EAU Guidelines on Renal Cell Carcinoma

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European Association of Urology

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1.   INTRODUCTION

1.1   Aims and scope

The European Association of Urology (EAU) Renal Cell Carcinoma (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/renalcellcarcinoma/.

1.3   Acknowledgement

The RCC Guidelines Panel is most grateful for the continued 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.

1.4   Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android 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]. All documents can be accessed on the EAU website: http://uroweb.org/guideline/renal-cell-carcinoma/.

1.5   Publication history and summary of changes

1.5.1   Publication history

The EAU RCC Guidelines were first published in 2000. This 2020 RCC Guidelines document presents a limited update of the 2019 publication.

1.5.2   Summary of changes

All chapters of the 2020 RCC Guidelines have been updated, based on the 2019 version of the Guidelines. References have been added throughout the document.

New data have been included in the following sections, resulting in changed recommendations in:

Section 3.4.5 **Summary of evidence and recommendations for the management of other renal tumours**

Recommendations	Strength rating
Treat angiomyolipoma (AML) with selective arterial embolisation or nephron-sparing surgery, in: • large tumours (a recommended threshold of intervention does not exist); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate; • persistent pain or acute or repeated bleeding episodes.	Weak
Only offer radical nephrectomy to patients with localised renal medullary carcinoma after a favourable response to systemic therapy.	Weak

7.1.4.3.7 Summary of evidence and recommendation for therapeutic approaches as alternative to surgery

Recommendations	Strength rating
When radiofrequency ablation, cryoablation and active surveillance are offered, inform patients about the higher risk of local recurrence and/or tumour progression.	Weak

7.4.2.5 Summary of evidence and recommendations for immunotherapy of metastatic clear-cell RRC

Summary of evidence	LE
The combination of pembrolizumab and axitinib in treatment-naïve patients with clear-cell-mRCC across all IMDC risk groups demonstrated overall survival and ORR benefits compared to sunitinib.	1b
Currently, PD-L1 expression is not used for patient selection.	2b
Axitinib can be continued if immune-related adverse events results in cessation of axitinib and pembrolizumab. Re-challenge with combination therapy requires expert support.	4
Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	4
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	1b
Nivolumab plus ipilimumab and pembrolizumab plus axitinib should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	4

Recommendations	Strength rating
Offer pembrolizumab plus axitinib to treatment-naïve patients with any IMDC-risk clear-cell metastatic RCC (cc-mRCC).	Strong
Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC.	Strong
Patients who do not receive the 4 four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible.	Weak
Offer axitinib as subsequent treatment to patients who experience treatment-limiting immune-related adverse events after treatment with the combination of axitinib and pembrolizumab.	Weak
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	Weak
Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable-, intermediate-, and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong*

While this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib in this population. This justified the same recommendation under exceptional circumstances.

7.4.7 Summary of evidence and recommendations for targeted therapy in metastatic RRC

Summary of evidence	LE
Single-agent VEGF-targeted therapy has been superseded by immune checkpoint-based combination therapy.	1b
Pazopanib is non-inferior to sunitinib in front-line metastatic RCC.	1b
Tivozanib has been EMA approved, but the evidence is still considered inferior over existing choices in the front-line setting.	3
Single-agent VEGF-targeted therapies are preferentially recommended after front-line PD-L1-based combinations. Re-challenge with treatments already used should be avoided.	3
Single-agent cabozantinib or nivolumab are superior to everolimus after one or more lines of VEGF-targeted therapy.	1b
Both mTOR inhibitors and VEGF-targeted therapies have limited activity in non-clear cell RCC. There is a non-significant trend for improved oncological outcomes for sunitinib over everolimus.	2a
Lenvatinib in combination with everolimus improved PFS over everolimus alone in VEGF-refractory disease. Its role after immune checkpoint inhibitors is uncertain. There is a lack of robust data on this combination making its recommendation challenging.	2a

Recommendations	Strength rating
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naive vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC).	Strong
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab.	Weak
Offer cabozantinib after VEGF-targeted therapy in clear-cell-mRCC.	Strong

Figure 7.1: Updated European Association of Urology Guidelines recommendations for the treatment of first-line and following lines in clear-cell metastatic renal cancer

IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium
*pazopanib for intermediate-risk disease only.
[1b] = based on one randomised controlled phase III trial.
[2a] = based on one randomised controlled phase II trial.

Figure 7.2: Guidelines Recommendations for later-line therapy

Standard of care	Alternative

Prior IO	Any VEGF-targeted therapy that has not been used preyioously in combination with IO [4]	
Prior TKI	Nivolumab [1b] Cabozantinib [1b]	Axitinib [2b]
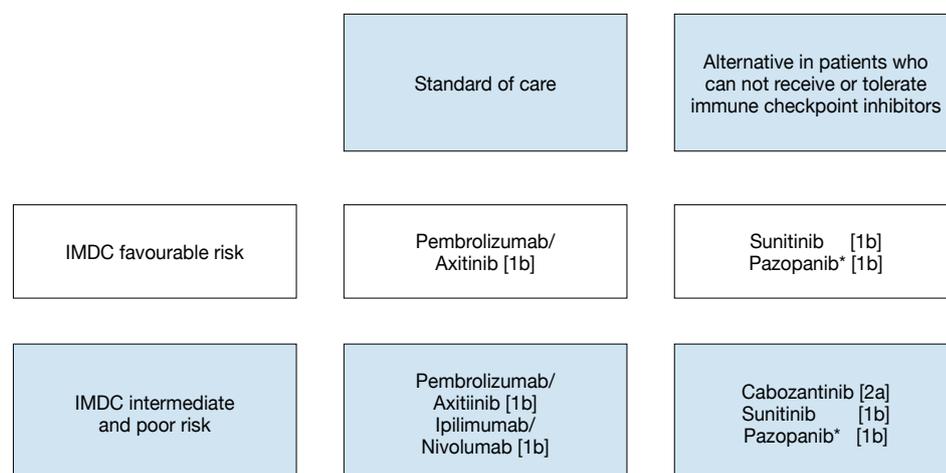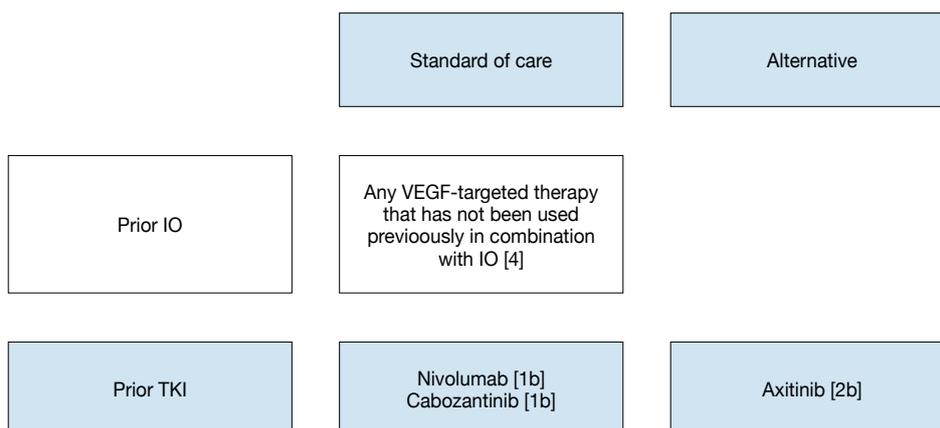
IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium; IO = immunotherapy;

TKI = tyrosine kinase inhibitors; VEGF = vascular endothelial growth factor.

[1b] = based on one randomised controlled phase III trial.

[2b] = subgroup analysis of a randomised controlled phase III trial.

[4] = expert opinion.

2.   METHODS

2.1   Data identification

For the 2018 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 search was performed, which was limited to studies representing high levels of evidence (i.e. systematic reviews [SRs] with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published between June 18th 2018 and April 5th, 2019. Databases covered included Medline, EMBASE, and the Cochrane Library. After deduplication, a total of 2,225 unique records were identified, retrieved and screened for relevance.

A total of 49 new references have been included in the 2020 RCC Guidelines publication. A search strategy is published online: https://uroweb.org/guideline/renal-cell-carcinoma/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [2]. Each strength rating form addresses a number of key elements namely:

1.   the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
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 rating of each recommendation.

The strength of each recommendation is represented by the words 'strong' or 'weak' [4]. 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 strength rating forms will be available online.

Specific chapters were updated by way of SRs, commissioned and undertaken by the Panel, based on

prioritised topics or questions. These reviews were performed using standard Cochrane SR methodology: http://www.cochranelibrary.com/about/aboutcochranesystematic-reviews.html.

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 narrative review, based on a structured literature assessment.
4. Staging and grading classification systems	This chapter was updated by a narrative review, based on a structured literature assessment. Section 3.3.5 Angiomyolipoma was updated by means of a SR [5].
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 narrative review, based on a structured literature assessment.
7. Treatment (Disease management)	Sections 7.1.2 and 7.2.4 (Treatment of localised and locally advanced disease) were revised based on an updated SR. Section 7.4.6.2 (Non-clear-cell carcinoma) was updated by means of a SR [7]. 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. Follow-up in RCC & Surveillance following radical or partial nephrectomy or ablative therapies	This chapter was updated by a narrative review, based on a structured literature assessment. The findings of a prospective database set up by the RCC Panel have been included [8, 9].

Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: http://uroweb.org/guidelines/. A list of Associations endorsing the EAU Guidelines can also be viewed on line at the above address.

2.2 Review
All publications ensuring from SRs have been peer reviewed. The 2019 print of the RCC Guidelines was peer-reviewed prior to publication.

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 (NSS) as first treatment;
* the proportion of patients treated within six weeks after diagnosis;
* the proportion of patients with metastatic RCC (mRCC) offered systemic therapy;
* the proportion of patients who undergo minimally invasive or operative treatment as first treatment who die within 30 days.

The panel have set up a database to investigate current practice in 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 2020 update of the RCC Guidelines:
* Ablative therapy vs. partial nephrectomy (PN) for T1-T2 renal cell carcinoma;
* What is the best treatment option for ≥ T2 tumours?;
* Systematic review and meta-analysis of systemic therapy of renal tumours (Cochrane Review);
* Adjuvant targeted therapy for renal cell carcinoma at high risk for recurrence.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology
Renal cell carcinoma represents around 3% of all cancers, with the highest incidence occurring in Western countries [10]. Generally, during the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe leading to approximately 99,200 new RCC cases and 39,100 kidney cancer-related deaths within the European Union in 2018 [10]. In Europe, overall mortality rates for RCC increased until the early 1990s, with rates generally stabilizing or declining thereafter [11]. There has been a decrease in mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend [10, 11].

3.2 Aetiology
Aetiological factors include lifestyle factors such as smoking, obesity, and hypertension [12, 13]. In a recent SR also diabetes was found to be detrimental [14]. Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC. A number of other factors have been suggested to be associated with higher or lower risk of RCC, including specific dietary habits and occupational exposure to specific carcinogens, but the literature is inconclusive [13, 15]. Moderate alcohol consumption appears to have a protective effect for reasons as yet unknown, while also any physical activity level seems to have a small protective effect [14, 16]. The most effective prophylaxis is to avoid cigarette smoking and reduce obesity [13].

Renal cell carcinoma is the most common solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. It comprises different RCC subtypes with specific histopathological and genetic characteristics [17]. There is a 1.5:1 predominance in men over women, with a peak incidence occurring between 60 and 70 years of age [18].

3.2.1 Summary of evidence and recommendation for epidemiology, aetiology and pathology

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	Strength rating
Increase physical activity, eliminate cigarette smoking and in obese patients reduce weight as the primary preventative measures to decrease risk of RCC.	Strong

3.3 Histological diagnosis
Renal cell carcinomas comprise a broad spectrum of histopathological entities described in the 2016 World Health Organization (WHO) classification [17]. There are three main RCC types: clear cell (ccRCC), papillary (pRCC- type I and II) and chromophobe (chRCC). The RCC type classification has been confirmed by cytogenetic and genetic analyses [17] (LE: 2b). Collecting duct carcinoma and other rare 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 [17].

3.3.1 Clear-cell RCC

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 [19]. In general, ccRCC has a worse prognosis compared to pRCC and chRCC [20, 21] even after stratification for stage and grade [22]. The 5-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), respectively [23]. For more details, see Section 6.3 - Histological factors.

3.3.2 Papillary RCC

Papillary RCC is the second most commonly encountered morphotype of RCC. Papillary RCC has traditionally been subdivided into two types [17]. Type I and II pRCC, which were shown to be clinically and biologically distinct; pRCC type I is associated with activating germline mutations of *MET* and pRCC type II is associated with activation of the NRF2-ARE pathway and at least three subtypes [24]. Future substratification is expected, e.g. oncocytic pRCC [17].

A typical histology of pRCC type I (narrow papillae without any binding, and only microcapillaries in papillae) explains its typical clinical signs. Narrow papillae without any binding and a tough pseudocapsule explain the ideal rounded shape (Pascal's law) and fragility (specimens have a "minced meat" structure). Tumour growth causes necrotisation of papillae, which is a source of hyperosmotic proteins that cause subsequent "growth" of the tumour, fluid inside the tumour, and only a serpiginous, contrast-enhancing margin. Only microcapillaries explain the minimal post-contrast attenuation on CT. Papillary RCC type 1 can imitate a pathologically changed cyst (Bosniak IIF or III). The typical signs of pRCC type 1 are as follows: an ochre colour, more frequently exophytic, extrarenal growth, low grade, and low malignant potential; over 75% of these tumours can be treated by NSS surgery. A substantial risk of renal tumour biopsy tract seeding exists (12.5%), probably due to the fragility of the tumour papillae [25]. Papillary RCC type I is more common and generally considered to have a better prognosis than pRCC type II [17, 26].

3.3.3 Chromophobe RCC

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 [17]. Loss of chromosomes Y, 1, 2, 6, 10, 13, 17 and 21 are typical genetic changes [17]. The prognosis is relatively good, with high 5-year recurrence-free survival (RFS), and 10-year CSS [27]. The new WHO/ISUP grading system merges former entity hybrid oncocytic chromophobe tumour with chRCC.

3.4 Other renal tumours

Other renal tumours constitute the remaining 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.

3.4.1 Renal medullary carcinoma

Renal medullary carcinoma (RMC) is a very rare tumour, comprising < 0.5% of all RCCs [28], predominantly diagnosed in young adults (median age 28 years) with sickle haemoglobinopathies (including sickle cell trait). It is mainly centrally located with ill-defined borders. Renal medullary carcinoma is one of the most aggressive RCCs [29, 30] and most patients (~67%) will present with metastatic disease [29, 31]. Even patients who present with seemingly localised disease may develop macrometastases shortly thereafter; often within a few weeks.

3.4.1.1 Treatment of renal medullary carcinoma

Despite treatment, median OS is 13 months in the most recent series [29]. Due to the infiltrative nature and medullary epicentre of RMC, radical nephrectomy (RN) is favoured over PN even in very early-stage disease. Retrospective data indicate that nephrectomy in localised disease results in superior OS (16.4 vs. 7 months) compared with systemic chemotherapy alone, but deferred treatment seems to be reasonable [29, 32]. There is currently no established role for distant metastasectomy or nephrectomy in the presence of metastases.

Palliative radiation therapy is an option and may achieve regression in the targeted areas but it will not prevent progression outside the radiation field [33, 34]. Renal medullary carcinoma is refractory to monotherapies with targeted anti-angiogenic regimens including tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors [29, 35, 36]. The mainstay systemic treatments for RMC

are cytotoxic combination regimens which produce partial or complete responses in ~29% of patients [35]. There are no prospective comparisons between different chemotherapy regimens but most published series used various combinations of platinum agents, taxanes, gemcitabine, and/or anthracyclines [29, 30]. High-dose-intensity combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has also shown efficacy against RMC [37] although a retrospective comparison did not show superiority of MVAC over cisplatin, paclitaxel, and gemcitabine (CPG) [30]. Single-agent anti-PD-1 (monoclonal antibodies against programmed death-1) immune checkpoint therapy has produced responses in a few case reports, although, as yet, insufficient data are available to determine the response rate to this approach [33, 34]. Whenever possible, patients should be enrolled in clinical trials of novel therapeutic approaches, particularly after failing first-line cytotoxic chemotherapy.

3.4.2 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 end-stage renal disease (ESRD). Renal cell carcinomas of native end-stage kidneys are found in approximately 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 ESRD are generally multicentric and bilateral, found in younger patients (mostly male), and are less aggressive [38, 39]. Whether the relatively indolent outcome of tumours in ESRD is due to the mode of diagnosis or a specific ACKD-related molecular pathway still has to be determined [39]. Although the histological spectrum of ESRD tumours is similar to that of sporadic RCC, the predominant form is pRCC. The remaining tumours are mostly ccRCC [38-40]. A specific subtype of RCC occurring only in end-stage kidneys has been described as Acquired Cystic Disease-associated RCC (ACD-RCC) [41] with indolent clinical behaviour, likely due to early detection in patients with ESRD on periodic follow-up [17].

3.4.3 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 [42], according to the WHO 2016 classification [17].

3.4.4 Hereditary kidney tumours

Five to eight percent of RCCs are hereditary; to date there are ten hereditary RCC syndromes 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 [43]. Hereditary kidney tumours are found in the following entities: VHL syndrome, hereditary pRCC, Birt-Hogg-Dubé syndrome, hereditary leiomyomatosis and RCC (HLRCC), tuberous sclerosis, germline succinate dehydrogenase (SDH) mutation, non-polyposis colorectal cancer syndrome, hyperparathyroidism-jaw tumour syndrome, phosphatase and tensin homolog (PTEN) hamartoma syndrome (PHTS), constitutional chromosome 3 translocation, and familial nonsyndromic ccRCC. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [41, 42, 44, 45].

Patients with hereditary kidney cancer syndromes may require repeated surgical intervention [46, 47]. In most hereditary RCCs nephron-sparing approaches are recommended. The exceptions are HLRCC and SDH syndromes for which immediate surgical intervention is recommended due to the aggressive nature of these lesions. For other hereditary syndromes such as VHL, surveillance is recommended until the largest tumour reaches 3 cm in diameter, to reduce interventions [48]. Active surveillance (AS) for VHL, BDH and HPRCC should, in individual patients, follow the growth kinetics, size and location of the tumours, rather than apply a standardised 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 [49].

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 diagnosed with RCC [50].

3.4.5 Angiomyolipoma

Angiomyolipoma (AML) is a benign mesenchymal tumour, which can occur sporadically or as part of tuberous sclerosis complex [51]. Overall prevalence is 0.44%, with 0.6% in female and 0.3% in male populations. Only 5% of these patients present with multiple AMLs [52]. Angiomyolipoma belongs to a family of so-called PEComas (perivascular epithelioid cell tumours), characterised by the proliferation of perivascular epithelioid cells. Some PEComas can behave aggressively and can even produce distant metastases. Classic AMLs are completely benign [17, 42, 53]. Ultrasound (US), CT, and magnetic resonance imaging (MRI) often lead to the diagnosis of AMLs due to the presence of adipose tissue, however in fat poor AML, diagnostic imaging cannot

reliably identify these lesions. Percutaneous biopsy is rarely useful. Renal tumours that cannot be clearly identified as benign during the initial diagnostic work-up should be treated according to the recommendations provided for the treatment of RCC in these Guidelines. In tuberous sclerosis, AML can be found in enlarged lymph nodes (LNs), which does not represent metastatic spread but a multicentric spread of AMLs. In rare cases, an extension of a non-malignant thrombus into the renal vein or inferior vena cava can be found, associated with an angiotrophic-type growth of AML. Epithelioid AML, a very rare variant of AML, consists of at least 80% epithelioid cells [42, 53]. Epithelioid AMLs are potentially malignant with a highly variable proportion of cases with aggressive behaviour [54]. Criteria to predict the biological behaviour in epithelioid AML were proposed by the WHO 2016 [42, 53]. Angiomyolipoma, in general, has a slow and consistent growth rate, and minimal morbidity [5].

In some cases, larger AMLs can cause local pain. The main complication of AMLs is spontaneous bleeding in the retroperitoneum or into the collecting system, which can be life threatening. Bleeding is caused by spontaneous rupture of the tumour. Little is known about the risk factors for bleeding, but it is believed to increase with tumour size and may be related to the angiogenic component of the tumour that includes irregular blood vessels [5]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of tuberous sclerosis [55, 56].

3.4.5.1 Treatment
Active surveillance is the most appropriate option for most AMLs (48%). In a group of patients on AS, only 11% of AMLs showed growth, spontaneous bleeding was reported in 2%, resulting in active treatment in 5% of patients [5, 57] (LE: 3). The association between AML size and the risk of bleeding remains unclear and the traditionally used 4-cm cut-off should not per se trigger active treatment [5]. When surgery is indicated, NSS is the preferred option, if technically feasible. Main disadvantages of less invasive selective arterial embolisation (SAE) are more recurrences and a need for secondary treatment (0.85% for surgery vs. 31% for SAE). For thermal ablation only limited data is available, and this option is used less frequently [5].

Active treatment (SAE, surgery or ablation) should be instigated in case of persistent pain, ruptured AML (acute or repeated bleeding) or in case of a very large AML. Specific patient circumstances may influence the choice to offer active treatment; such as patients at high risk of abdominal trauma, females of childbearing age or patients in whom follow-up or access to emergency care may be inadequate.

In patients diagnosed with tuberous sclerosis, size reduction of often bilateral AMLs can be induced by inhibiting the mTOR pathway using everolimus, as demonstrated in RCTs [58, 59].

3.4.6 Renal oncocytoma
Oncocytoma is a benign tumour representing 3-7% of all solid renal tumours and its incidence increases to 18% when tumours < 4 cm are considered [17, 57]. The diagnostic accuracy of imaging modalities (CT, MRI) in renal oncocytoma is limited and histopathology remains the only reliable diagnostic modality [17, 57]. Standard treatment for renal oncocytoma is similar to that of other renal tumours; surgical excision by partial- or RN with subsequent histopathological verification. However, due to the inability of modern imaging techniques to differentiate benign from malignant renal masses, there is a renewed interest in renal mass biopsy (RMB) prior to surgical intervention. Accuracy of the biopsy and management of advanced/progressing oncocytomas need to be considered in this context since oncocytic renal neoplasms diagnosed by RMB at histological examination after surgery showed oncocytoma in only 64.6% of cases. The remainder of the tumours were mainly chRCC (18.7% including 6.3% hybrid oncocytic/chromophobe tumours which have now been grouped histologically with chRCC) [17], other RCCs (12.5%), and other benign lesions (4.2%) [60]. The majority of oncocytomas slowly progress in size with an annual growth rate < 14 mm [61-63]. Preliminary data show that AS may be a safe way to manage oncocytoma in appropriately selected patients.

Table 3.1: Other renal cortical tumours, and recommendations for treatment (strength rating: weak) [17]

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. Nivolumab and ipilimumab. Sunitinib, gemcitabine plus doxorubicin is also an option [64].
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 [21].	High, very aggressive. Median survival 30 months [65].	Surgery. Response to targeted therapies is poor [66].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait.	High, very aggressive, median survival is five months [65].	Surgery. Different chemotherapy regimens, radiosensitive.
Translocation RCC (TRCC) Xp11.2	Rare, mainly younger patients < 40, more common in females. Less commonly, *TFEB* located on the short arm of chromosome 6 (6p21) [67].	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 [17].	High	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.	Variable	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 [68, 69].	Benign	Observation (when histologically confirmed) [62, 63, 70]. NSS.

Renal cysts	Simple cysts are frequently occurring, while occurring septa, calcifications and solid components require follow-up and/or management.	Malignant or benign	Treatment or follow-up Recommendation based on Bosniak classification. See table 5.1

3.4.7 **Cystic renal tumours**

Cystic renal lesions are classified according to the Bosniak classification (see Section 5.2.5). Bosniak I and II cysts are benign lesions which do not require follow up [71]. Bosniak IV cysts are mostly malignant tumours with pseudocystic changes only. Bosniak IIF and III cysts remain challenging for clinicians. The differentiation of benign and malignant tumour in categories IIF/III is based on imaging, mostly CT, with an increasing role of MRI and contrast enhanced ultrasound (CEUS). Computed tomography shows poor sensitivity (36%) and specificity (76%; κ [kappa coefficient] = 0.11) compared with 71% sensitivity and 91% specificity (κ = 0.64) for MRI and 100% sensitivity and 97% specificity for CEUS (κ = 0.95) [72]. Surgical and radiological cohorts pooled estimates show a prevalence of malignancy of 0.51 (0.44-0.58) in Bosniak III and 0.89 (0.83-0.92) in Bosniak IV cysts, respectively. In a SR, less than 1% of stable Bosniak IIF cysts showed malignancy during follow-up. Twelve percent of Bosniak IIF cysts had to be reclassified to Bosniak III/IV during radiological follow-up, with 85% showing malignancy, which is comparable to the malignancy rates of Bosniak IV cysts [71]. The updated Bosniak classification strengthens the classification and includes MRI diagnostic criteria [73].

The most common histological type for Bosniak III cysts is ccRCC with pseudocystic changes and low malignant potential [74, 75]; multilocular cystic renal neoplasm of low malignant potential ([MCRNLMP], formerly mcRCC (see Section 3.2 and Table 3.1); pRCC type I (very low malignant potential); benign multilocular cyst; benign group of renal epithelial and stromal tumours (REST); and other rare entities. Surgery in Bosniak III cysts will result in overtreatment in 49% of the tumours which are lesions with a low malignant potential. In view of the excellent outcome of these patients in general, a surveillance approach may also be an alternative to surgical treatment [71, 73, 76, 77].

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

Summary of evidence	LE
A variety of renal tumours exist of which approximately 15% are benign.	1b
Recent histological work up of Bosniak III cysts shows low risk of malignant potential.	2

3.6 Recommendations for the management of other renal tumours

Recommendations	Strength rating
Treat Bosniak type III cysts the same as RCC or offer active surveillance.	Weak
Treat Bosniak type 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); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate; • persistent pain or acute or repeated bleeding episodes.	Weak
Offer systemic therapy to patients at need for therapy with surgically unresectable AMLs not amendable to embolisation or surgery.	Weak
Prior to management, perform pre-operative renal mass biopsies in patients with unclear kidney lesions.	Weak
Offer active surveillance to patients with biopsy-proven oncocytomas, as an acceptable alternative to surgery or ablation.	Weak
Only offer radical nephrectomy to patients with localised renal medullary carcinoma after a favourable response to systemic therapy.	Weak
Base systemic therapy for renal medullary carcinoma on chemotherapy regiments containing cisplatinum such as cisplatin plus gemcitabine.	Weak

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 [17, 79]. A supplement was published in 2012, 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].
- 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]

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		
pTNM 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 anatomic classification systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the R.E.N.A.L. nephrometry score, 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 [88-90]. 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 PN and tumour ablation series. However, when selecting the most optimal treatment option, anatomic scores must 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, 91] (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 [36, 92] (LE: 3). Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs [93] (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [94] (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 [95], 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 [96, 97] (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   maging investigations
Most renal tumours are diagnosed by abdominal US or CT performed for other medical reasons [91] (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 [98] (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 [99-101] (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 [102] (LE: 3). Computed tomography or MRI allows accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free

AML from malignant renal neoplasms [68, 103-105] (LE: 3). Abdominal CT provides information on [106]:
- function and morphology of the contralateral kidney [107] (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 when detailed information on the renal vascular supply is needed [108, 109]. If the results of CT are indeterminate, 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 [110-113] (LE: 3).
Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [111, 114] (LE: 3). Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored for renal mass assessment [115].

For the diagnosis of complex renal cysts (Bosniak IIF-III) MRI may be preferable. The accuracy of CT is limited in these cases, with poor sensitivity (36%) and specificity (76%; κ = 0.11); MRI had 71% sensitivity and 91% specificity (κ = 0.64). Contrast-enhanced US showed high sensitivity (100%) and specificity (97%), with a negative predictive value of 100% (κ = 0.95) [72].
In younger patients who are worried about the radiation exposure of frequent CT scans, MRI may be offered as alternative although only limited data exist correlating diagnostic radiation exposure to the development of secondary cancers [116].

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 [96, 97] (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 system classifies renal cysts into five categories, based on CT imaging appearance, to predict malignancy risk [125, 126] (LE: 3), and also advocates treatment for each category (Table 5.1). A new updated Bosniak classification has been proposed that strengthens the classification and includes MRI diagnostic criteria [73].

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 intra-renal, 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 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). A multicentre study assessing 542 surgically removed small renal masses showed that the likelihood of benign findings at pathology is significantly lower in centres where biopsies are performed (5% vs. 16%), suggesting that biopsies can reduce surgery for benign tumours and the potential for short-term and long-term morbidity associated with these procedures [133].

Percutaneous sampling can be performed under local anaesthesia with needle core biopsy and/ or fine needle aspiration (FNA). Biopsies can be performed under US or CT guidance, with a similar diagnostic yield [130, 134] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [127, 131, 135] (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 are preferred for the characterisation of solid renal masses while a combination with FNA can improve accuracy [136-138] (LE: 2a). An SR and meta-analysis of the diagnostic performance and complications of renal tumour biopsy was performed by the Panel. Fifty-seven articles with 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 [138]. Other studies showed that solid pattern, larger tumour size and exophytic location are predictors of a diagnostic core biopsy [127, 130, 134] (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 [138] (LE: 2b). However, 0-22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [128-132, 134, 135, 139] (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, 140-142].

Accuracy of renal tumour biopsies for the diagnosis of tumour histotype is good. The median concordance rate between tumour histotype on renal tumour biopsy and on the surgical specimen of the following PN or RN was 90.3% in the pooled analysis [138].

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 vs. low grade) [138] (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, 143, 144] (LE: 2b). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [145] (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 [146].

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, 138] (LE: 2b).

Combined FNA and core biopsies can provide complementary results, especially for complex cystic lesions [131, 139, 140, 147, 148] (LE: 3).

Overall, percutaneous biopsies have a low morbidity [138]. Tumour seeding along the needle tract has been regarded as anecdotal in large series and pooled analyses on renal tumour biopsies. Especially the coaxial technique has been regarded as a safe method to avoid any seeding of tumour cells. However, authors recently reported on 7 patients in whom tumour seeding was identified on histological examination of the resection specimen after surgical resection of RCC following diagnostic percutaneous biopsy [149]. Six of the 7 cases were of the pRCC type. The clinical significance of these findings is still uncertain but only one of these patients developed local tumour recurrence at the site of the previous biopsy [149].

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 [138].

Percutaneous biopsy of renal hilar masses is technically feasible with a diagnostic yield similar to that of cortical masses, but with significantly higher post-procedural bleeding compared with cortical masses [150].

5.4 Summary of evidence and recommendations for the diagnostic assessment of RCC

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 mRCC.	2
Magnetic resonance imaging has a slightly higher sensitivity and specificity for small cystic renal masses and tumour thrombi as compared to CT.	2
Contrast enhanced ultrasound has a high sensitivity and specificity for characterisation of renal masses.	2
Ultrasound, power-Doppler US and positron-emission tomography CT have a low sensitivity and specificity for detection and characterisation of RCC.	2

Recommendations	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Use magnetic resonance imaging to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, mainly contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses.	Strong
Do not routinely use bone scan and/or positron-emission tomography CT for staging of renal cell carcinoma.	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 considering 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.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation of solid renal tumours.	Strong

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 [151] (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 [152, 153]. Fuhrman nuclear grade is the most widely accepted grading system [154]. Although affected by intra- and inter-observer variability, Fuhrman nuclear grade is an independent prognostic factor [155]. A simplified two- or three-strata system may be as accurate for prognostication as the classical four-tiered grading scheme [156, 157] (LE: 3). The new WHO/ISUP grading system that will replace the Fuhrman grading, needs to be validated for prognostic systems and nomograms [158].

In a univariate analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [159, 160]. However, prognostic information provided by the RCC type is lost when stratified to tumour stage [20, 160] (LE: 3). In a cohort study of 1,943 patients with ccRCC and pRCC significant survival differences were shown, whereas pRCC type I displayed a significantly reduced risk of death compared with ccRCC and pRCC type II [161]. 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 [20, 21, 162]

Type	Percentage of RCC (~)	Advanced disease at diagnosis (T3-4, N+, M+)	Fuhrman grade 3 or 4 [163]	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.
CSS = cancer-specific survival; HR = hazard ratio.

In all RCC types, prognosis worsens with stage and histopathological grade (Tables 6.2 and 6.3). The 5-year overall survival (OS) for all types of RCC is 49%, which has improved since 2006 probably due to an increase in incidentally detected RCCs and the introduction of TKIs [164, 165]. 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 [21]

Grade	HR (95% CI)
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 [162] (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 [166]. Type I have a favourable prognosis. Type II are mostly high-grade tumours with a propensity for metastases (LE: 3). For more details, see Section 3.2 - Histological diagnosis. Renal cell carcinoma with Xp 11.2 translocation has a poor prognosis [167]. Its incidence is low, but it should be systematically addressed in young patients. Renal cell carcinoma type classification has been confirmed by cytogenetic and genetic analyses [163, 168, 169] (LE: 2b).

6.4 Clinical factors
Clinical factors include performance status (PS), local symptoms, cachexia, anaemia, platelet count, neutrophil-to-lymphocyte ratio, C-reactive protein (CRP) and albumin [94, 170-174] (LE: 3). Even though obesity is an aetiological factor for RCC, obesity has also been observed to provide prognostic information. In a Korean cohort study, obesity appeared to be a favourable prognostic factor in male, but not in female, patients with non-metastatic RCC [175].

6.5 Molecular factors
Numerous molecular markers such as carbonic anhydrase IX (CaIX), VEGF, hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, p21 [176], PTEN (phosphatase and tensin homolog) cell cycle, E-cadherin, osteopontin [177] CD44 (cell adhesion) [178, 179], CXCR4 [180], and other cell cycle and proliferative markers are being investigated [181, 182] (LE: 3). As yet, none of these markers have been shown to improve the predictive accuracy of current prognostic systems and, so far, none have been externally validated. Their routine use in clinical practice is, at present, not recommended. In a pre-diagnostic study, elevated plasma Kidney Injury molecule-1 (KIM-1) concentrations were found to predict RCC up to 5 years prior to diagnosis and were associated with a shorter survival time [183]. KIM-1 is a protein which is expressed at low levels in a healthy kidney.

Several retrospective studies and large molecular screening programs 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 [184-186]. These published reports suggest that patients with *BAP1*-mutant tumours have worse outcomes compared with patients with *PBRM1*-mutant tumours [185]. Validated data from surgical series can predict relapse using a 16-gene signature. This signature is likely to be adopted in clinical trials and may be helpful in the clinical setting in due time [187].

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. A meta-analysis established a correlation between PD-L1 expression, poor prognosis and advanced clinicopathological features of RCC [188]. 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 [189, 190]. 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 [191-197]. 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, allowing all new predictive parameters to be objectively evaluated. Before being adopted, new prognostic variables or systems should demonstrate that its predictive accuracy is superior to conventional post-operative prognostic schemes [198]. Recently, new pre-operative nomograms with excellent predictive accuracy have been designed [199, 200].

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 [201].	2

Recommendations	Strength rating
Use the current Tumour, Node, Metastasis classification system.	Strong
Use grading systems and classify renal cell carcinoma type.	Strong
Use prognostic systems in the metastatic setting.	Strong
In localised disease, use integrated prognostic systems or nomograms to assess risk of recurrence.	Strong

Table 6.4: Anatomical, histological, and clinical variables in the commonly used prognostic models for localised and metastatic RCC

Prognostic Models	Variables	TNM Stage [151]	ECOG PS [202]	Karnofsky PS [203]*	RCC related symptoms	Fuhrman grade [154]**	Tumour necrosis	Tumour size	Delay between diagnosis and treatment	LDH	Corrected calcium	Haemoglobin	Neutrophil count	Platelet count
Localised RCC	UISS [192]***	x	x											
	SSIGN [193]	x				x	x	x						
	Post-operative Karakiewicz's nomogram [196]	x			x	x		x						
Metastatic RCC	MSKCC prognostic system [204]****			x					x	x	x	x		
	IMDC [205]			x					x		x	x	x	x

ECOG-PS = Eastern Cooperative Oncology Group - performance status (see details; Section 7.4.2.1, Table 7.1); IMDC = International Metastatic Renal Cancer Database Consortium; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status; SSIGN = Stage Size Grade Necrosis; TNM = Tumour, Node Metastasis (classification); UISS = University of California Los Angeles integrated staging system.

*Karnofsky score calculator: https://www.thecalculator.co/health/Karnofsky-Score-for-Performance-Status-Calculator-961.html

**Fuhrman nuclear grade: https://www.mdcalc.com/fuhrman-nuclear-grade-clear-cell-renal-carcinoma

***UISS: https://qxmd.com/calculate/calculator_170/prognosis-in-renal-cell-carcinoma-uiss

****MSKCC: https://www.mdcalc.com/memorial-sloan-kettering-cancer-center-mskcc-motzer-score-metastatic-renal-cell-carcinoma-rcc

7.   DISEASE MANAGEMENT

7.1   Treatment of localised RCC

7.1.1   *Introduction*

Sections 7.1.2 and 7.2.4.2 are underpinned by a SR which includes all relevant published literature comparing surgical management of localised RCC (T1-2N0M0). 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. Historically, surgery has been the benchmark for the treatment of localised RCC.

7.1.2   *Surgical treatment*

7.1.2.1   *Nephron-sparing surgery versus radical nephrectomy*

Most studies comparing the oncological outcomes of PN and RN are retrospective and include cohorts of varied and, overall, limited size [206]. There is only one prospective RCT including patients with organ-confined RCCs of limited size (< 5 cm), showing comparable CSS for PN vs. RN [207]. Partial nephrectomy demonstrated to preserve kidney function better after surgery, thereby potentially lowering the risk of development of cardiovascular disorders [206, 208-212].

When compared with a radical surgical approach, several retrospective analyses of large databases have suggested a decreased cardiovascular-specific mortality [209, 213] as well as improved OS for PN 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 [214, 215].

A Cochrane review found that PN for clinically localised RCC was associated with a reduced time-to-death of any cause compared to RN, whereas serious adverse event rates, CSS and time-to-recurrence were similar between the two groups [216].

An analysis of the Medicare database [217] 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 who underwent PN for RCC with a non-cancer healthy control group via a retrospective database analysis; showing an OS benefit for the cancer cohort [218]. These conflicting results may be an indication 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 did not demonstrate an inferiority of RN vs. PN in terms of OS [207]. Taken together, the OS advantage suggested for PN vs. RN remains an unresolved issue.

Patients with a normal pre-operative renal function and a decreased GFR due to surgical treatment (either RN or PN), generally present with stable long-term renal function [212]. 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 chronic kidney disease (CKD) [219]. However, in particular in patients with pre-existing CKD, PN is the treatment of choice to limit the risk of development of ESRD 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 [220, 221].

In terms of the intra- and peri-operative morbidity/complications associated with PN vs. RN, an EORTC randomised trial showed that PN for small, easily resectable, incidentally discovered RCC, in the presence of a normal contralateral kidney, can be performed safely with slightly higher complication rates than after RN [221].

In view of the above, and since oncological safety (CSS and RFS) of PN has been proven to be similar for RN, PN is the treatment of choice for T1 RCC since it preserves kidney function better and in the long term potentially limits the incidence of 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 ESRD and the need for haemodialysis.

A study compared the survival outcomes in patients with larger (≥ 7 cm) ccRCC treated with PN vs. RN with long-term follow-up (median 102 months). Compared to the RN group, the PN group had a significantly longer

median OS (p = 0.014) and median CSS (p = 0.04) [222]. A SR and meta-analysis of comparative studies of PN vs. RN for cT1b and T2 RCCs observed that the PN group had a lower likelihood of tumour recurrence (OR 0.6, p < 0.001), cancer-specific mortality (OR 0.58, p = 0.001), and all-cause mortality (OR 0.67, p = 0.005) compared to the RN group. For T2 tumours the estimated blood loss was higher for PN (p < 0.001), as was the likelihood of complications (RR: 2.0, p < 0.001). Both the recurrence rate (RR: 0.61, p = 0.004) and cancer-specific mortality (RR: 0.65, p = 0.03) were lower for PN [223].

7.1.2.2   Associated procedures
7.1.2.2.1   Adrenalectomy
One prospective NRS compared the outcomes of RN with or without, ipsilateral adrenalectomy [224]. Multivariate analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at 5 or 10 years was seen with, or without, adrenalectomy. Adrenalectomy was justified using criteria based on radiographic- and intra-operative findings. Only 48 of 2,065 patients underwent concurrent ipsilateral adrenalectomy of which 42 interventions were for benign lesions [224].

7.1.2.2.2   Lymph node dissection for clinically negative lymph nodes (cN0)
The indication for LN dissection (LND) together with PN or RN is still controversial [225]. The clinical assessment of LN status is based on the detection of an enlargement of LNs either by CT/MRI or intraoperative palpability of enlarged nodes. Less than 20% of suspected metastatic nodes (cN+) are positive for metastatic disease at histopathological examination (pN+) [226]. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [227]. For clinically positive LNs (cN+) see Section 7.2.2.

Smaller retrospective studies have suggested a clinical benefit associated with a more or less extensive LND preferably in patients at high risk for lymphogenic spread. In a large retrospective study, the outcomes of RN with or without LND in patients with high-risk non-metastatic RCC were compared using a propensity score analysis. In this study LND was not significantly associated with a reduced risk of distant metastases, or cancer-specific or all-cause mortality. Neither eLND nor the extent of LND was associated with improved oncologic outcomes [228]. The number of LN metastases (< / > 4) as well as the intra- and extracapsular extension of intra-nodal metastasis correlated with the patients´ clinical prognosis in some studies [227, 229-231]. 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 Surveillance, Epidemiology and End Results (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 [232]. However, in patients with pathologically proven lymphogenic spread (pN+), an increase of 10 for the number of nodes dissected resulted in a 10% absolute increase in DSS. In addition, in a larger cohort of 1,983 patients, Capitanio *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) [233]. As to morbidity related to eLND, a recent retrospective propensity score analysis from a large single-centre database showed that eLND is not associated with an increased risk of Clavien grade ≥ 3 complications. Furthermore, LND was not associated with length of hospital stay or estimated blood loss [234].

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%, the risk of lymphatic spread appears to be very low. Recognising the latter, only a staging effect was attributed to LND [226]. 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 underwent a complete LND. The LN template used by the authors was also not clearly stated.
            The optimal extent of LND 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 [227, 235, 236]. At least 15 LNs should be removed [233, 237]. Sentinel LND is an investigational technique [238, 239].

7.1.2.2.3   Embolisation
Before routine nephrectomy, tumour embolisation has no benefit [240, 241]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [242, 243]. These indications will be revisited 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 for the treatment of localised RCC

Summary of evidence	LE
The oncological outcome in terms of OS following PN equals that of RN in patients with c/p T1 RCC.	1b
Ipsilateral adrenalectomy during RN or PN has no survival advantage in the absence of clinically evident adrenal involvement.	3
In patients with localised disease without evidence of LN metastases, a survival advantage of LND in conjunction with RN is not demonstrated in randomised trials.	2b
Retrospective studies suggest a clinical benefit associated with lymphadenectomy in high-risk patients.	2b
In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.	3

Recommendations	Strength rating
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
Offer an extended lymph node dissection to patients with adverse clinical features, including a large diameter of the primary tumour.	Weak
Offer embolisation to patients unfit for surgery presenting with massive haematuria or flank pain.	Weak

7.1.3   *Radical and partial nephrectomy techniques*
7.1.3.1   *Radical nephrectomy techniques*
No RCTs have assessed the oncological outcomes of laparoscopic vs. open RN. A cohort study [244] and retrospective database reviews are available, mostly of low methodological quality, showing similar oncological outcomes even for higher stage disease and locally more advanced tumours [245-247]. Based on a SR, less morbidity was found for laparoscopic vs. open RN [206].

Data from one RCT [246] and two NRSs [248, 249] 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 [249]. 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 3 studies [246, 248, 249]. 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 [248].

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 [247, 249, 250]. Intra-operative and post-operative complications were similar in the two groups and no significant differences in CSS, PFS and OS were reported [247, 249, 250] (LE: 2b). Another multi-centre propensity matched analysis compared laparoscopic- and open surgery for pT3a RCC, showing no significant difference in 3-year RFS between groups [251]. The best approach for RN was the retroperitoneal or transperitoneal approach with similar oncological outcomes in two RTCs [251, 252] and one quasi-randomised study [253]. Quality of life variables were similar for both approaches.

Hand-assisted vs. standard laparoscopic RN was compared in one quasi-randomised study [253] and one database review and estimated 5-year OS, CSS, and RFS rates were comparable [254]. 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 [253, 254]. However, the sample size was small.

A SR reported on robot-assisted laparoscopic vs. conventional laparoscopic RN, showing no substantial differences in local recurrence rates, nor in all-cause cancer-specific mortality [255]. Similar results were seen in observational cohort studies comparing 'portless' and 3-port laparoscopic RN, with similar peri-operative outcomes [256, 257].

7.1.3.2   *Partial nephrectomy techniques*
Studies comparing laparoscopic and open PN found no difference in PFS [258-261] and OS [260, 261] in centres with laparoscopic expertise. However, the oncological safety of laparoscopic vs. open PN has, so far,

only been addressed in studies with relatively limited follow-up. Gill *et al.* suggested comparable oncological efficacy even in case of higher stage tumours (pT1b/pT3a). However, the higher number of patients treated with open surgery in this series might reflect a selection bias by offering laparoscopic surgery in case of a less complex anatomy [262]. The mean estimated blood loss was found to be lower with the laparoscopic approach [258, 260, 263], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events were similar [258, 260]. Operative time is generally longer with the laparoscopic approach [259-261] and warm ischaemia time is shorter with the open approach [258, 260, 263, 264]. In a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [261], 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 [264]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [265]. Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [266].

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. Three months after the operation, glomerular filtration rate was lower in the HALPN than in the open PN group [267].

The feasibility of laparo-endoscopic single-site PN has been shown in selected patients but larger studies are needed to confirm its safety and clinical role [268].

In a retrospective propensity-score-matched study, comparing open-, laparoscopic- and robot-assisted PN, with 5 years of median follow-up, similar rates of local recurrence, distant metastasis and cancer-related death rates were found [269].

One 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 in creatinine levels and pathologic margins were similar among the groups [270]. Another study included the 50 last patients having undergone laparoscopic and robotic PN for T1-T2 renal tumours by two different surgeons with an experience of over 200 procedures each in laparoscopic and robotic PN and robotic-assisted partial nephrectomy (RAPN), respectively, at the beginning of the study. Peri-operative and short-term oncological and functional outcomes appeared broadly comparable between RAPN and LPN when performed by highly experienced surgeons [271].

A multicentre French prospective database compared the outcomes of 1,800 patients who underwent open PN and robot-assisted PN. Although the follow-up was shorter, there was a decreased morbidity in the robotic-assisted PN group with less overall complications, less major complications, less transfusions and a much shorter hospital stay [272].

A 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 hospital 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 [273].

In a recent analysis of 8,753 patients who underwent PN, an inverse non-linear relationship of hospital volume with morbidity of PN was observed, with a plateauing seen at 35 to 40 cases per year overall, and 18 to 20 cases for the robotic approach [274]. A retrospective study of a U.S. National Cancer Database looked at the prognostic impact of hospital volume and the outcomes of robot-assisted PN, including 18,724 cases. This study shows that undergoing RAPN at higher-volume hospitals may have better peri-operative outcomes (conversion to open and length of hospital stay) and lower positive surgical margin rates [275]. A French study, including 1,222 RAPN, has shown that hospital volume is the main predictive factor of Trifecta achievement after adjustment for other variables, including surgeon volume [276].

7.1.3.3 Positive margins on histopathological specimens of resected tumours

A positive surgical margin is encountered in about 2-8% of PNs [273]. Studies comparing surgical margins with different surgical approaches (open, laparoscopic, robotic) are inconclusive [277, 278]. Most trials showed that intra-operative frozen section analysis had no influence on the risk of definite positive surgical margins [279]. A positive surgical margin status occurs more frequently in cases in which surgery is imperative (solitary kidneys and bilateral tumours) and in patients with adverse pathological features (pT2a, pT3a, grade III-IV) [280-283]. The potential negative impact of a positive margin status on the oncologic outcome is still controversial [277].

The majority of retrospective analyses reported so far indicated that positive surgical margins do not translate into a higher risk of metastases or a decreased CSS [281, 282]. On the other hand, another retrospective study of a large single institutional series showed that positive surgical margins are an independent predictor of PFS due to a higher incidence of distant and local relapses [284].

However, only a proportion of patients with an uncertain margin status actually harbour residual malignancy [285]. Local tumour bed recurrences were found in 16% in patients with positive surgical margins compared with 3% in those with negative margins [280], Therefore, RN or re-resection of margins can result in overtreatment in many cases. Patients with positive surgical margins should be informed that they will need a more intense surveillance (imaging) follow-up and that they are at increased risk of secondary local therapies [281, 286]. On the other hand, protection from recurrence is not ensured by negative surgical margins [287].

7.1.3.4   Summary of evidence and recommendations for radical and partial nephrectomy techniques

Summary of evidence	LE
Laparoscopic radical nephrectomy (RN) has lower morbidity than open nephrectomy.	1b
Short-term oncological outcomes for T1-T2a tumours are equivalent for laparoscopic and open RN.	2a
Partial nephrectomy can be performed, either by 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 to RN.	3

Recommendations	Strength rating
Offer laparoscopic radical nephrectomy (RN) to patients with T2 tumours and localised masses not treatable by partial nephrectomy (PN).	Strong
Do not perform minimally invasive RN in patients with T1 tumours for whom a PN is feasible by any approach, including open.	Strong
Do not perform minimally invasive surgery if this approach may compromise oncological-, functional- and peri-operative outcomes.	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 [217, 288, 289]. However, the patients assigned to the surveillance arm were older and likely to be frailer and less suitable for surgery. Other-cause mortality rates in the non-surgical group significantly exceeded that of the surgical group [288]. Analyses of older patients (> 75 years) failed to show the same benefit in cancer-specific mortality for surgical treatment [290-292].

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 [293, 294]. 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 [295]. 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 [296, 297].

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, a multi-variate analysis, management type was not associated with OS after adjusting for age, comorbidity, and other variables [293]. 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 [298].

Results from the multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry were recently published [299]. This prospective NRS enrolled 497 patients with solid renal masses < 4 cm who selected either AS or primary active intervention. Patients who selected AS were older, had worse ECOG scores, more comorbidities, smaller tumours, and more often had multiple and bilateral lesions. In patients who elected AS in this study the overall median small renal mass growth rate was

0.09 cm/year with a median follow-up of 1.83 years. The growth rate and variability decreased with longer follow-up. No patients developed metastatic disease or died of RCC [300].

Overall survival for primary intervention and AS was 98% and 96% at 2 years, and 92% and 75% at 5 years, respectively (p = 0.06). At 5 years, CSS was 99% and 100%, respectively (p = 0.3). Active surveillance was not predictive of OS or CSS in regression modelling with relatively short follow up [299]. Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/ or comorbidities, AS is appropriate for initially monitoring small renal masses, followed, if required, by treatment for progression [295-297, 301-304].

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 [305].

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 [306-308]. One comparative study reported similar OS, CSS, and RFS in 145 laparoscopic patients with a longer follow up compared with 118 patients treated percutaneously with a shorter follow up [307]. A shorter average length of hospital stay was found with the percutaneous technique [307-309].

A recent systematic review including 82 articles reported complication rates ranging between 8 and 20% with most complications being minor [310]. 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, disease-free survival (DFS), local recurrence or progression to metastatic disease [311, 312], with some showing significant benefit for the PN techniques for some or all of these outcomes [313-316]. 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 [311-313], whilst also finding no differences in other peri-operative outcomes such as recovery times, complication rates or post-operative serum creatinine levels. Two studies [315, 316] 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 [314-316]. Estimates of new CKD were also mixed, with one study in favour of cryoablation [314], another strongly in favour of PN [315], and the third showing no difference [316]. One study compared PN with ablation therapy, either cryoablation or RFA [317], and showed significantly improved DSS at both 5 and 10 years for PN.

A 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 [214].

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 [318-321]. 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 found a higher rate of incomplete ablation in patients treated by percutaneous RFA [320]. 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. Some studies retrospectively compared RFA to surgery in patients with T1a tumours [322-324].

One study compared T1a patients who underwent either RFA (percutaneous or laparoscopic) or PN and found no difference in OS and CSS [298]. Another study retrospectively reviewed 105 T1a patients treated

by percutaneous RFA or RN. Cancer-specific survival was 100% in both groups [322]. Overall survival was lower in the RFA group but patients treated with surgery were younger [322].

A retrospective evaluation comparing RFA with LPN concluded after a median follow-up time of 27.5 months that both methods achieved equivalent secondary efficacy rates. Radiofrequency ablation included several treatment sessions, but session and hospitalisation times were shorter, and complications were less frequent than for LPN. The differences remained after adjustment for renal tumour complexity [325].

A meta-analysis reported comparable complication rates and post-operative estimated glomerular filtration rates (eGFR) between RFA and PN [326]. 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.

A retrospective analysis of 264 patients treated with either percutaneous RFA or PN and a median follow up of 78 months showed that T1b ccRCC patients have less favourable outcomes for percutaneous RFA as compared to PN. However, percutaneous RFA provides comparable oncological outcomes to PN in patients with T1b non-ccRCC. The authors conclude that it may be necessary to take RCC subtypes into consideration when selecting either PN or percutaneous RFA as a surgical approach to treat T1b RCC [327].

A recent large systematic review and meta-analysis including 3,974 patients who had undergone an ablative procedure (RFA or cryoablation) or PN showed higher all-cause mortality and cancer-specific mortality rates for ablation than for PN (HR: 2.11 and 3.84, respectively). No statistically significant difference in local recurrence rates or risk of metastasis was seen. Complication rates were lower for ablation than for PN (13% vs. 17.6%, $p < 0.05$). A significantly greater decrease in eGFR was observed after PN vs. ablation therapy [328].

7.1.4.3.5 Cryoablation and thermal ablation versus deferred therapy

An analysis of the SEER registry included 733 patients with histopathologically confirmed localised T1a ccRCC who either received cryosurgery (n = 315) or thermal ablation (n = 155), as well as patients who had deferred therapy (n = 263) [329]. Patients treated with cryosurgery and thermal ablation had a statistically significant CSS benefit compared to those who had deferred therapy (cryosurgery HR: 0.25, 95% CI: 0.14–0.45, $p < 0.001$; thermal ablation HR: 0.27, 95% CI: 0.13–0.55, $p < 0.001$, after adjustment for age at diagnosis, tumour grade, and size).

However, in a systematic review and meta-analysis of 99 studies representing 6,471 small renal lesions, no statistical differences were detected in the incidence of metastatic progression regardless of whether the lesions were excised, ablated with cryotherapy or radiofrequency or observed [330].

7.1.4.3.6 Cryoablation versus radiofrequency ablation

Two studies compared RFA and cryoablation [331, 332]. No significant differences were reported for OS, CSS, or RFS in either study. For local RFS at 5 years, one study [331] reported improvement with RFA, while the other [332] reported a benefit with cryoablation. One study [331] reported no differences in Clavien complication rates between the techniques.

A recent retrospective series including 384 patients (mean age 71 years; range 22-88 years) evaluated the peri-operative outcomes of thermal ablation with microwave, RFA, and cryoablation for stage T1c RCC. Complication rates and immediate renal function changes were similar among the three ablation modalities. Microwave ablation was associated with a significantly decreased ablation time ($p < 0.05$), procedural time ($p < 0.05$), and dosage of sedative medication ($p < 0.05$) compared with RF ablation and cryoablation. The authors conclude that CT-guided percutaneous microwave ablation is comparable to RF ablation or cryoablation for the treatment of stage T1N0M0 RCC with regard to treatment response and is associated with shorter treatment times and less sedation than RF ablation or cryoablation [333].

7.1.4.3.7 Other ablative techniques

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

7.1.4.3.8   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	Strength rating
Offer active surveillance, radiofrequency ablation or cryoablation to frail and/or comorbid patients with small renal masses.	Weak
When radiofrequency ablation, cryoablation and active surveillance are offered, inform patients about the higher risk of local recurrence and/or tumour progression.	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 [23]. However, the extent of LND remains controversial [227]. A systematic review and meta-analysis attempted to evaluate the role of retroperitoneal LND in non-metastatic and mRCC [334]. The review included several studies which recruited patients at high risk of LN metastases, including cN1 patients. Lymph node dissection was not associated with any survival benefit.

However, LND may provide additional staging information. A recent analysis also indicates that LND is not associated with improved oncologic outcomes in patients with radiographic lymphadenopathy (cN1) and across increasing probability thresholds of pN1 disease [228].

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 [242, 243, 335]. The use of systemic 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 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 [336-344]. However, uncertainties remain as to the best approach for surgical treatment of these patients.

7.2.4.1   The evidence base for surgery in patients with venous tumour thrombus
Data whether patients with venous tumour thrombus should undergo surgery is derived from case series only. In one of the largest published studies a higher level of thrombus was not associated with increased tumour dissemination to LNs, perinephric fat or distant metastasis [341]. 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. The surgical technique and approach for each case should be selected based on the extent of tumour thrombus.

7.2.4.2   The evidence base for different surgical strategies
A systematic review was undertaken which included only comparative studies on the management of venous tumour thrombus in non-metastatic RCC [345, 346]. Only 5 studies were eligible for final inclusion, with high risk of bias across all studies.

Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [347, 348]. Pre-operative embolisation was associated with increased operating time,

blood loss, hospital stay and peri-operative mortality in patients with T3 RCC [349]. 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 [350].

No surgical method was shown to be superior for the excision of venous tumour thrombus. The surgical method selected depended on the level of tumour thrombus and the grade of occlusion of the IVC [345, 347, 348, 350]. 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 (LNs), the survival benefit of LN dissection is unproven but LN dissection adds 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	Strength rating
In patients with clinically enlarged lymph nodes (LNs), perform LN dissection for staging purposes or local control.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	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 [351-355] (LE: 1b). Results from prior adjuvant trials studying interferon-alpha (IFN-α) and interleukin-2 (IL-2) did not show a survival benefit [356]. Heat shock protein-peptide complex-96 (vitespen) may have a benefit in a subgroup of patients but the overall data from phase III trials were negative [357]. A similar observation was made in an adjuvant trial of girentuximab, a monoclonal antibody against carboanhydrase IX (CAIX) (ARISER Study) [358]. 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 trials investigating adjuvant sunitinib, sorafenib or pazopanib have reported whilst studies investigating sorafenib, axitinib and everolimus have completed accrual and are expected to report in the next years.

At present, there is no OS data supporting the use of adjuvant VEGFR or mTOR inhibitors. Thus far, three RCTs comparing VEGFR-TKI vs. placebo have been published. One of the largest adjuvant trials compared sunitinib vs. sorafenib vs. placebo (ASSURE). Its interim results published in 2015 demonstrated no significant differences in DFS or OS between the experimental arms and placebo [359]. The study published its updated analysis on a subset of high-risk patients in 2018, which demonstrated 5-year DFS rates of 47.7%, 49.9%, and 50.0%, respectively for sunitinib, sorafenib, and placebo (HR: 0.94 for sunitinib vs. placebo; and HR: 0.90, 97.5% CI: 0.71-1.14 for sorafenib vs. placebo), and 5-year OS of 75.2%, 80.2%, and 76.5% (HR: 1.06, 97.5% CI: 0.78-1.45, p = 0.66, sunitinib vs. placebo; and HR: 0.80; 97.5% CI: 0.58-1.11, p = 0.12 for sorafenib vs. placebo). The results indicated that adjuvant therapy with sunitinib or sorafenib should not be given [360].

The PROTECT study included 1,135 patients between pazopanib (n = 571) and placebo (n = 564) in a 1:1 randomisation [361]. The primary endpoint was amended after 403 patients were included on pazopanib 800 mg vs. placebo, to DFS with pazopanib 600 mg. The primary analysis results of DFS in the intention to treat (ITT) pazopanib 600 mg arm were not significant (HR: 0.86; 95% CI: 0.7-1.06, p = 0.16). Disease-free survival in the ITT pazopanib 800 mg population was improved (HR: 0.69; 95% CI: 0.61 0.94, 1.06, p = 0.02). No benefit in OS was seen in the ITT pazopanib 600 mg population (HR: 0.79 [0.57-1.09, p = 0.16]). A subset analysis of these studies suggests that full-dose therapy is associated with improved DFS. Furthermore, no strong association of DFS with OS has been established for RCC [362, 363].

In contrast, the S-TRAC study included 615 patients randomised to either sunitinib or placebo [364]. The results showed a benefit of sunitinib over placebo for DFS (HR: 0.76; 95% CI: 0.59-0.98, p = 0.03) but data for OS remained immature. 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. The study published its updated

results in 2018; the results for DFS had not changed significantly (HR: 0.74; 95% CI: 0.55-0.99, p = 0.04) and median OS was not reached in either arm (HR: 0.92, 95% CI: 0.66-1.28, p = 0.6).

In summary, there is conflicting data in the three available studies of adjuvant therapy. A recent systematic review and meta-analysis combined the results of all three RCTs [365]. The pooled analysis of VEGFR-TKIs vs. placebo demonstrated that VEGFR-targeted therapy was not statistically significantly associated with improved DFS (HR: 0.92, 95% CI: 0.82-1.03, p = 0.16) nor OS (HR: 0.98, 95% CI: 0.84-1.15, p = 0.84) compared with placebo. The adjuvant therapy group experienced significantly higher odds of grade 3-4 adverse events (OR: 5.89, 95% CI: 4.85-7.15, p < 0.001).

In summary, there is currently a lack of proven benefits of adjuvant therapy with VEGFR-TKIs for patients with high-risk RCC after nephrectomy.

The European Medicines Agency (EMA) has not approved sunitinib for adjuvant treatment of high-risk RCC in adult patients after nephrectomy.

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
After nephrectomy in selected high-risk patients, adjuvant sunitinib improved disease-free survival (DFS) in one of the two available studies, but not overall survival (OS).	1b
Adjuvant sorafenib, pazopanib or axitinib does not improve DFS or OS after nephrectomy.	1b

Recommendations	Strength rating
Do not offer adjuvant therapy with sorafenib, pazopanib or axitinib.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma.	Weak

7.3   Advanced/metastatic RCC
7.3.1   Local therapy of advanced/metastatic RCC
7.3.1.1   Cytoreductive nephrectomy
Tumour resection is potentially curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligometastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary. In a meta-analysis comparing CN+ INF-based immunotherapy vs. INF-based immunotherapy only, increased long-term survival was found in patients treated with CN [366]. However, INF-based immunotherapy is no longer relevant in contemporary clinical practice. In order to investigate the role and sequence of CN in the era of targeted therapy, a structured literature assessment was performed to identify relevant RCTs and systematic reviews published between July 1st - June 30th 2019. Two RCTs [367, 368] and a narrative systematic review were identified [369]. The narrative systematic review included both RCTs and 10 NRSs. CARMENA, a phase III non-inferiority RCT investigating immediate CN followed by sunitinib vs. sunitinib alone, showed that sunitinib alone was not inferior to CN followed by sunitinib with regard to OS [370]. The trial included 450 patients with metastatic ccRCC of intermediate- and MSKCC poor risk of whom 226 were randomised to immediate CN followed by sunitinib and 224 to sunitinib alone. Patients in both arms had a median of two metastatic sites. Patients in both arms had a tumour burden of a median/mean of 140 mL of measurable disease by Response Evaluation Criteria In Solid Tumours (RECIST) 1.1, of which 80 mL accounted for the primary tumour. The study did not reach the full accrual of 576 patients and the Independent Data Monitoring Commission (IDMC) advised the trial steering committee to close the study. In an ITT analysis after a median follow-up of 50.9 months, median OS with CN was 13.9 months vs. 18.4 months with sunitinib alone (HR: 0.89; 95% CI: 0.71-1.10). This was found in both risk groups. For MSKCC intermediate-risk patients (n = 256) median OS was 19.0 months with CN and 23.4 months with sunitinib alone (HR: 0.92; 95% CI: 0.60-1.24) and for MSKCC poor risk (n = 193) 10.2 months and 13.3 months, respectively (HR: 0.86; 95% CI: 0.62-1.17). Non-inferiority was also found in two per-protocol analyses accounting for patients in the CN arm who either did not undergo surgery (n = 16) or did not receive sunitinib (n = 40), and patients in the sunitinib-only arm who did not receive the study drug (n = 11). Median PFS in the ITT population was 7.2 months with CN and 8.3 months with sunitinib alone (HR: 0.82; 95% CI: 0.67-1.00). The clinical benefit rate, defined as disease control beyond 12 weeks was 36.6% with CN and 47.9% with sunitinib alone (p = 0.022). Of note, 38 patients in the sunitinib-only arm required secondary CN due to acute symptoms or for complete or near-complete response. The median time from randomisation to secondary CN was 11.1 months.

The randomised EORTC SURTIME study revealed that the sequence of CN and sunitinib did not affect PFS (HR: [95% CI: 0.88 [0.59-1.37], p = 0.569). The trial accrued poorly and therefore results are mainly exploratory. However, in secondary endpoint analysis a strong OS benefit was observed in favour of the deferred CN approach in the ITT population with a median OS of 32.4 (range 14.5-65.3) months in the deferred CN arm vs. 15.0 (9.3-29.5) months in the immediate CN arm (HR: [95% CI] 0.57 [0.34-0.95], p = 0.032). The deferred CN approach appears to select out patients with inherent resistance to systemic therapy. This confirms previous findings from single-arm phase II studies [371]. Moreover, deferred CN and surgery appears safe after sunitinib which supports the findings, with some caution, of the only available RCT.

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 [372]. These data are confirmed by CARMENA [370].

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 [242, 243, 335] (see recommendations Section 7.1.2.2.4).

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

Summary of evidence	LE
Deferred CN with pre-surgical sunitinib in intermediate-risk patients with cc-mRCC shows a survival benefit in secondary endpoint analyses and selects out patients with inherent resistance to systemic therapy.	2b
Sunitinib alone is non-inferior compared to immediate CN followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with VEGFR-TKI.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3
Patients with MSKCC or IMDC poor risk (≥ 4 risk factors) do not benefit from local therapy.	1a

Recommendations	Strength rating
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform immediate CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI).	Weak
Start systemic therapy without CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.	Weak
Discuss delayed CN in MSKCC intermediate-risk patients under VEGFR-TKI therapy who derive long-term sustained benefit and/or minimal residual metastatic burden.	Weak
Perform immediate CN in patients with good performance who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak

7.3.2 Local therapy of metastases in metastatic RCC
A SR of the local treatment of metastases from RCC in any organ was undertaken [373]. 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 [374]. 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 [375-382]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC metastases in bone, including the spine [383-385], two in the brain [386, 387] and one each in the liver [388] lung [389] and pancreas [390]. Three studies were published as abstracts only [378, 380, 389]. Data were too heterogeneous to meta-analyse. 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
An systematic review, including only 8 studies, compared complete vs. no and/or incomplete metastasectomy of RCC metastases in various organs [375-382]. In one study complete resection was achieved in only 45%

of the metastasectomy cohort, which was compared with no metastasectomy [382]. Non-surgical modalities were not applied. Six studies [376-378, 380-382] 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 [375] showed no significant difference in CSS between complete and no metastasectomy, and one [379] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases in the lung [389], liver [388], and pancreas [390], respectively. The lung study reported a significantly higher median OS for metastasectomy vs. medical therapy only for both target therapy and immunotherapy. Similarly, the liver and pancreas study reported a significantly higher median OS and 5-year OS for metastasectomy vs. no metastasectomy.

7.3.2.2   Local therapies for RCC bone metastases
Of the three studies identified, one compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with RCC bone metastases [385]. Single-dose IGRT (≥ 24 Gy) had a significantly better 3-year actuarial local PFS rate, also shown by Cox regression analysis. Another study compared metastasectomy/curettage and local stabilisation with no surgery of solitary RCC bone metastases in various locations [383]. A significantly higher 5-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 in patients with RCC bone metastases to the spine [384]. 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 [386] compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS and 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 intra-cerebral control were equivalent in patients treated with SRS alone and SRS plus 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 and WBRT in a subgroup analysis of RPA class I showed significantly better 2-year OS and intra-cerebral control for SRS plus WBRT based on only three participants. The other study compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy and conventional radiotherapy or conventional radiotherapy alone [387]. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. One-, two- and 3-year survival rates were higher but not significantly so for FSRT as for metastasectomy and conventional radiotherapy, or conventional radiotherapy alone. Fractionated stereotactic radiotherapy did not result in a significantly better 2-year local control rate compared with metastasectomy plus conventional radiotherapy.

7.3.2.4   Embolisation of metastases
Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss [391]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [392] (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 studies included in the Panel systematic review 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	Strength rating
To control local symptoms, offer ablative therapy, including metastasectomy, to patients with metastatic disease and favourable disease factors and in whom complete resection is achievable.	Weak
Offer stereotactic radiotherapy for clinically relevant bone- or brain metastases for local control and symptom relief.	Weak

7.4 Systemic therapy for advanced/metastatic RCC

7.4.1 Chemotherapy
Chemotherapy has proven to be generally ineffective in the treatment of RCC but can be offered in rare patients, with the exception of collecting duct and medullary carcinoma [393].

7.4.1.1 Recommendation for systemic therapy in advanced/metastatic RCC

Recommendation	Strength rating
Do not offer chemotherapy to patients with metastatic renal cell carcinoma.	Strong

7.4.2 Immunotherapy

7.4.2.1 IFN-α monotherapy and combined with bevacizumab
All studies comparing targeted drugs to IFN-α monotherapy therapy showed superiority for sunitinib, bevacizumab plus IFN-α, and temsirolimus [394-397]. Interferon-α has been superseded by targeted therapy in clear-cell-mRCC (cc-mRCC).

Table 7.1: The Metastatic Renal Cancer Database Consortium (IMDC) risk model [398]*

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 [204].
**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 7-27% [397, 399, 400]. Complete and durable responses have been achieved with high-dose bolus IL-2, however, this can be achieved at less toxicity with immune checkpoint inhibitor combination therapy and IL-2 is no longer widely used.

7.4.2.3 Immune checkpoint blockade
7.4.2.3.1 Immuno-oncology monotherapy
Immune checkpoint blockade with monoclonal antibodies targets and blocks the inhibitory T-cell receptor PD-1 or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-signalling to restore tumour-specific T-cell immunity [401]. Immune checkpoint inhibitor monotherapy has been investigated as second- and third-line therapy. 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 [182]. 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. Progression-free survival does not appear to be a reliable surrogate of outcome for PD-1 therapy in RCC. Currently PD-L1 biomarkers are not used to select patients for this therapy.

There are no RCTs supporting the use of single-agent immune checkpoint blockade in treatment-naïve patients. Randomised phase II data for atezolizumab vs. sunitinib showed a HR of 1.19 (95% CI: 0.82-1.71)

which did not justify further assessment of atezolizumab as single agent as first-line treatment option in this group of patients, despite high complete response rates in the biomarker-positive population [402]. Single-arm phase II data for pembrolizumab from the Keynote-427 trial show high response rates of 38% (up to 50% in PD-L1+ patients), but a PFS of 8.7 months (95% CI: 6.7-12.2) [403]. Based on these results and in the absence of randomised phase III data, single-agent checkpoint inhibitor therapy is not recommended as an alternative in a first-line therapy setting.

7.4.2.4   Immunotherapy/combination therapy
The phase III trial CheckMate 214 (NCT 02231749) showed a superiority of nivolumab and ipilimumab over sunitinib. The primary endpoint population focused on the IMDC intermediate- and poor-risk population where the combination demonstrated an OS benefit (HR 0.63 95% CI: 0.44-0.89) which led to regulatory approval [404] and a paradigm shift in the treatment of mRCC [1]. Results from CheckMate 214 further established that the combination of ipilimumab and nivolumab was associated with higher response rates (RR) (39% in the ITT population), complete response rates (8% in the ITT population [central radiology review]) and duration of response compared to sunitinib. Progression-free survival did not achieve the predefined endpoint. The exploratory analysis of OS data in the PD-L1-positive population was 0.45 (95% CI: 0.29-0.41). Frequency of grade 3-4 adverse events and QoL data favoured the immune combination.

Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity including 1.5% treatment-related deaths. It should therefore be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team (LE: 4). PD-L1 biomarker is currently not used to select patients for therapy.

The frequency of steroid use has generated controversy and further analysis, as well as real world data, are required.

A recent update with 32-month data shows ongoing benefits for the immune combination with investigator-assessed CR rates of 11% and an OS HR in the IMDC intermediate- and poor-risk group of 0.66 (95% CI 0.54-0.80) [406]. The IMDC good-risk group continues to perform well with sunitinib although this appears less marked than in earlier analyses (HR for OS 1.22 [95% CI: 0.73-2.04]). For these reasons the Guidelines Panel continues to recommend ipilimumab and nivolumab in the intermediate- and poor-risk population.

The Keynote-426 trial (NCT02853331) has recently reported results for the combination of axitinib plus pembrolizumab vs. sunitinib in 861 treatment-naïve cc-mRCC patients [407]. Overall survival and PFS assessed by central independent review in the ITT population were the co-primary endpoints. Response rates and assessment in the PD-L1-positive patient population were secondary endpoints. With a median follow-up of 12.8 months, at first interim analysis both primary endpoints were reached, The median PFS in the pembrolizumab plus axitinib arm was 15.1 months vs. 11.1 in the sunitinib arm (HR 0.69; 95% CI: 0.57-0.84, p < 0.001). Median OS has not been reached in either arm, but the risk of death was 47% lower in the axitinib plus pembrolizumab arm when compared to the sunitinib arm (OS HR: 0.53; 95% CI: 0.38–0.74, p < 0.0001). Response rates were also higher in the experimental arm (59.3% vs. 35.7%). Efficacy occurred irrespective of IMDC group and PD-L1 status. Treatment-related AEs (≥ grade 3) occurred in 63% of patients receiving axitinib and pembrolizumab vs. 58% of patients receiving sunitinib. Treatment-related deaths occurred in approximately 1% in both arms.

The JAVELIN trial investigated 886 patients in a phase III RCT of avelumab plus axitinib vs. sunitinib [408]. It met one of its co-primary endpoints (PFS in the PD-L1-positive population at first interim analysis [median follow up 11.5 months]). Progression-free survival and OS in the ITT population was HR 0.69 (95% CI: 0.56-0.84) and 0.78 (95% CI: 0.55-1.08), respectively. The same applies to the atezolizumab/bevacizumab combination which also achieved a PFS advantage over sunitinib in the PD-L1-positive population at interim analysis and ITT (HR: 0.74 [95% CI: 0.57-0.96]), but has not yet shown a significant OS advantage (HR: 0.81 [95% CI: 0.63-1.03]) [409]. Results are awaited and the combination cannot currently be recommended.

Table 7.2: Cross trial comparison is not recommended and should occur with caution

Study	N	Experimental arm	Primary endpoint	Risk groups	PFS Median (95% CI) HR
KEYNOTE-426 **NCT02853331** [407]	861	Pembrolizumab 200 mg. IV Q3W plus axitinib 5 mg. PO BID vs. sunitinib 50 mg PO QD 4/2 weeks	PFS and OS in the ITT by BICR	**IMDC** FAV 31% IMD 56% POOR 13% **MSKCC** Not determined	(ITT) PEMBRO + AXI 15.1 (12.6-17.7) SUN 11.1 (8.7-12.5) HR: 0.69 (95% CI: 0.57, 0.84) p = < 0.0001
JAVELIN 101 **NCT02684006** [408]	886	Avelumab 10 mg/kg IV Q2W plus axitinib, 5 mg PO BID vs. sunitinib 50 mg PO QD 4/2 weeks	PFS in the PD-L1+ population and OS in the ITT by BICR	**IMDC** FAV 22% IMD 62% POOR 16% **MSKCC** FAV 23% IMD 66% POOR 12%	(PD-L1+) AVE + AXI 13.8 (11.1-NE) SUN 7.2 (5.7-9.7) HR: 0.61 (95% CI: 0.475, 0.790) p < .0001
Immotion 151 **NCT02420821** [409]	915	Atezolizumab 1200 mg fixed dose IV plus bevacizumab 15 mg/kg IV on days 1 and 22 of each 42-day cycle vs. sunitinib 50 mg. PO QD 4/2 weeks	PFS in the PD-L1+ population and OS in the ITT by IR	**IMDC** Not determined **MSKCC** FAV 20% IMD 70% POOR 10%	(PD-L1+) ATEZO + BEV 11.2 (8.9-15.0) SUN 7.7 (6.8-9.7) HR: 0.74 (95% CI: 0.57, 0.96) p = 0.02
Checkmate 214 **NCT02231749** [405, 410]	1096	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W vs. sunitinib 50 mg. PO QD 4/2 weeks	PFS and OS in the IMDC intermediate and poor population by BICR	**IMDC** FAV 23% IMD 61% POOR 17% **MSKCC** Not determined	(IMDC intermediate/poor) NIVO + IPI 11.8 (8.7-15.5) SUN 8.4 (7.0-10.8) HR: 0.82 (99.1% CI: 0.64, 1.05) p = 0.03

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; CI = confidence interval; FAV = favourable; HR = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = profession-free survival; PO QD = by mouth, once a day; SUN = sunitinib.

Whilst this table gives a broad overview of the available, data direct cross trial comparisons should be avoided.

Patients who stop nivolumab plus ipilimumab because of toxicity require expert guidance and support from a multidisciplinary team before re-challenge occurs (LE: 1). Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible (LE: 4). Treatment past progression with nivolumab plus ipilimumab can be justified but requires close scrutiny and the support of an expert multidisciplinary team [405, 410] (LE: 1).

Patients who stop axitinib and pembrolizumab due to immune-related toxicity can receive single-agent axitinib once the adverse event has resolved (LE: 1). Adverse event management, including transaminitis and diarrhoea, require particular attention as both agents may be causative. Expert advice should be sought on re-challenge of immune checkpoint inhibitors after significant toxicity (LE: 4). Treatment past progression on axitinib and pembrolizumab requires careful consideration as it is biologically distinct from treatment past progression on ipilimumab and nivolumab.

Generally, the Panel is of the opinion that nivolumab plus ipilimumab and pembrolizumab plus axitinib should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team (LE: 4).

7.4.2.5   Summary of evidence and recommendations for immunotherapy in metastatic RCC

Summary of evidence	LE
Interferon-α monotherapy is inferior to VEGF-targeted therapy or mTOR inhibition in mRCC.	1b
Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.	1b
The combination of nivolumab and ipilimumab in treatment-naïve patients with clear-cell-mRCC (cc-mRCC) of IMDC intermediate and poor risk demonstrated overall survival (OS) and objective response rate (ORR) benefits compared to sunitinib.	1b
The combination of pembrolizumab and axitinib in treatment-naïve patients with cc-mRCC across all IMDC risk groups demonstrated OS and ORR benefits compared to sunitinib.	1b
Currently, PD-L1 expression is not used for patient selection.	2b
Axitinib can be continued if immune-related adverse events results in cessation of axitinib and pembrolizumab. Re-challenge with immunotherapy requires expert support.	4
Patients who do not receive the full 4 doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	4
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	1b
Nivolumab plus ipilimumab and pembrolizumab plus axitinib should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	4
The combination of nivolumab and ipilimumab in the ITT population of treatment-naïve unselected patients with cc-mRCC leads to superior survival compared to sunitinib.	2b
Due to the exploratory nature of PD-L1 tumour expression, the small sample size, the lack of OS data and the premature results in this subpopulation, definitive conclusions cannot be drawn relative to the usefulness of PD-L1 expression.	2b
Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity and 1.5% treatment-related deaths.	1b

Recommendations	Strength rating
Offer pembrolizumab plus axitinib to treatment-naïve patients with any IMDC-risk clear-cell metastatic renal cell carcinoma (cc-mRCC).	Strong
Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC.	Strong
Administer nivolumab plus ipilimumab and pembrolizumab plus axitinib in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	Weak
Patients who do not receive the full 4 doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible.	Weak
Offer axitinib as subsequent treatment to patients who experience treatment-limiting immune-related adverse events after treatment with the combination of axitinib and pembrolizumab.	Weak
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	Weak
Do not re-challenge patients who stopped immune checkpoint inhibitors because of toxicity without expert guidance and support from a multidisciplinary team.	Strong
Offer nivolumab after one or two lines of vascular endothelial growth factor-targeted therapy in mRCC.	Strong
Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable-, intermediate-, and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong[a]

a While this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib in this population. This justified the same recommendation under exceptional circumstances.

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 [411-413]. This process substantially contributes to the development and progression of RCC. Several targeting drugs for the treatment of mRCC are approved 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 IMDC risk model (Table 7.1) [205].

Table 7.3: Median OS and percentage of patients surviving two years treated in the era of targeted therapy per IMDC risk group*,**

IMDC Model	Patients**		Median OS* (months)	2-yr 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 [205]; ** based on [398].
CI = confidence interval; IMDC = Metastatic Renal Cancer Database Consortium; n = number of patients;
OS = overall survival; yr = year.

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 (HR: 0.44; 95% CI: 0.35-0.55, p < 0.01) [414]. Overall survival improved in patients initially assigned to placebo who were censored at crossover [415]. 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 TKI inhibitor and has anti-tumour and anti-angiogenic activity. First-line monotherapy with sunitinib demonstrated significantly longer PFS compared with IFN-α. Overall survival was greater in patients treated with sunitinib (26.4 months) vs. INF-α (21.8 months) despite crossover [417].

In the EFFECT trial, sunitinib 50 mg/day (4 weeks on/2 weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with cc-mRCC [418]. 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 time to progression with the standard 50 mg dosage, the authors recommended using this regimen. Alternate scheduling of sunitinib (2 weeks on/one week off) is being used to manage toxicity, but robust data to support its use is lacking [419, 420].

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 [421].

A non-inferiority trial comparing pazopanib with sunitinib (COMPARZ) established pazopanib as an alternative to sunitinib. It showed that pazopanib was not associated with significantly worse PFS or OS compared to sunitinib. The two drugs had different toxicity profiles, and QoL was better with pazopanib [422]. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%, p < 0.05) due to symptomatic toxicity [423]. 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 who had previously failed cytokine treatment or targeted agents (mainly sunitinib) [424].

The overall median PFS was greater for axitinib than sorafenib. Axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months) after progression on sunitinib. Axitinib showed grade 3 diarrhoea in 11%, hypertension in 16%, and fatigue in 11% of patients. Final analysis of OS showed no significant differences between axitinib or sorafenib [425, 426]. 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, although the study was underpowered, raising the possibility of a type II error [427]. As a result of this study, axitinib is not approved for first-line therapy.

7.4.3.1.5 Cabozantinib

Cabozantinib is an oral inhibitor of tyrosine kinase, 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 [180]. Based on these results an RCT investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapies (METEOR) [181, 428]. Cabozantinib delayed PFS compared to everolimus in VEGF-targeted therapy refractory disease (HR: 0.58 95% CI: 0.45-0.75) [181] (LE: 1b). 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) [428]. 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.

The Alliance A031203 CABOSUN randomised phase II trial comparing cabozatinib and sunitinib in first-line in 157 intermediate- and poor-risk patients favoured cabozantinib for RR and PFS, but not OS [429, 430]. Cabozantinib significantly increased median PFS (8.2 vs. 5.6 months, adjusted HR: 0.66; 95% CI: 0.46 to 0.95; one-sided p = 0.012). Objective response rate was 46% (95% CI: 34-57) for cabozantinib vs. 18% (95% CI: 10-28) for sunitinib. All-causality grade 3 or 4 adverse events were similar for cabozantinib and sunitinib. No difference in OS was seen. Due to limitations of the statistical analyses within this trial the evidence is inferior over existing choices.

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 [(PDGFR-α), re-arranged during transfection (RET) and receptor for stem cell factor (KIT). It has recently been investigated in a 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) [431].

7.4.3.1.7 Tivozanib

Tivozanib is a potent and selective TKI of VEGFR1, VEGFR2, and VEGFR3 and was compared in two phase III trials with sorafenib in patients with mRCC [432, 433]. Tivozanib was approved by the EMA in front-line mRCC. While it is associated with a PFS advantage in both studies, no OS advantage was seen. In view of the choice of sorafenib as the control arm in the front-line trial, the Panel feels there is too much uncertainty, and too many attractive alternatives, to support its use in this setting.

7.4.4 *Monoclonal antibody against circulating VEGF*
7.4.4.1 *Bevacizumab monotherapy and bevacizumab plus IFN-α*
Bevacizumab is a humanised monoclonal antibody.

The double-blind AVOREN study compared bevacizumab plus IFN-α with INF-α monotherapy in mRCC. Overall response was higher in the bevacizumab plus IFN-α group. Median PFS increased from 5.4 months with IFN-α to 10.2 months with bevacizumab plus 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 months) [434].

An open-label trial (CALGB 90206) of bevacizumab plus IFN-α vs. IFN-α showed a higher median PFS for the combination group [435, 436]. Objective response rate was also higher in the combination group. Overall toxicity was greater for bevacizumab plus IFN-α, with significantly more grade 3 hypertension, anorexia, fatigue, and proteinuria.

Bevacizumab, alone, or in combinations, is not widely recommended or used in mRCC due to more attractive alternatives.

7.4.5 *mTOR inhibitors*
7.4.5.1 *Temsirolimus*
Temsirolimus is a specific inhibitor of mTOR [437]. Its use has been superseded as front-line treatment option.

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 plus best supportive care (BSC) vs. placebo plus BSC in patients with previously failed anti-VEGFR treatment (or previously intolerant of VEGF-targeted therapy) [438]. The data showed a median PFS of 4 vs. 1.9 months for everolimus and placebo, respectively [438].

The RCC Guidelines Panel consider, even in the absence of conclusive data, that everolimus may present a therapeutic option in patients who were intolerant to, or previously failed, immune- and VEGFR-targeted therapies (LE: 4). Recent phase II data suggest adding levantinib is attractive.

7.4.6 *Therapeutic strategies*
7.4.6.1 *Therapy for treatment-naïve patients with clear-cell metastatic RCC*
The combination of pembrolizumab and axitinib as well as nivolumab and ipilimumab is the standard of care in all IMDC and IMDC intermediate- and poor-risk patients (Figure 7.1). Therefore, the role of VEGFR-TKIs alone in front-line mRCC has been superseded. Sunitinib, pazopanib, and cabozantinib (IMDC intermediate- and poor-risk disease), remain alternative treatment options for patients who cannot receive or tolerate immune checkpoint inhibition in this setting (Figure 7.1).

7.4.6.1.1 Sequencing systemic therapy in clear-cell metastatic RCC

The sequencing of targeted therapies is established in mRCC and maximises outcomes [181, 182, 431]. Pembrolizumab plus axitinib and nivolumab plus ipilimumab are the new standard of care for front-line therapy. The impact of front-line immune checkpoint inhibition on subsequent therapies is unclear. Randomised data on patients with disease refractory to either nivolumab plus ipilimumab or pembrolizumab plus axitinib in a first-line setting are lacking, and available cohorts are limited [439]. Prospective data on cabozantinib and axitinib are available for patients progressing on immune therapy, but these studies do not focus solely on the front-line setting, involve subset analysis, and are too small for definitive conclusions [181, 440].

Retrospective data on VEGFR-TKI therapy after progression on front-line immune combinations exist but have significant limitations. When considering this data in totality, there is some activity but it is still too early to recommend one VEGFR-TKI above another after immunotherapy-immunotherapy or immunotherapy-VEGFR combination (Figure 7.2). After the axitinib plus pembrolizumab combination, changing the VEGFR-TKI at progression is recommended which may be cabozantinib or any other TKI not previously used.

The Panel do not favour the use of mTOR inhibitors unless VEGF-targeted therapy is contraindicated as they have been outperformed by other VEGF-targeted therapies in mRCC [441]. Drug choice in the third-line setting, after immune checkpoint inhibitor combinations and subsequent VEGF-targeted therapy, is unknown. The Panel recommends a subsequent agent which is approved in VEGF-refractory disease, with the exception of re-challenge with immune checkpoint blockade. Cabozantinib is the only agent in VEGF-refractory disease with a survival advantage in an RCT and should be used preferentially [424]. Axitinib has positive PFS data in VEGF-refractory disease. Both sorafenib and everolimus have been outperformed by other agents in VEGF-refractory disease and are therefore less attractive [441]. The Lenvatinib and everolimus combination appears superior to everolimus alone and has been granted EMA regulatory approval based on randomised phase II data. This is an alternative despite the availability of phase II data only [431]. Tivozinib has PFS superiority to sorafenib in VEGF-refractory disease as shown in a study which also included patients on immune checkpoint inhibitors [442].

7.4.6.2 Non-clear-cell metastatic RCC

No phase III trials of patients with non-cc-mRCC 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-cc-mRCC has focused on temsirolimus, everolimus, sorafenib, sunitinib and pembrolizomab [396, 443-445].

The most common non-clear-cell subtypes are papillary type I and non-type I papillary RCCs. There are small single-arm trials for sunitinib and everolimus [445-448]. A trial of both types of pRCC treated with everolimus (RAPTOR) [448], showed a median PFS of 3.7 months per central review in the ITT population with a median OS of 21.0 months.

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 [449]. The final results showed a non-significant trend favouring sunitinib (6.1 vs. 4.1 months). Based on a systematic review 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 [7, 139, 450]. Patients with non-cc-mRCC should be referred to a clinical trial, where appropriate. Efficacy for pembrolizumab (n = 165; response rates of 24%, PFS 4.1 months [95% CI: 2.8-5.6 months] 72% one-year OS) was noted but these results are based on a single-arm phase II study [403]. Pembrolizumab can be conceded in this setting due to the high unmet need.

Subset analysis has shown impressive results for PD-L1 inhibitors combined with CTLA4 or VEGF-targeted therapy in renal tumours with sarcomatoid features. Bevacizumab/atezolizumab, ipilimumab/nivolumab, axitinib/pembrolizumab and avelumab/axitinib can all be recommended instead of VEFG-targeted therapy alone. These options have impressive OS advantages over sunitinib and superseded VEGF-targeted therapy.

Collecting-duct cancers and renal medullary cancers are highly resistant to systemic therapy. Only case reports have been published for a spectrum of treatment options so far and no clear recommendations can be provided until data from international registries (RARECARE) or clinical trials become available.

Figure 7.1: Updated European Association of Urology Guidelines recommendations for the treatment of first-line and following lines in clear-cell metastatic renal cancer

	Standard of care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	Pembrolizumab/ Axitinib [1b]	Sunitinib [1b] Pazopanib* [1b]
IMDC intermediate and poor risk	Pembrolizumab/ Axitiinib [1b] Ipilimumab/ Nivolumab [1b]	Cabozantinib [2a] Sunitinib [1b] Pazopanib* [1b]

IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium
*pazopanib for intermediate-risk disease only.
[1b] = based on one randomised controlled phase III trial.
[2a] = based on one randomised controlled phase II trial.

Figure 7.2: Guidelines Recommendations for later-line therapy

	Standard of care	Alternative
Prior IO	Any VEGF-targeted therapy that has not been used prev;oously in combination with IO [4]	
Prior TKI	Nivolumab [1b] Cabozantinib [1b]	Axitinib [2b]

IO = immunotherapy; TKI = tyrosine kinase inhibitors; VEGF = vascular endothelial growth factor.
[1b] = based on one randomised controlled phase III trial.
[2b] = subgroup analysis of a randomised controlled phase III trial.
[4] = expert opinion.

Summary of evidence	LE
Single agent VEGF-targeted therapy has been superseded by immune checkpoint based combination therapy.	1b
Pazopanib is non-inferior to sunitinib in front-line mRCC.	1b
Cabozantinib in intermediate- and poor-risk treatment-naïve clear-cell RCC leads to better response rates and PFS but not OS when compared to sunitinib.	2b
Tivozanib has been EMA approved, but the evidence is still considered inferior over existing choices in the front-line setting.	3
Single-agent VEGF-targeted therapies are preferentially recommended after front-line PD-L1-based combinations. Re-challenge with treatments already used should be avoided.	3
Single-agent cabozantinib or nivolumab are superior to everolimus after one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS after VEGF-targeted therapy when compared to placebo. This is no longer widely recommended before third-line therapy.	1b
Both mTOR inhibitors and VEGF-targeted therapies have limited activity in non-cc-mRCC. There is a non-significant trend for improved oncological outcomes for sunitinib over everolimus.	2a
Lenvatinib in combination with everolimus improved PFS over everolimus alone in VEGF-refractory disease. Its role after immune checkpoint inhibitors is uncertain. There is a lack of robust data on this combination making its recommendation challenging.	2a

Recommendations	Strength rating
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naive vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC).	Strong
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab.	Weak
Offer cabozantinib after VEGF-targeted therapy in cc-mRCC.	Strong
Sequence systemic therapy in treating mRCC.	Strong

7.5 Recurrent RCC

Locally recurrent disease can either affect the tumour-bearing kidney after PN, or focal ablative therapy such as RFA and cryotherapy, or occur outside the kidney following PN or RN for RCC.

After NSS for pT1 disease, recurrences within the remaining kidney occur in about 1.8-2.2% of patients [451, 452]. Although the impact of positive margins on the clinical prognosis is still unclear [287, 452, 453] the preferred management, when technically feasible, is repeat surgical intervention to avoid the potential risk of tumour recurrence.

Following thermal ablation or cryotherapy generally intra-renal, but also peri-renal, recurrences have been reported in up to 14% of cases [454]. Whereas repeat ablation is still recommended as the preferred therapeutic option after treatment failure, the most effective salvage procedure as an alternative to complete nephrectomy has not yet been defined.

Most studies reporting on the oncological efficacy of surgery for recurrent disease after removal of the kidney, have not considered the traditional definition of local recurrence after RN, PN and thermal ablation, which is: "tumour growth exclusively confined to the true renal fossa". Instead, recurrences within the renal vein, the ipsilateral adrenal gland or the regional LNs were included under this term. Isolated tumour recurrence within the true renal fossa only is a rare event. Recurrent tumour growth in the regional LNs or ipsilateral adrenal gland may reflect metachronous metastatic spread (see Section 7.3).

Only retrospective and non-comparative data on the frequency and efficacy of available therapeutic options have been reported. One of the largest series including 2,945 patients treated with RN reported on 54 patients with recurrent disease localised in the renal fossa, the ipsilateral adrenal gland or the regional LNs as sole metastatic sites [455]. Another recent series identified 33 local recurrences within a cohort of 2,502 surgically treated patients, confirming the efficacy of surgical treatment vs. conservative approaches (observation, medical therapy). In a series of 1,955 patients with clinical T1 RCCs treated with PN, 95 patients (4.9%) had a pT3a upstaging, indicating a high risk for local and intra-renal recurrence and reduced survival

[456]. These data were further confirmed by an analysis of the SEER database showing that up-staging to pT3a with worse CSS occurred in 4.2% of cT1a tumours and in 9.5% of cT1b tumours [457].

In summary, the limited available evidence suggests that in selected patients surgical removal of locally recurrent disease can induce durable tumour control. Since local recurrences develop early, with a median time interval of 10-20 months after treatment of the primary tumour [458], a guideline-adapted follow-up scheme for early detection is recommended (see Chapter 8 - Follow-up). Data show that both adequate pre-operative assessment and careful surgical technique are crucial in reducing local recurrence risk.

Adverse prognostic parameters are a short time interval (< 3-12 months) since treatment of the primary tumour [459], sarcomatoid differentiation of the recurrent lesion and an incomplete surgical resection [455]. In case complete surgical removal is unlikely to be performed or when significant comorbidities are present (especially when combined with poor prognostic tumour features), palliative therapeutic approaches including radiation therapy aimed at symptom control and prevention of local complications should be considered (see Sections 7.3 and 7.4).

7.5.1 *Summary of evidence and recommendation for advanced/metastatic RCC*

Summary of evidence	LE
Isolated recurrence in the local renal fossa is rare.	3
In the absence of adverse prognostic factors such as sarcomatoid features or median time interval of < 12 months since treatment of the primary tumour, resection of local recurrences can induce durable tumour local control.	3
Most local recurrences develop within the first two years following treatment of the primary tumour. A guideline-adapted follow-up regimen is advised for early detection.	3

Recommendation	Strength rating
Offer surgical resection of locally recurrent disease when a complete resection is possible and significant comorbidities are absent.	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. Intensive radiological surveillance for all patients is not necessary. 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. The outcome after surgery for T1a low-grade tumours is almost always excellent. It is therefore reasonable to stratify follow up, taking into account the risk of developing recurrence or metastases. Although there is no randomised evidence, large studies have examined prognostic factors with long follow-up periods [20, 460, 461] (LE: 4). One study has shown a survival benefit for patients who were followed within a structured surveillance protocol vs. patients who were not [462]; patients undergoing follow-up seem to have a longer OS when compared to patients not undergoing routine follow-up [462].

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 [463]. For patients with low-stage disease but with a Charlson comorbidity index > 2, the risk of non-RCC death exceeded that of abdominal recurrence risk already one month after surgery, regardless of patient age. The RECUR database consortium initiated by this Panel collects similar data with the aim to provide comparators for guideline

recommendations. Preliminary data support a risk-based approach. In the near future, genetic profiles may refine the existing prognostic scores and external validation in datasets from adjuvant trials were promising [8, 464].

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 [465, 466] and non-cancer survival [208, 209, 467] can be optimised by performing NSS, whenever possible, for T1 and T2 tumours [468] (LE: 3). Recurrence after PN is rare, but early diagnosis is useful, as the most effective treatment is surgery [469, 470]. Recurrence in the contralateral kidney is also rare (1-2%), can occur late (median 5-6 years), and might be related to positive margins, multifocality, and grade [471] (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?

- The sensitivity of chest radiography and US for small metastases is poor. The sensitivity of chest radiography is significantly lower than CT-scans, as proven in histology controlled comparative trials [472-474].
- Surveillance with these imaging modalities are less sensitive [475].
- 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, abdomen and pelvis 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.
- After injection of contrast medium, the risk of acute renal failure seems to be negligible in patients with a GFR > 20 mL/min and chronic renal impairment [476].

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 [477] (LE: 3). Several authors have designed scoring systems and nomograms to quantify the likelihood of patients developing tumour recurrences, metastases, and subsequent death [194, 196, 478, 479]. These systems have been compared and validated [480] (LE: 2). Using prognostic variables, several stage-based surveillance regimens have been proposed but none include ablative therapies [481, 482]. A post-operative nomogram is available to estimate the likelihood of freedom from recurrence at five years [191]. Recently, a pre-operative prognostic model based on age, symptoms and TNM staging has been published and validated [200] (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. The most suitable approach to define high-risk patients is the utilisation of nomograms.

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 [360, 483].

Table 8.1: Proposed surveillance schedule following treatment for RCC, taking into account patient risk profile and treatment efficacy (based on expert opinion [LE: 4])

Risk profile	Surveillance				
	6 mo	1 y	2 y	3 y	> 3 y
Low	US	CT	US	CT	CT once every 2 years; Counsel about recurrence risk of ~10%
Intermediate / High	CT	CT	CT	CT	CT once every 2 years

CT = computed tomography of chest and abdomen, alternatively use magnetic resonance imaging for the abdomen; 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
Repeated CT scans do not reduce renal function in chronic kidney disease patients.	3

Recommendations	Strength rating
Base follow-up after RCC on the risk of recurrence.	Strong
Intensify follow-up in patients after nephron-sparing surgery 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: http://urology.ucla.edu/body.cfm?id=443 or the SSIGN score.	Strong

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/renalcell-carcinoma/?type=panel/.

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11.   CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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