.	strong	↑↑
Do not perform a renal tumour biopsy of cystic renal masses.	weak	↓

6. PROGNOSTIC FACTORS

6.1 Classification

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

6.2 Anatomical factors

Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system [78] (Table 4.1).

6.3 Histological factors

Histological factors include tumour grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system [146]. Fuhrman nuclear grade is the most widely accepted grading system [147]. Although affected by intra- and inter-observer discrepancies, Fuhrman nuclear grade is an independent prognostic factor [148]. A simplified two- or three-strata system may be as accurate for prognostication as the classical four-tiered grading scheme [149, 150] (LE: 3). The new WHO/ISUP (International Society of Urological Pathology) grading system [151] that will replace the Fuhrman grading, needs to be validated for prognostic systems and nomograms.

In a univariate analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [152, 153]. However, prognostic information provided by the RCC type is lost when stratified to tumour stage [35, 153] (LE: 3).

Differences in tumour stage, grade and CSS between the RCC types are illustrated in Table 6.1.

Table 6.1: Basic characteristics of three main types of RCC [35, 36, 154]

Type	Percentage of RCC	Advanced disease at diagnosis (T3-4, N+, M+)	Fuhrman grade 3 or 4 [155]	CSS (HR)
clear-cell RCC	80-90%	28%	28.5%	Referent
papillary RCC	6-15%	17.6%	28.8%	0.64 - 0.85
chromophobe RCC	2-5%	16.9%	32.7%*	0.24 - 0.56

** The Fuhrman grading system is validated for ccRCC, but is unreliable for chRCC.*
HR = hazard ratio.

In all RCC types, prognosis worsens with stage and histopathological grade (Tables 6.2 and 6.3). The five-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 inhibitors (TKIs) [156, 157]. Sarcomatoid changes can be found in all RCC types and are equivalent to high grade and very aggressive tumours.

Table 6.2: Cancer-specific survival by stage and histopathological grade in RCCs - HR (95% CI) [36]**.**

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. HR = hazard ratio.

Long-term survival in RCC patients treated by RN or PN between 1970 and 2003; for unilateral, sporadic ccRCC, pRCC or chRCC in a cohort study [154] (Table 6.3).

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

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

Two subgroups of pRCC with different outcomes have been identified [158]. Type 1 have a favourable prognosis. Type 2 are mostly high-grade tumours with a propensity for metastases (LE: 3). For more details, see Section 3.2 Histological diagnosis. Renal cell cancer with Xp 11.2 translocation has a poor prognosis [159]. Its incidence is low, but it should be systematically addressed in young patients. Renal cell cancer type classification has been confirmed by cytogenetic and genetic analyses [155, 160, 161] (LE: 2b).

6.4 Clinical factors

These include performance status (PS), local symptoms, cachexia, anaemia, platelet count, neutrophil/lymphocyte ratio, C-reactive protein (CRP) and albumin [95, 162-166] (LE: 3).

6.5 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CaIX), vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, p21 [167], PTEN (phosphatase and tensin homolog) (cell cycle), E-cadherin, osteopontin [168] CD44 (cell adhesion) [169, 170], CXCR4 [171], and other cell cycle and proliferative markers [64, 172] are being investigated (LE: 3). None of these markers have clearly improved the predictive accuracy of current prognostic systems, none have been externally validated, and their routine use in clinical practice is at present not recommended. Several retrospective studies and large molecular screening programmes have identified mutated genes in ccRCC with distinct clinical outcomes. The expression of the BAP1 and PBRM1 genes, situated on chromosome 3p in a region that is deleted in more than 90% of ccRCCs, have shown to be independent prognostic factors for tumour recurrence [173-175]. These published reports suggest that patients with BAP1-mutant tumours have worse outcomes compared with patients with PBRM1-mutant tumours [174]. Validated data from surgical series can predict relapse using a sixteen gene signature. This signature is likely to be adopted in clinical trials and may be helpful in the clinical setting in due time [176].

The recognition of the potential relevance of immunotherapy as an approach to RCC management is growing. Prognostic information of cytokines and blockade of immune-inhibitory molecules such as PD-L1 have shown promising therapeutic results. Emerging evidence of chromosomal alterations, through Genome-Wide Association Studies (GWAS), miRNA, SNPs and gene methylations all contribute to improving diagnostic and prognostic information. A number of studies have confirmed prognostic information based on gain of chromosomal regions 7q, 8q and 20q, and chromosomal losses of regions 9p, 9q and 14q, which are associated with poor survival. CpG-methylation-based assays also independently predict survival in ccRCC [177, 178]. An international collaboration is currently investigating GWAS loci for prognostic information.

6.6 Prognostic systems and nomograms

Post-operative prognostic systems and nomograms combining independent prognostic factors have been developed and externally validated [179-185]. 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 prognostic schemes [186]. Recently, new pre-operative nomograms with excellent PA have been designed [187, 188].

Table 6.4 summarises the current most relevant prognostic systems.

6.7 Summary of evidence and recommendations for prognostic factors

Summary of evidence	LE
In RCC patients, TNM stage, tumour nuclear grade, and RCC subtype provide important prognostic information [22].	2

Recommendations	grade	
Use the current Tumour, Node, Metastasis classification system.	strong	↑↑
Use grading systems and classify RCC subtype.	strong	↑↑
Use prognostic systems in the metastatic setting.	strong	↑↑
In localised disease do not routinely use integrated prognostic systems or nomograms for patient selection. Prognostic systems or nomograms can provide a rational for enrolling patients into clinical trials.	weak	↓
Do not use molecular prognostic markers in routine clinical practice.	weak	↓
In patients receiving targeted treatments, use molecular prognostic markers to predict response.	weak	↑

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		
	IMDC			x	x						x	x	x	x
	Heng's model			x					x		x	x	x	x

ECOG-PS = Eastern Cooperative Oncology Group - performance status; IMDC = International Metastatic Renal Cancer Database Consortium; 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 to 7.2.4.2. The review included all relevant published literature comparing surgical management of localised RCC (T1-2N0M0) [189, 190]. Randomised or quasi-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.

7.1.2 Surgical treatment

7.1.2.1 Nephron-sparing surgery vs. radical nephrectomy

Multiple retrospective series as well as one prospective RCT including patients with organ-confined RCC of limited size, respectively T-stage (pT1), have demonstrated a comparable CSS for PN vs. RN [191-195]. However, trials that directly compared both approaches in terms of their oncological safety are rarely available, therefore, the data presented is based on a comparison of data available from retrospective series that have included patient cohorts of different and, in part, limited size.

In addition, PN vs. RN was demonstrated to better preserve general kidney function, thereby lowering the risk of development of metabolic or cardiovascular disorders.

When compared with a radical surgical approach, for NSS, several retrospective analyses of large databases have suggested a decreased cardiac-specific mortality [196, 197] as well as improved OS as compared to RN. However, in some series this held true only for a younger patient population and/or patients without significant comorbidity at the time of the surgical intervention [198, 199]. An analysis of the Medicare database [200] could not demonstrate an OS benefit for patients > 75 years of age when RN or PN were compared with non-surgical management. Another series that addressed this question and also included Medicare patients suggested an OS benefit in an older RCC patient population (75-80 years) when subjected to surgery rather than non-surgical management. Shuch *et al.* compared patients subjected to PN for RCC with a non-cancer, healthy control group via a retrospective database analysis, showing an OS benefit for the cancer cohort, [201]. These conflicting results indicate that unknown statistical confounders hamper the retrospective analysis of population-based tumour registries.

In contrast, the only prospectively randomised but prematurely closed and heavily underpowered, trial available so far did not demonstrate an inferiority of RN vs. PN in terms of OS. Taken together, the OS advantage suggested for PN vs. RN remains an unresolved issue.

It has been suggested that the more pronounced deterioration of renal function after RN negatively affects patients´ OS [98, 202]. Patients with a normal pre-operative renal function and a decreased GFR due to surgical treatment, generally present with a stable renal function longer term [203]. In contrast, adverse OS in patients with a pre-existing GFR reduction does not seem to result from further renal function impairment following surgery, but rather from other medical comorbidities causing pre-surgical CKD. However, in particular in patients with pre-existing CKD, PN is the treatment of choice to limit the risk of development of ESKD which requires haemodialysis.

Only a limited number of studies are available addressing quality of life (QoL) following PN vs. RN irrespective of the surgical approach used (open- vs. minimally invasive). Quality of life was ranked higher following PN as compared to RN, but in general, patients' health status deteriorated following both approaches [191, 192, 194, 204-208].

In terms of the intra- and peri-operative morbidity/complications associated with PN vs. RN, there was no difference in the length of hospital stay [192, 193, 207], the number of red blood cell (RBC) units applied [192, 207, 208], or the mean intra-operative blood loss [192, 207]. Complication rates were inconsistently reported and one intervention was not favoured over another [209]. One study indicated a longer operation time for open PN [209], but this was not confirmed by others [210].

In view of the above and since oncological safety (CSS and FS) of PN has been proven to be similar for RN, PN is the treatment of choice for T1b RCC since it preserves kidney function better and in the long term limits development of metabolic as well as cardiovascular disorders. Whether decreased mortality from any cause can be attributed to PN is still unresolved, but in patients with pre-existing CKD, PN is the preferred surgical treatment option as it avoids further deterioration of kidney function, the latter being associated with a higher risk of development of ESKD and the need for haemodialysis.

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

- insufficient volume of remaining parenchyma to maintain proper organ function;
- renal vein thrombosis;
- unfavourable tumour location e.g. adherence to the renal vessels;
- use of anticoagulants.

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 [211]. Multivariate analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at five or ten 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)

The indication for lymph node dissection (LND) together with PN or RN is still controversial [212]. The clinical assessment of LN status is based on the detection of an enlargement of LNs; either by CT/MRI or the intra-operative palpability of enlarged nodes. Less than 20% of suspected metastatic nodes (cN+) are positive for metastatic disease at histopathological examination (pN+) [213]. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [214]. For clinically positive LNs (cN+) see Section 7.2.2.

For patients with clinically negative LNs (cN0) six clinical trials have evaluated the clinical value of LND [212], the latter including one RCT [213] and five comparative studies [215-219].

Smaller retrospective studies have suggested a clinical benefit associated with a more or less extensive lymphadenectomy preferably in patients at high risk for lymphogenic spread. The number of LN metastases (< / > 4) as well as the intra– and extracapsular extension of intranodal metastasis correlated with the patients´ clinical prognosis in some studies [214, 220-222]. Better survival outcomes were seen in patients with a low number of positive LNs (< 4) and no extranodal extension. On the basis of a retrospective SEER database analysis of > 9,000 patients no effects of an extended LND on the disease-specific survival (DSS) of patients with pathologically confined negative nodes was demonstrated [223]. However, in patients with pathologically proven lymphogenic spread (pN+), an increase of ten for the number of nodes dissected resulted in a 10% absolute increase in DSS. In addition, in a larger cohort of 1,983 patients Capitano *et al.* demonstrated that extended LND results in a significant prolongation of CSS in patients with unfavourable prognostic features (e.g., sarcomatoid differentiation, large tumour size) [224].

Only one prospective RCT evaluating the clinical value of LND combined with surgical treatment of primary RCC has been published so far. With an incidence of only 4%, lymphatic spread appears to be very low. Recognising the latter, only a staging effect was attributed to a (super)extended LND [213]. This trial included a very high percentage of patients with pT2 tumours, which are not at increased risk for LN metastases. Additionally, only 25% of patients with pT3 tumours were subjected to a complete LND. The LN template used by the authors was also not clearly stated.

The most optimal surgical approach remains controversial. Retrospective studies suggest that an extended LND should involve the LNs surrounding the ipsilateral great vessel and the inter-aortocaval region from the crus of the diaphragm to the common iliac artery. Involvement of inter-aortocaval LNs without regional hilar involvement is reported in up to 35-45% of cases [214, 215, 225]. At least fifteen LNs should be removed [224, 226]. Sentinel LND is an investigational technique [227, 228].

7.1.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [229, 230]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [231-233]. 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
The oncological outcome in terms of DSS following PN equals that of a radical approach in patients with c/p T1 RCC.	1b
Ipsilateral adrenalectomy, in the absence of clinical evident adrenal involvement during RN or PN, has no survival advantage.	3
In patients with localised disease without evidence of lymph node metastases, a survival advantage of LND in conjunction with RN is not demonstrated in randomised trials.	1b
In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.	3

Recommendations	grade	
Offer surgery to achieve cure in localised renal cell cancer.	strong	↑↑
Offer partial nephrectomy to patients with T1 tumours.	strong	↑↑
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	strong	↓↓
Consider an extended lymph node dissection in patients with adverse clinical features including a large diameter of the primary tumour or sarcomatoid histological features.	weak	↑

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 [234] and retrospective database reviews are available, mostly of low methodological quality [192, 235, 236]. Similar oncological outcomes for laparoscopic vs. open RN were found. Data from one RCT [237] and two NRSs [192, 234] showed a significantly shorter hospital stay and lower analgesic requirement for the laparoscopic RN group as compared with the open group. Convalescence time was also significantly shorter [234]. 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 [192, 234, 237]. Surgical complication rates were low with 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 [192].

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 hospital stay and convalescence compared to those who underwent open RN [234, 238-240]. Intra-operative and post-operative complications were similar in the two groups [234, 238-241]. No significant differences in CSS, PFS and OS were reported [226, 234, 239, 241, 242] (LE: 2b).

The best approach for RN was the retroperitoneal or transperitoneal approach with similar oncological outcomes in the two RTCs [243, 244] and one quasi-randomised study [245]. Quality of life variables were similar for both approaches.

Hand-assisted vs. standard laparoscopic RN was compared in one RCT [245] and one database review [209]. Estimated five-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 cohort [209, 245]. However, the sample size was small.

Robot-assisted laparoscopic RN vs. laparoscopic RN was compared in one study [246]. 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 [247, 248]. Peri-operative outcomes were similar.

7.1.3.2 Partial nephrectomy techniques

Studies comparing laparoscopic PN and open PN found no difference in PFS [249-252] and OS [251, 252] in centres with laparoscopic expertise. The mean estimated blood loss was lower with the laparoscopic approach [249, 251, 253], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events are similar [249, 251]. Operative time is generally longer with the laparoscopic approach [250-252] and warm ischaemia time is shorter with the open approach [249, 251, 253, 254]. In a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [252], but not after follow-up of 3.6 years. In another comparative study, the surgical approach was not an independent predictor for post-operative CKD [254]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [255]. Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [256, 257].

Hand-assisted laparoscopic PN (HALPN) is rarely performed. A recent comparative study of open vs. HALPN showed no difference in OS or RFS at intermediate-term follow-up. The authors observed a lower rate of intra-operative and all-grade post-operative 30-day complications in HALPN than in open PN patients, but there was no significant difference in high Clavien Grade complications. Glomerular filtration rate three months after operation was lower in the HALPN than in the open PN group [258].

The feasibility of off-clamp laparoscopic PN and laparo-endoscopic single-site PN has been shown in selected patients but larger studies are needed to confirm their safety and clinical role [259, 260].

At present, the oncological outcomes of robot-assisted vs. laparoscopic or open PN have been compared only in studies with short-term follow-up. 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 ischaemia time, operative time, immediate- early- and short-term complications, variation of creatinine levels, and pathologic margins were similar among the groups [261].

A recent meta-analysis, including a series of NSS, 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 ischaemia time, smaller change in 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 (PSMs) [262].

7.1.3.3 Positive margins on histopathological specimens of resected tumours

A positive surgical margin is encountered in about 8% of PNs [263]. Studies comparing different resection techniques (open, laparoscopic, robotic) are inconclusive [264, 265]. Most trials showed that intra-operative frozen section analysis had no influence on the risk of definite PSMs [266]. A PSM status occurs more frequently in cases in which surgery is imperative, including bilateral tumours [267, 268]. Positive surgical margins increase the risk of disease recurrence, primarily in patients with adverse pathological features (pT2a-pT3a, grade III-IV) [263, 267, 268]. The effect of margin status on long-term oncologic outcomes remains to be determined [264], but PSMs need not translate into worse CSS [267, 268]. Therefore, RN or re-resection of margins presents overtreatment in many cases, but a small percentage of patients will harbour residual malignancy [269]. Patients with PSMs should be informed that they will be subjected to a more intense surveillance (imaging) programme and are at increased risk for secondary local therapies [267, 270]. However, protection from recurrence is not ensured by negative surgical margins [271].

7.1.3.4 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
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared with radical nephrectomy.	3

Recommendations	**grade**	
Offer laparoscopic radical nephrectomy to patients with T2 tumours and localised masses not treatable by partial nephrectomy.	strong	↑↑
Do not perform radical nephrectomy in patients with T1 tumours for whom partial nephrectomy is indicated.	strong	↓↓

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 in patients treated with surgery [200, 272]. 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 [272]. Analyses of older patients (> 75 years) failed to show the same benefit in cancer-specific mortality for surgical treatment [273-275].

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 [276, 277]. 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 [278]. The concept of AS differs from the concept of watchful waiting. Watchful waiting is reserved for patients whose comorbidities contraindicate any subsequent active treatment and do not require follow-up imaging, unless clinically indicated.

In the largest reported series of AS, the growth of renal tumours was low and progression to metastatic disease was reported in only a limited number of patients [279, 280].

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 multi-variate analysis, management type was not associated with OS after adjusting for age, comorbidity, and other variables [276]. No statistically significant difference in OS and CSS were observed in another study of RN vs. PN vs. AS for T1a renal masses with a follow-up of 34 months [281].

The initial results of the multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry were recently published. This prospective, NRS enrolled 497 patients with solid renal masses < 4 cm in size who chose AS or primary active intervention. Patients who selected AS were older, had worse ECOG scores, more comorbidities, smaller tumours, and more often multiple and bilateral lesions. Overall survival for primary intervention and AS was 98% and 96% at two years, and 92% and 75% at five years, respectively ($p = 0.06$). At five years, CSS was 99% and 100%, respectively ($p = 0.3$). Active surveillance was not predictive of OS or CSS in regression modelling with relatively short follow up [282].

Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, AS is appropriate to initially monitor small renal masses, followed, if required, by treatment for progression [278-280, 283-286].

A multicentre study assessed QoL of patients undergoing immediate intervention vs. AS. Patients undergoing immediate intervention had higher QoL scores at baseline, specifically for physical health. The perceived benefit in physical health persisted for at least one year following intervention. Mental health, which includes domains of depression and anxiety, was not adversely affected while on AS [287].

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 [288-290]. One comparative study reported similar OS, CSS, and RFS in 172 laparoscopic patients with a longer follow up compared with 123 patients treated percutaneously with a shorter follow up [289]. A shorter average length of hospital stay was found with the percutaneous technique [289, 290]. No studies are available comparing surveillance strategies to cryoablation.

A recent SR including 82 articles reported complication rates ranging between 8 and 20% with most complications being minor [291]. Although a precise definition of tumour recurrence is lacking, the authors reported a lower RFS as compared to that of PN.

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, DFS, local recurrence or progression to metastatic disease [292, 293], with some showing significant benefit for the PN techniques for some or all of these outcomes [294-297]. Not all studies reported all outcomes listed, and some were small and included benign tumours. No study showed an oncological benefit for cryoablation over PN.

Peri-operative outcomes, complication rates and other QoL measures were mixed. Some studies found the length of hospital stay was shorter and surgical blood loss was less with cryoablation [292-294], whilst also finding no differences in other peri-operative outcomes such as recovery times, complication rates or post-operative serum creatinine levels. Two studies [296, 297] 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 two of the studies, but in favour of cryoablation in a third [295-297]. Estimates of new CKD were also mixed, with one study in favour of cryoablation [295], another strongly in favour of PN [296], and the third showing no difference [297]. One study compared PN with ablation therapy, either cryoablation or RFA [223], and showed significantly improved DSS at both five and ten years for PN.

A recent study compared 1,057 patients treated by PN to 180 treated by RFA and 187 treated by cryoablation for a cT1 tumour and found no difference regarding RFS between the three techniques. Metastasis-free survival was superior after PN and cryoablation compared to RFA for cT1a patients. However, follow-up of patients treated by thermal ablations was shorter [198].

7.1.4.3.3 Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Four studies compared patients with T1a tumours treated by laparoscopic or percutaneous RFA [298-301].

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 [300] 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 [302-304].

One study [303] 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. Cancer-specific survival was 100% in both groups. Overall survival was lower in the RFA group but patients treated with surgery were younger [302].

In a monocentric study that compared 34 RFA patients to sixteen open PN patients, a higher rate of complications and transfusions was shown in the PN group. Although the tumours were larger in PN patients, progression rates were similar (0%) [304].

A recent meta-analysis [305] reported comparable complication rates and post-operative eGFRs between RFA and PN. The local tumour recurrence rate was higher in the RFA group than in the PN group (OR = 1.81) but there was no difference regarding the occurrence of distant metastasis.

7.1.4.3.5 Cryoablation versus radiofrequency ablation

Two studies compared RFA and cryoablation [306, 307]. No significant differences were reported for OS, CSS, or RFS in either study. For local RFS at five years, one study [306] reported improvement with RFA, while the other [307] reported a benefit with cryoablation. One study [306] 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 recommendation for therapeutic approaches as alternative to surgery

Summary of evidence	**LE**
Most population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management.	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 thermal ablation therapies compared to partial nephrectomy.	3

Recommendation	grade	
Offer active surveillance, radiofrequency ablation and cryoablation to elderly and/or comorbid patients with small renal masses.	weak	↑

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 for 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 [38]. However, the extent of LND remains controversial [214].

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 [231-233]. The use of neoadjuvant targeted therapy to downsize tumours is experimental and cannot be recommended outside clinical trials.

7.2.4 Management of RCC with venous tumour thrombus

Tumour thrombus formation in the IVC in RCC patients is a significant adverse prognostic factor. Traditionally, patients with venous tumour thrombus undergo surgery to remove the kidney and tumour thrombus. Aggressive surgical resection is widely accepted as the default management option for patients with venous tumour thrombus [308-316]. 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 venous tumour thrombus

The data on whether patients with venous tumour thrombus should undergo surgery is derived from case series. In one of the largest published studies [313] 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 venous tumour thrombus, and an acceptable 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 tumour thrombus (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 venous tumour thrombus, in non-metastatic RCC [317, 318]. Only five studies were eligible for final inclusion, with high risks of bias across all studies.

Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [319, 320]. Pre-operative embolisation [321] 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 [322].

No surgical method was shown to be superior for the excision of venous tumour thrombus. The surgical method was dependent on the level of tumour thrombus, and the grade of occlusion of the IVC [317, 319, 320, 322]. 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 for the management of RCC with venous tumour thrombus

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	grade	
In patients with clinically enlarged lymph nodes, perform lymph node dissection for staging purposes or local control.	weak	↑
In patients with non-metastatic RCC, excise the kidney tumour and the vena cava thrombus.	strong	↑↑

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 [323-327] (LE: 1b). Results from prior adjuvant trials studying interferon-alpha (IFN-α) and interleukin-2 (IL-2) did not show a survival benefit [328]. Heat shock protein-peptide complex-96 (vitespen) [329], 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) [330]. 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 investigating adjuvant sunitinib, sorafenib, pazopanib, axitinib and everolimus are ongoing. At present, there is no evidence for the use of adjuvant VEGF-R or 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% of the data available. 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 [162]. The S-TRAC study included 615 patients in a 1:1 randomisation (HR: 0.76; 95% CI: 0.59-0.98; p = 0.03 for DFS and an immature OS). Grade 3/4 toxicity in the study was 60.5% for patients receiving sunitinib, which translated into significant differences in QoL for loss of appetite and diarrhoea. Based on the conflicting results in the two available studies, the Panel rated the quality of the evidence, harms-benefits ratio, patient preferences and costs. Finally, the panel, including representatives from a patient advocacy group (IKCC), voted and reached a consensus decision to not recommend adjuvant therapy with sunitinib for patients with high-risk RCC after nephrectomy [331].

7.2.5.1 *Summary of evidence and recommendations for adjuvant therapy*

Summary of evidence	LE
Adjuvant cytokines do not improve survival after nephrectomy.	1b
Adjuvant sunitinib improved disease-free survival in one of the two available studies, but not overall survival, after nephrectomy in selected high-risk patients.	1b

Recommendations	grade	
Do not offer adjuvant therapy with sorafenib.	strong	↓↓
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell cancer.	weak	↓

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 [332]. 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 a good PS, large primary tumours and low metastatic volume. In patients with poor PS or Metastatic Renal Cancer Database Consortium (IMDC) risk, 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 [231-233] (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

Recommendation	grade	
Offer cytoreductive nephrectomy to favourable- and intermediate-risk patients with metastatic RCC.	weak	↑

7.3.2 Local therapy of metastases in mRCC

A systematic review of the local treatment of metastases from RCC in any organ was undertaken [333]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes assessed were OS, CSS and PFS, local symptom control and adverse events. A risk-of-bias assessment was conducted [334]. Of the 2,235 studies identified only sixteen non-randomised comparative studies were included.

Eight studies reported on local therapies of RCC-metastases in various organs [335-342]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC metastases in bone, including the spine [343-345], two in the brain [346, 347] and one each in the liver [348] lung [349] and pancreas [350]. Three studies [339, 341, 349] were abstracts. Data were too heterogeneous for 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 [335-342] on RCC metastases in various organs compared complete vs. no and/or incomplete metastasectomy. However, in one study [338], 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 [335, 337-339, 341, 342] reported a significantly longer median OS or CSS following complete metastasectomy (the median value for OS or CSS was 40.75 months, range 23-122 months) compared with incomplete and/or no metastasectomy (the median value for OS or CSS was 14.8 months, range 8.4-55.5 months). Of the two remaining studies, one [336] showed no significant difference in CSS between complete and no metastasectomy, and one [340] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases to the lung [349], liver [348], and pancreas [350], 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 five-year OS for metastasectomy vs. no metastasectomy.

7.3.2.2 Local therapies for RCC bone metastases

Of the three studies identified, one compared single-dose image-guided radiotherapy (IGRT) with hypo-fractionated IGRT in patients with RCC bone metastases [345]. Single-dose IGRT (≥ 24 Gray) had a significantly better three-year actuarial local PFS rate, also shown by Cox regression analysis. Another study [343] compared metastasectomy/curettage and local stabilisation with no surgery of solitary RCC bone metastases in various locations. A significantly higher five-year CSS rate was observed in the intervention group.

After adjusting for prior nephrectomy, gender and age, multi-variate analysis still favoured metastasectomy/curettage and stabilisation. A third study 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 [344]. 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 [346] 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 two-year OS and intracerebral control for SRS + WBRT based on only three participants. The other study compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy (MTS) + CRT or CRT alone [347]. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. One-, two- and three-year survival rates were higher but not significantly so for FSRT as for metastasectomy + CRT, or CRT alone. Fractionated stereotactic radiotherapy did not result in a significantly better two-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 [351]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [352] (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	grade	
Consider local therapy for metastatic disease (including metastasectomy) in patients with a favourable risk profile in whom complete resection is achievable or when local symptoms need to be controlled.	weak	↑
Stereotactic radiotherapy for clinically relevant bone or brain metastases can be considered for local control and symptom relief.	weak	↑

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 [353]. However, in one study, interferon-alpha (IFN-α) showed equivalent efficacy to IFN-α + interleukin-2 (IL-2) + 5-FU [354].

A combination of gemcitabine and doxorubicin could be an option in sarcomatoid and rapidly progressive RCC [69, 355].

7.4.1.1 Summary of evidence and recommendation for systemic therapy for advanced/metastatic renal cell cancer

Summary of evidence	LE
In metastatic RCC, 5-FU combined with immunotherapy has equivalent efficacy to INF-α.	1b
In metastatic RCC, chemotherapy is otherwise not effective with the exception of gemcitabine and doxorubicine in sarcomatoid and rapidly progressive disease.	3

Recommendations	grade	
Do not offer chemotherapy as first-line therapy in patients with metastatic clear-cell renal cell cancer (RCC).	strong	↓↓
Consider offering a combination of gemcitabine and doxorubicin to patients with sarcomatoid or rapidly progressive RCC.	weak	↑

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 [356]. Interferon-α resulted in a response rate of 6-15%, a 25% decrease in tumour progression risk and a modest survival benefit compared to placebo [357, 358]. However, patients with intermediate-risk disease, failed to confirm this benefit [359].

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 [356]. The moderate efficacy of immunotherapy was confirmed in a Cochrane meta-analysis [358]. Bevacizumab + IFN-α increased response rates and PFS in first-line therapy compared with IFN-α monotherapy [360]. All studies comparing targeted drugs to IFN-α monotherapy therapy showed superiority for sunitinib, bevacizumab + IFN-α, and temsirolimus [360-363]. Interferon-α has been superseded by targeted therapy in cc-mRCC.

Table 7.1: The Metastatic Renal Cancer Database Consortium (IMDC) risk model [364]

Risk factors**	Cut-off point used
Karnofsky performance status	< 80%
Time from diagnosis to treatment	< 12 months
Haemoglobin	< Lower limit of laboratory reference range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)
Absolute neutrophil count (neutrophilia)	> upper limit of normal
Platelets (thrombocytosis)	> upper limit of normal

** The MSKCC (Motzer) criteria are also widely used in this setting [357].*

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

7.4.2.2 *Interleukin-2*

Interleukin-2 has been used to treat mRCC since 1985, with response rates ranging from 7% to 27% [363, 365, 366]. Complete and durable responses have been achieved with high-dose bolus IL-2, however IL-2 remains the only drug to date that can cure a small percentage of RCC patients. [367]. The toxicity of IL-2 is substantially greater than that of IFN-α [358].

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 [368]. 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 [369], 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 PD-1 or cytotoxic T-lymphocyte associated antigen 4 (CTLA-4)signalling to restore tumour specific T-cell immunity [370]. A randomised dose-ranging phase II trial of nivolumab in metastatic RCC patients revealed a high objective response rate with rapid and durable responses in heavily pre-treated patients [371]. A phase III trial of nivolumab vs. everolimus after one or two lines of VEGF-targeted therapy (CheckMate 025, NCT01668784) reported a longer OS, better QoL and fewer Grade 3 or 4 adverse events with nivolumab than with everolimus [172, 372, 373]. Nivolumab has superior OS to everolimus ([HR]: 0.73, 95% CI: 0.57-0.93, $p < 0.002$) in VEGF-refractory RCC 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. A phase III trial is currently investigating the combination of nivolumab and ipilumimab vs. sunitinib in first-line treatment (CheckMate 214, NCT 02231749) [167]. Combinations of VEGF-targeted therapy and immune therapy are also being investigated and include:

- Javelin Renal 101 - NCT02684006;
- IMmotion151 - NCT02420821;
- pembrolizumab + axitinib - NCT02133742;
- lenvatinib + everolimus or pembrolizumab - NCT02811861.

7.4.2.5 Summary of evidence and recommendations for immunotherapy in mRCC

Summary of evidence	LE
Interferon-α monotherapy is inferior to VEG-targeted therapy or mTOR inhibition in mRCC.	1b
Interleukin-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
High dose (HD)-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 ccRCC.	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	grade	
Offer nivolumab after one or two lines of vascular endothelial growth factor-targeted therapy in metastatic RCC.	strong	↑↑
Do not offer monotherapy with interferon-α or high-dose bolus interleukin-2 as first-line therapy in metastatic RCC.	weak	↓

*7.4.3 **Targeted therapies***

In sporadic ccRCC, hypoxia-inducible factor (HIF) accumulation due to VHL-inactivation results in over-expression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis [374-376]. 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.

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 [356] (Table 7.1). Since the MSKCC (Motzer) criteria were developed during the cytokine era, the IMDC risk model has been established and validated to aid accurate prognosis of 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 [364].

The IMDC published data on conditional survival which may be used in patient counselling [377]. 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 [378]. Both the MSKCC and IMDC developed models for second-line treatment in the era of targeted therapy based, in part, on their risk models for treatment-naïve patients [379].

Table 7.2: Median OS and percentage of patients surviving two years treated in the era of targeted therapy per IMDC risk group (based on references [364, 378])

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 [378]; ** based on [364]*
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 multi-kinase inhibitor. A trial compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unfit for immunotherapy. Sorafenib improved PFS [380] (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 [381]. 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 [382]). First-line monotherapy with sunitinib demonstrated significantly longer PFS compared with IFN-α. Overall survival was greater in patients treated with sunitinib (26.4) vs. INF-α (21.8 months) despite crossover [383].

In the EFFECT trial, sunitinib 50 mg/day (four weeks on/two weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with cc-mRCC [384]. 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 (two weeks on/one week off) is being used to manage toxicity, but robust data to support its use is lacking [385].

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 [386]. 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-pre-treated 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 [387], 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 [388]. 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) [389].

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%. Overall survival was a secondary end-point of the trial in which crossover was not permitted. Final analysis of OS showed no significant differences between axitinib or sorafenib [390, 391].

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 [392]. 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 TK, 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 [171]. Based on these results a randomised phase III trial investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapies (METEOR) [64]. Cabozantinib delayed PFS compared to everolimus in VEGF-targeted therapy refractory disease by 42% (HR: 0.58 95% CI: 0.45-0.75) [64] (LE: 1b). The median PFS for cabozantinib was 7.4 months (95% CI: 5.6-9.1) vs. 3.8 months (95% CI: 3.7-5.4) for everolimus. The trial recruited 658 patients although PFS was assessed on the first 375 patients. The median OS was 21.4 months (95% CI: 18.7 to not estimable) with cabozantinib and 16.5 months (95% CI 14.7-18.8) with everolimus in VEGF- resistant RCC. The HR for death was 0.66 (95% CI: 0.53-0.83; p = 0.0003) [393]. Grade 3 or 4 adverse events were reported in 74% 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 two drugs. The trial included 16% MSKCC poor-risk patients.

7.4.3.1.6 Lenvatinib

Lenvatinib is an oral multi-target TKI of VEGFR1, VEGFR2, and VEGFR3, with inhibitory activity against fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3, and FGFR4), platelet growth factor receptor α (PDGFRα), re-arranged during transfection (RET), and receptor for stem cell factor (KIT). It has recently been investigated in randomised phase II study in combination with everolimus vs. lenvatinib or everolimus alone (see Section 7.4.6.1.1.5 for discussion of results).

*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 double-blind AVOREN study compared bevacizumab + IFN-α with INF-α monotherapy in mRCC [360]. 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) [394].

An open-label trial (CALGB 90206) [395, 396], of bevacizumab + IFN-α vs. IFN-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 [397]. Patients with modified high-risk mRCC in the NCT00065468 trial received first-line temsirolimus or IFN-α monotherapy, or a combination of both [362]. Median OS was higher in the temsirolimus group. However, OS in the temsirolimus + IFN-α group was not significantly superior to IFN-α alone [362]. Interferon-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 [398]. 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) [399]. The initial data showed a median PFS of four months vs. 1.9 months for everolimus and placebo, respectively [399]. This was extended to 4.9 months in the final analysis (HR: 0.33) [400]. Subset analysis of PFS for patients receiving only one previous VEFG TKI was 5.4 months [401]. This included some patients who were intolerant rather than progressed on therapy (PFS was also 5.4 months) [402]. RECORD-1 included patients who failed multiple lines of VEGF-targeted therapy, and received everolimus in a third- and fourth-line setting [399].

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 [403]. 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***

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

Key trials have established sunitinib, pazopanib 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 evidence for subsequent therapies after temsirolimus in poor-risk patients is unclear. It is therefore more appealing to treat poor-risk patients with sunitinib or pazopanib, both of which were tested in pivotal trials in this population.

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 therapy until disease progression, followed by everolimus as one of the treatment options for patients with mRCC [399]. However, both nivolumab and cabozantinib were superior to everolimus following a similar trial design as RECORD-1 [172]. 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 both a superior PFS and OS compared to everolimus. Both nivolumab and cabozantinib have different toxicity profiles.

Axitinib is superior to sorafinib in terms of PFS in sunitinib-refractory ccRCC [388]. Neither nivolumab nor cabozantinib has been tested directly against axitinib in the second-line setting. However, the OS advantage of both drugs and tolerability of nivolumab over everolimus in this setting makes them preferable to axitinib.

Tolerability is an important consideration when recommendations cannot be made for 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 [389-391, 399].

INTORSECT compared temsirolimus vs. sorafenib after disease progression on sunitinib [398]. 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 difference in OS, 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-refractory RCC (LE: 1a). There is a strong rationale for using both drugs in sequence in the second and third line following VEGF-targeted therapy. This creates a new a standard for the majority of patients.

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 (Panel consensus in conjunction with Motzer *et al.* [404]).

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 [389-391].

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

Based on the results of the nivolumab and cabozantinib trials, a strong rationale exists for preferring both drugs as third-line treatment upon failure of two VEGF-targeted therapies [64, 172] (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 [404]. This sequence is not recommended when alternative superior drugs are available.

7.4.6.1.1.4.3 Combination of targeted agents

No combinations of targeted agents are currently recommended, however, there have been a number of trials with VEFG-targeted therapy and mTOR inhibitors [405-409]. A small randomised phase II trial in which 153 patients received either lenvatinib plus everolimus (n = 51), single-agent lenvatinib (n = 52), or single-agent everolimus (n = 50) demonstrated a PFS benefit for the combination [410]. Lenvatinib plus everolimus significantly prolonged PFS compared with everolimus alone (median 14.6 months [95% CI: 5.9-20.1] vs. 5.5 months [3.5-7.1]; HR: 0.40; 95% CI: 0.24-0.68; p = 0.0005), but not compared with lenvatinib alone (7.4 months [95% CI: 5.6-10.2]; HR: 0.66; 95% CI: 0.30-1.10; p = 0·12). In a post-hoc updated analysis (data cut-off Dec 10, 2014), the difference in OS between lenvatinib plus everolimus vs. single-agent everolimus was significantly increased, median OS 25.5 months [95% CI: 16.4-NE] vs. 15.4 months [11.8-19.6]; HR: 0.51; 95% CI: 0.30-0.88; p = 0.024. Grade 3 or worse serious adverse events occurred in 23 (45%) patients allocated to lenvatinib plus everolimus, 23 (44%) allocated to single-agent lenvatinib, and 19 (38%) allocated to single-agent everolimus.

7.4.6.2 Non-clear-cell renal cancer

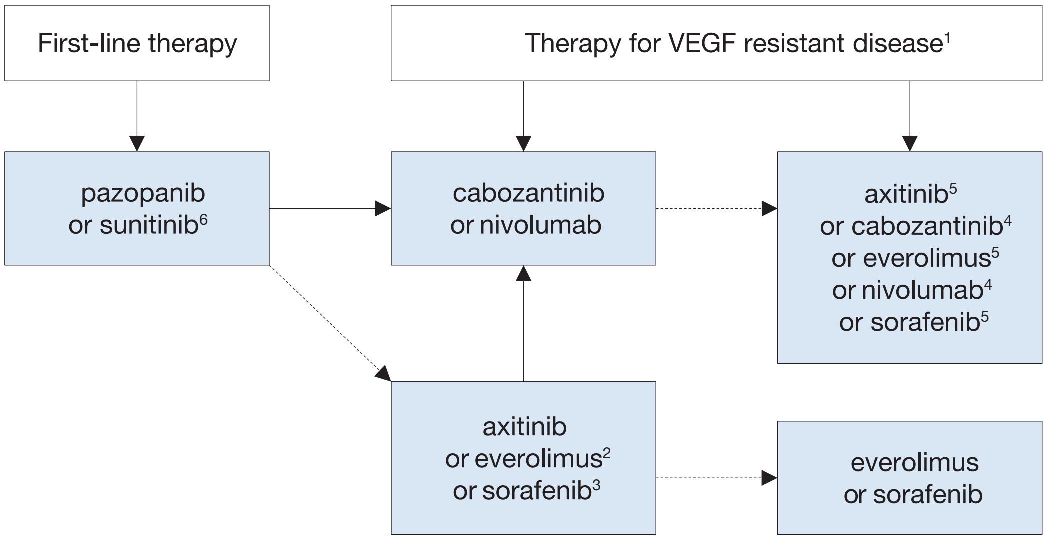
No phase III trials of patients with non-ccRCC have been reported. Expanded access programmes and subset analysis from RCC studies suggest the outcome of these patients with targeted therapy is poorer than for ccRCC. Targeted treatment in non-ccRCC has focused on temsirolimus, everolimus, sorafenib and sunitinib [362, 411-413].

The most common non-clear-cell subtypes are papillary type 1 and non-type 1 papillary RCCs. There are small single-arm trials for sunitinib and everolimus [413-416]. A trial of both types of pRCC treated with everolimus (RAPTOR) [416], showed a 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 foretinib (a dual MET/VEGFR2 inhibitor) in patients with pRCC. Toxicity was acceptable with a high relative risk in patients with germline MET mutations [417]. However, a randomised phase II trial of everolimus vs. sunitinib (ESPN) with crossover design in non-cc-mRCC including 73 patients (27 with pRCC) was stopped after a futility analysis for PFS and OS [418]. 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 [136, 419, 420]. Patients with non-cc-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 [362, 411].

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



[1] Switch to therapies not given previously.
[2] Nivolumab and cabozantinib have not been given after everolimus and therefore cannot be recommended above other agents.
[3] Sorafenib has an inferior progression-free survival to axitinib.
[4] These drugs have shown a survival advantage in VEGF-resistant disease but not in this specific setting.
[5] These drugs were given after progression in the pivotal cabozantinib or nivolumab trials [64, 172].
[6] Sunitinib and pazopanib can be recommended in all MSKCC risk groups. Bevacizumab/interferon (favourable- and intermediate-risk disease) and temsirolimus (poor-risk disease) have not been widely used as first-line therapy in the pivotal VEGF-resistant trials and therefore recommendations are not possible.

Table 7.3: EAU 2017 evidence-based recommendations for systemic therapy in patients with mRCC

RCC type	MSKCC risk group [356]	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 cabozantinib based on PFS: axitinib sorafenib# everolimus&	 2b 2b 2b 2b 2b	**after VEGF therapy**: nivolumab cabozantinib everolimus& **after VEGF and mTOR therapy**: sorafenib **after VEGF and nivolumab**: cabozantinib axitinib everolimus	 2b 2b 2b 1b 4 4 4	any targeted agent	4
Clear cell*	poor¶	temsirolimus sunitinib pazopanib	1b 2b 2b	any targeted agent	4				

Non-clear cell §	any	sunitinib	1b^^	Any targeted agent	4				

IFN-α = interferon alpha; LE = level of evidence; MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin inhibitor; RCC = renal cell cancer; TKI= tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

*Doses: IFN-α - 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg bi-weekly intravenously; sunitinib 50 mg daily orally for four weeks, followed by two 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 [356] 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 [391].

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

^^ Based on a SR [420].

7.4.6.3 Summary of evidence and recommendations for systemic therapy in metastatic renal cell cancer

Summary of evidence	**LE**
VEGF and 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
First line 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 and OS 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 when compared to placebo.	1b
Sorafenib has broad activity in a spectrum of settings in ccRCC 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, with the exception of the combination of lenvatinib plus everolimus.	1a

Recommendations	grade	
Offer sunitinib or pazopanib as first-line therapy for metastatic clear-cell renal cell cancer (ccRCC).	strong	↑↑
Consider offering bevacizumab + Interferon (IFN)-α as first-line therapy for metastatic RCC in favourable and intermediate-risk ccRCC.	weak	↑
Consider offering temsirolimus as first-line treatment in poor-risk RCC patients.	weak	↑
Offer cabozantinib for ccRCC after one or two lines of vascular endothelial growth factor (VEGF)-targeted therapy in metastatic RCC.	strong	↑↑
Offer nivolumab after one or two lines of VEGF-targeted therapy in metastatic RCC.	strong	↑↑
Offer axitinib or everolimus to ccRCC patients who failed VEGF-targeted therapy, and when nivolumab or cabozantinib are not safe, tolerable or available.	strong	↑↑
Sequence targeted agents in treating metastatic RCC.	strong	↑↑
Sunitinib can be offered as first-line therapy for non-clear cell mRCC.	weak	↑

7.5 Recurrent RCC

*7.5.1 **Introduction***

Locally recurrent disease can occur after RN, PN and thermal ablation. After nephron-sparing treatment 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 for pT1 tumours after PN are observed in 2.2% and are generally managed surgically depending on the extent of the loco-regional recurrence [421]. After thermal ablation loco-regional recurrences (intrarenal and regional) have been described in up to 12% [422]. 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 non-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 (see Section 7.3). Isolated local recurrence, however, is rare.

The largest series on the treatment of isolated recurrence was published in 2009 [423]. In 2,945 patients who underwent nephrectomy the authors identified 54 isolated local recurrences in the renal fossa. These, however, included recurrences 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 [423]. 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	grade	
Offer surgical resection of local recurrent disease, when feasible.	weak	↑

8. FOLLOW-UP IN 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 a urologist, who should record the time to recurrence or the development of metastases. Patients undergoing follow-up seem to have a longer OS when compared to patients not undergoing routine follow-up [424].

An individualised, risk-based, approach to RCC surveillance was recently proposed. The authors use competing risk models, incorporating patient age, pathologic stage, relapse location and comorbidities, to calculate when the risk of non-RCC death exceeds the risk of RCC recurrence [425]. For patients with low-stage disease but with a Charlson comorbidity index $\geq$ 2, the risk of non-RCC death exceeded that of abdominal recurrence risk already one month after surgery, regardless of patient age.

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 [426, 427] and non-cancer survival [196, 428, 429] can be optimised by performing NSS, whenever possible, for T1 and T2 tumours [430] (LE: 3). Recurrence after PN is rare, but early diagnosis is useful, as the most effective treatment is redux surgery [431, 432]. Recurrence in the contralateral kidney is also rare and might be related to positive margins, multifocality, and grade [433] (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, which is 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 [35, 434, 435] (LE: 4). One study has shown a survival benefit for patients who were followed within a structured surveillance protocol vs. patients who were not [424]:

- The sensitivity of chest radiography and US for small metastases is poor. Surveillance with these imaging modalities should not be done [436].
- In low-risk tumours, surveillance intervals should be adapted taking into account radiation exposure and benefit. To reduce radiation exposure, MRI can be used outside the thorax.
- When the risk of relapse is intermediate or high, CT of the chest and abdomen should be performed.
- Surveillance should also include evaluation of renal function and cardiovascular risk factors.
- Positron-emission tomography and PET-CT as well as bone scintigraphy should not be used in RCC surveillance, due to their limited specificity and sensitivity.
- The risk of acute renal failure seems to be negligible in patients with a GFR > 20 mL/min and chronic renal impairment [437].

Controversy exists on 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 [438] (LE: 3).

Several authors [182, 184, 439, 440], 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 [441] (LE: 2). Using prognostic variables, several stage-based surveillance regimens have been proposed [442, 443], but none include ablative therapies. A post-operative nomogram is available to estimate the likelihood of freedom from recurrence at five years [179]. Recently, a pre-operative prognostic model based on age, symptoms, and TNM staging has been published and validated [188] (LE: 3). A surveillance algorithm for monitoring patients after treatment for RCC is needed, recognising not only the patient's 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.

Data from adjuvant trials are generally based on the University of California Los Angeles integrated staging system (UISS) risk stratification, which makes it the most widely used, and validated system [162, 444].

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

Risk profile	Surveillance					
	6 mo	**1 y**	**2 y**	**3 y**	**4 y**	**5 y**	**> 5 y**
Low	US	CT	US	CT	US	CT	Discharge
Intermediate	CT	CT	CT	US	CT	CT	CT once every 2 years
High	CT	CT	CT	CT	CT	CT	CT once every 2 years

CT = computed tomography of chest and abdomen, alternatively use MRI;
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
Patients undergoing surveillance have a better overall survival than patients not undergoing surveillance.	3

Recommendations	grade	
Base follow-up after RCC on the risk of recurrence.	strong	↑↑
For low-risk disease, computed tomography (CT)/magnetic resonance imaging (MRI) can be used infrequently.	weak	↑
In intermediate-risk patients, offer intensified follow-up, including chest and abdominal CT/MRI scans at regular intervals in accordance with a risk-stratified nomogram.	weak	↑
In high-risk patients, include chest and abdominal CT/MRI scans in follow-up examinations.	weak	↑
Intensify follow-up in patients after NSS for tumours > 7 cm or in patients with a positive surgical margin.	weak	↑
Base risk stratification on pre-existing classification systems such as the University of California Los Angeles integrated staging system integrated risk assessment score (http://urology.ucla.edu/body.cfm?id=443).	strong	↑↑

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: https://uroweb.org/guideline/renal-cell-carcinoma/?type=panel/.

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