EAU Guidelines on
Renal Cell Carcinoma

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1. INTRODUCTION

1.1 Aims and scope
The European Association of Urology (EAU) Renal Cell Cancer (RCC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of RCC.

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

1.2 Panel composition
The RCC Guidelines Panel is an international group of clinicians consisting of urological surgeons, oncologists, methodologists, a pathologist and a radiologist, with particular expertise in the field of renal cancer care. Since 2015, the Panel has incorporated a patient advocate to provide a consumer perspective for its guidelines.

All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/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 2021 RCC Guidelines document presents a substantial update of the 2020 publication.

1.5.2 Summary of changes
All chapters of the 2021 RCC Guidelines have been updated, based on the 2020 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 5.4 Summary of evidence and recommendations for the diagnostic assessment of RCC

Recommendations	Strength rating
Omit chest CT in patients with incidentally noted cT1a disease due to the low risk of lung metastases in this cohort.	Weak
Use non-ionising modalities, including MRI and contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses, if the results of contrast-enhanced CT are indeterminate.	Strong

Section 6.7 Summary of evidence and recommendations for prognostic factors

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

Recommendations	Strength rating
Use the WHO/ISUP grading system and classify renal cell carcinoma type.	Strong
Use prognostic models in localised and metastatic disease.	Strong
Do not routinely use molecular markers to assess prognosis.	Strong

7.1.2.2.4 Summary of evidence and recommendations for the treatment of localised RCC

Summary of evidence	LE
Retrospective studies suggest that oncological outcomes are similar following PN vs. RN in patients with larger (≥ 7 cm) RCC. Post-operative complication rates are higher in PN groups.	3b
In patients with localised disease without radiographic evidence of LN metastases, a survival advantage of LND in conjunction with RN is not demonstrated in randomised trials.	2b

Recommendations	Strength rating
Offer partial nephrectomy to patients with T2 tumours and a solitary kidney or chronic kidney disease, if technically feasible.	Weak
Do not offer an extended lymph node dissection to patients with organ-confined disease.	Weak

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

Summary of evidence	LE
Robotic-assisted and laparoscopic PN are associated with shorter length of stay and lower blood loss compared to open PN.	2b
Hospital volume in PN might impact on surgical complications, warm ischaemia and surgical margins.	3
Radical nephrectomy after positive surgical margins can result in over-treatment in many cases.	3

Recommendation	Strength rating
Intensify follow-up in patients with a positive surgical margin.	Weak

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

Summary of evidence	LE
Low quality studies suggest high disease recurrence rates after radiofrequency ablation of tumours > 3 cm and after cryoablation of tumours > 4 cm.	3
Low quality studies suggest a higher local recurrence rate for thermal ablation therapies compared to PN, but the quality of the data does not allow definitive conclusions.	3

Recommendations	Strength rating
Offer active surveillance (AS) or thermal ablation (TA) to frail and/or comorbid patients with small renal masses.	Weak
Perform a percutaneous renal mass biopsy prior to, and not concomitantly with TA.	Strong
When TA or AS are offered, discuss with patients about the harms/benefits with regards to oncological outcomes and complications.	Strong
Do not routinely offer TA for tumours > 3 cm and cryoablation for tumours > 4 cm.	Weak

Section 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, the survival benefit of lymph node (LN) dissection is unproven but LN dissection has significant staging, prognosis and follow-up implications.	3

Recommendations	Strength rating
In patients with clinically enlarged lymph nodes (LNs), perform LN dissection to guide staging, prognosis and follow-up.	Weak
In case of metastatic disease, discuss surgery within the context of a multidisciplinary team.	Weak

Section 7.2.5.1 Summary of evidence and recommendations for adjuvant therapy

Summary of evidence	LE
Adjuvant therapy does not improve survival after nephrectomy.	1b
In one single RCT, in selected high-risk patients, adjuvant sunitinib improved disease-free survival (DFS) but not overall survival (OS).	1b
Adjuvant sorafenib, pazopanib, everolimus, girentuximab or axitinib does not improve DFS or OS after nephrectomy.	1b
Adjuvant RCTs are ongoing to evaluate the benefit of adjuvant immunotherapy after nephrectomy in high-risk patients.	1b

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

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

Summary of evidence	LE
Patients with their primary tumour in place treated with ICI-based combination therapy have better PFS and OS in exploratory subgroup analyses compared to treatment with sunitinib.	2b

Recommendation	Strength rating
Discuss delayed cytoreductive nephrectomy in patients who derive clinical benefit from systemic therapy.	Weak

Section 7.3.2.6 Summary of evidence and recommendations for local therapy of metastases in metastatic RCC

Summary of evidence	LE
Tyrosine kinase inhibitors treatment after metastasectomy in patients with no evidence of disease did not improve RFS when compared to placebo or observation.	1b

Recommendation	Strength rating
Do not offer tyrosine kinase inhibitor treatment to mRCC patients after metastasectomy and no evidence of disease.	Strong

Section 7.4.2.5 Summary of evidence and recommendations for immunotherapy in metastatic RCC

Summary of evidence	LE
The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naive patients with cc-mRCC across all IMDC risk group demonstrated PFS, OS and ORR benefits compared to sunitinib.	1b
Axitinib, cabozantinib or lenvatinib can be continued if immune-related adverse events result in cessation of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus pembrolizumab. Re-challenge with immunotherapy requires expert support.	4
Nivolumab plus ipilimumab, pembrolizumab plus axitinib, nivolumab plus cabozantinib and lenvatinib plus pembrolizumab 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 plus ipilimumab in the IMDC intermediate- and poor-risk population of treatment-naive patients with cc-mRCC leads to superior survival compared to sunitinib while OS was higher in IMDC good-risk patients with sunitinib.	2b

Recommendations	Strength rating
Offer pembrolizumab plus axitinib, lenvatinib plus pembrolizumab or nivolumab plus cabozantinib to treatment-naive patients in clear-cell metastatic renal cell carcinoma (cc-mRCC).	Strong
Administer nivolumab plus ipilimumab, pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	Weak
Offer axitinib, cabozantinib or lenvatinib as subsequent treatment to patients who experience treatment-limiting immune-related adverse events after treatment with the combination of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak

Figure 7.1: Updated EAU Guidelines recommendations for the first-line treatment of metastatic ccRCC

	Standard of Care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b]	sunitinib* [1b] pazopanib* [1b]
IMDC intermediate and poor risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b] nivolumab/ipilimumab [1b]	cabozantinib* [2a] sunitinib*[1b] pazopanib* [1b]

Section 7.4.7 ***Summary of evidence and recommendations for targeted therapy in metastatic RCC***

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) after one or two lines of therapy.	Strong
Offer VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak

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

Summary of evidence	LE
Functional follow-up after curative treatment for RCC is useful to prevent renal and cardiovascular deterioration.	4
Oncological follow-up can detect local recurrence or metastatic disease while the patient may still be surgically curable.	4
Prognostic models provide stratification of RCC risk of recurrence based on TNM and histological features	3
In competing-risk models, risk of non-RCC-related death exceeds that of RCC recurrence or related death in low-risk patients.	3
Life expectancy estimation is feasible and may support counselling of patients on duration of follow-up.	4

Recommendations	Strength rating
Perform functional follow-up (renal function assessment and prevention of cardiovascular events) both in nephron-sparing (NSS) and radical nephrectomy (RN) patients.	Weak
Consider curtailing follow-up when the risk of dying from other causes is double that of the recurrence risk of RCC.	Weak

2. METHODS

2.1 Data identification

For the 2021 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 certainty of evidence (i.e. systematic reviews with or without meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only for therapeutic interventions, and systematic reviews and prospective studies with well-defined reference standards for diagnostic accuracy studies) published in the English language. In case no higher level data exists for a particular topic, lower level evidence is considered for inclusion. The search was restricted to articles published between April 1st 2019 and June 25th 2020. Databases covered included Medline, EMBASE, and the Cochrane Library. After de-duplication, a total of 1,973 unique records were identified, retrieved and screened for relevance.

A total of 106 new references have been included in the 2021 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 systematic reviews, commissioned and undertaken by the Panel, based on prioritised topics or questions. These reviews were performed using standard Cochrane systematic review 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 3.4.5.1 (Treatment of angiomyolipoma) was updated by means of a systematic review [5].
5. Diagnostic evaluation	Section 5.2 (Diagnostic imaging) was revised based on a systematic review [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 systematic review. Sub-section 7.1.4.3.2 (Cryoablation versus partial nephrectomy) was updated by means of a systematic review [7]. Section 7.4.6.2 (Non-clear-cell metastatic RCC) was updated by means of a systematic review [8]. Some aspects of Section 7.4 (Targeted therapy for metastatic RCC) were updated by way of a Cochrane systematic review [9]. The remainder of the chapter was updated using a structured literature assessment. Systemic therapy for metastatic disease: this section was updated by a systematic review.
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 [10, 11].

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

2.2 Review

All publications ensuing from systematic reviews have been peer reviewed. The 2021 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 systematic reviews will be included in the 2022 update of the RCC Guidelines:
- What is the best treatment option for ≥ T2 tumours?
- Adjuvant targeted therapy for renal cell carcinoma at high risk for recurrence;
- Systematic review of prevalence of intraperitoneal recurrences following robotic/laparoscopic partial nephrectomy;
- Systematic review of individual, unit and hospital surgical volume for radical and partial nephrectomy and their impact on outcomes;
- RECUR database analysis of recurrent disease/follow-up.

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 [12, 13]. In Europe and worldwide the highest incidence rates are found in the Czech Republic and Lithuania [13]. 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 [12, 13]. In Europe, overall mortality rates for RCC increased until the early 1990s, with rates generally stabilising or declining thereafter [14]. 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 [12, 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 [15]. There is a 1.5:1 predominance in men over women with a higher incidence in the older population [13, 16].

3.2 Aetiology

Established risk factors include lifestyle factors such as smoking, obesity, and hypertension [13, 16]. In a recent systematic review also diabetes was found to be detrimental [17]. 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 [16]. 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 [13, 17]. The most effective prophylaxis is to avoid cigarette smoking and reduce obesity [13, 16].

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 are 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 [15]. 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 [15, 18] (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 [15].

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. The loss of von Hippel-Lindau protein function contributes to tumour initiation, progression, and metastases. The 3p locus harbours at least four additional cRCC tumour supressor genes (*UTX, JARID1C, SETD2, PBRM1*) [18]. In general, ccRCC has a worse prognosis compared to pRCC and chRCC, but this difference disappears after adjustment for stage and grade [19, 20]. For details about prognosis, 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 [15]. 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 [21]. Type II pRCC presents a heterogenous group of tumours and future substratification is expected, e.g. oncocytic pRCC [15].

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. Stagnation in the 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 [22]. Papillary RCC type I is more common and generally considered to have a better prognosis than pRCC type II [15, 20, 23].

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 [15]. Loss of chromosomes Y, 1, 2, 6, 10, 13, 17 and 21 are typical genetic changes [15]. The prognosis is relatively good, with high 5-year recurrence-free survival (RFS), and 10-year CSS [24]. 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 [25], 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 [26, 27] and most patients (~67%) will present with metastatic disease [26, 28]. 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 [26]. 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 longer survival was noted in patients who achieved an objective response to first-line chemotherapy. [26, 29]. 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 [30, 31]. Renal medullary carcinoma is refractory to monotherapies with targeted anti-angiogenic regimens including tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors [26, 32]. The mainstay systemic treatments for RMC are cytotoxic combination regimens which produce partial or complete responses in ~29% of patients [32]. There are no prospective comparisons between different chemotherapy regimens but most published series used various combinations of platinum agents, taxanes, gemcitabine, and/or anthracyclines [26, 27]. High-dose-intensity combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has also shown efficacy against RMC [33] although a retrospective comparison did not show superiority of MVAC over cisplatin, paclitaxel, and gemcitabine [27]. 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 [30, 31]. 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. 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. Although the histological spectrum of ESRD tumours is similar to that of sporadic RCC; pRCC occur relatively more frequently [34, 35]. A specific subtype of RCC occurring only in end-stage kidneys has been described as Acquired Cystic Disease-associated RCC (ACD-RCC) with indolent clinical behaviour, likely due to early detection in patients with ESRD on periodic follow-up [15, 18, 36].

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 [37], according to the WHO 2016 classification [15].

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 [38]. Hereditary kidney tumours are found in the following entities: VHL syndrome, hereditary pRCC, Birt-Hogg-Dube 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 non-syndromic ccRCC. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [37, 39-41].

Patients with hereditary kidney cancer syndromes may require repeated surgical intervention [42, 43]. 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 this lesion. For other hereditary syndromes such as VHL, surveillance is recommended until the largest tumour reaches 3 cm in diameter, to reduce interventions [44]. 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. Multidisciplinary and co-ordinated care should be offered, where appropriate [45].

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 [46].

A recent phase II trial demonstrated clinical activity of an oral HIF-2α (hypoxia-inducible factor) inhibitor MK-6482 in VHL patients. In VHL-associated RCC the objective response rate (ORR) was 28%

and stable disease rate was observed in 71% of 61 evaluated patients with a median decline of the linear growth rate by -6.4 mm (range 23.3–4.5) per year. Eighty seven per cent of patients showed a decrease from baseline in target lesions as evaluated by independent review, which, despite a follow-up of 36 weeks only, are promising but, as yet, unvalidated results [47].

Genetic counselling is suggested for younger patients, in case of bilateral and multiple tumours, a past family history of RCC and uncommon morphology.

3.4.5 ***Angiomyolipoma***

Angiomyolipoma (AML) is a benign mesenchymal tumour, which can occur sporadically or as part of tuberous sclerosis complex [48]. 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 [49]. 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 [15, 37, 50]. 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 [37, 50]. Epithelioid AMLs are potentially malignant with a highly variable proportion of cases with aggressive behaviour [51]. Criteria to predict the biological behaviour in epithelioid AML were proposed by the WHO 2016 [37, 50]. 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 [52, 53].

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, and spontaneous bleeding was reported in 2%, resulting in active treatment in 5% of patients [5, 54] (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 are 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. Selective arterial embolisation is an option in case of life-threatening AML bleeding.

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 [55, 56]. In a small phase II trial (n = 20), efficacy of everolimus was demonstrated in sporadic AML as well. A 25% or greater reduction in tumour volume at 4 and 6 months was demonstrated in 55.6% and 71.4% of patients, respectively. Twenty per cent of patients were withdrawn due to toxicities and 40% self-withdrew from the study due to side effects [57].

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 [15, 54]. The diagnostic accuracy of imaging modalities (CT, MRI) in renal oncocytoma is limited and histopathology remains the only reliable diagnostic modality [15, 54]. 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) [15], other RCCs (12.5%), and other benign lesions (4.2%) [58]. The majority of oncocytomas slowly progress in size with an annual growth rate < 14 mm [59-61]. Preliminary data show that AS may be a safe option to manage oncocytoma in appropriately selected patients. Potential triggers to change management of patients on AS are not well defined [62].

Table 3.1: Other renal cortical tumours, and recommendations for treatment (strength rating: weak) [15]

Entity	Clinical relevant notes	Malignant potential	Treatment
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 [63].
Multilocular cystic renal neoplasm of low malignant potential	Formerly multilocular cystic RCC	Benign	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) for CSS in comparison with ccRCC is 4.49 [20].	High, very aggressive. Median survival is 30 months [64].	Surgery. Response to targeted therapies is poor [65].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait.	High, very aggressive, median survival is five months [64].	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) [66].	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, NSS.
Clear-cell papillary RCC	Also reported as renal angiomyomatous tumour (RAT).	Low	Surgery, NSS.
Hereditary leiomyomatosis and RCC-associated RCC	Rare, germline mutation of the fumarate hydratase gene [15]. 21% lifetime risk of RCC [67].	High	Surgery. No data about treatment of metastatic disease. Imaging screening is recommended [67].
Tubulocystic RCC	Mainly men, imaging can show Bosniak III or IV.	Low (90% indolent)	Surgery, NSS.
Succinate dehydrogenase-deficient RCC	Rare.	Variable	Surgery, NSS.
Metanephric tumours	Divided into metanephric adenoma, adenofibroma, and metanephric stromal tumours.	Benign	Surgery, NSS.
Cystic nephroma/Mixed epithelial and stromal tumour	The 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.	Benign	Observation (when histologically confirmed). NSS. See Section *3.4.6.*
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 [68]. 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) [69]. 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 systematic review, 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% of these showing malignancy, which is comparable to the malignancy rates of Bosniak IV cysts [68]. The updated Bosniak classification strengthens the classification and includes also MRI diagnostic criteria [70].

The most common histological type for Bosniak III cysts is ccRCC with pseudocystic changes and low malignant potential [71, 72]; 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 over-treatment 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 is an alternative to surgical treatment [68, 70, 73, 74].

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
Manage Bosniak type III cysts the same as localised RCC, or offer active surveillance.	Weak
Manage Bosniak type IV cysts the same as localised 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 in need of therapy with surgically unresectable AMLs not amendable to embolisation or surgery.	Weak
Offer active surveillance to patients with biopsy-proven oncocytomas, as an acceptable alternative to surgery or ablation.	Weak
Offer radical nephrectomy to patients with localised renal medullary carcinoma.	Weak
Base systemic therapy for renal medullary carcinoma on chemotherapy regimens 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 [75], but requires continuous re-assessment [15, 76]. A supplement was published in 2012, and the latter's prognostic value was confirmed in single and multi-institution studies [77, 78]. 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 [79].
- Renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion, but, is nevertheless included in the same pT3a stage group [80-82] (LE: 3).
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [78].
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [83, 84] (LE: 4).

Table 4.1: 2017 TNM classification system [75]

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 extends into the renal vein or its segmental branches, or invades the pelvicalyceal system or invades perirenal and/or renal sinus 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.
**Adapted based on the American Joint Committee on Cancer (AJCC), 8th Edn. 2017 [85].*

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 [86-88]. 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 [78, 89] (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 [90, 91] (LE: 3). Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs [92] (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [93] (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 [94], 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 [95, 96] (LE: 2b):

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

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

5.2 Imaging investigations

Most renal tumours are diagnosed by abdominal US or CT performed for other medical reasons [89] (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 [97] (LE: 3). Traditionally, US, CT and MRI are used for detecting and characterising renal masses. Most renal masses are diagnosed accurately by imaging alone.

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

Computed tomography or MRI are used to characterise renal masses. Imaging must be performed unenhanced, in an early arterial phase, and in a parchymal phase with 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 HU, or more, in the solid tumour parts demonstrates enhancement and thus vital tumour parts [98] (LE: 3). Computed tomography or MRI allows accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free AML from

malignant renal neoplasms [99-102] (LE: 3). Abdominal CT provides information on [103]:
- function and morphology of the contralateral kidney [104] (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 [105, 106]. If the results of CT are indeterminate, CEUS is a valuable alternative to further characterise renal lesions [6, 107-109] (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). In MRI, especially high-resolution T2 weighted images provide a superior delineation of the uppermost tumour thrombus, as the inflow of the enhanced blood may be reduced due to extensive occlusive tumour thrombus growth in the inferior vena cava. The T2 weighted images with its intrinsic contrast allows a good delineation [113].

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [113, 114] (LE: 3). Magnetic resonance imaging allows the evaluation of a dynamic enhancement without radiation exposure. Advanced MRI techniques such as diffusion-weighted (DWI) and perfusion-weighted imaging are being explored for renal mass assessment [115]. Recently, the use of multiparametric MRI (mpMRI) to diagnose ccRCC via a clear cell likelihood score (ccLS) in small renal masses was reported [116]. The ccLS is a 5-tier classification that denotes the likelihood of a mass representing ccRCC, ranging from 'very unlikely' to 'very likely'. The authors prospectively validated the diagnostic performance of ccLS in 57 patients with cT1a tumours and found a high diagnostic accuracy. The diagnostic performance of mpMRI-based ccLS was further validated in a larger retrospective cohort (n = 434) across all tumour sizes and stages [117], and ccLS was found to be an independent prognostic factor for identifying ccRCC. The system is promising and deserves further validation.

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, due to a higher sensitivity for enhancement, showed a 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) [69].

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 [118].

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 [95, 96] (LE: 2a). Positron-emission tomography (PET) is not recommended [6, 119] (LE: 1b).

5.2.4 ***Radiographic investigations to evaluate RCC metastases***
Chest CT is accurate for chest staging [83, 84, 120-122] (LE: 3). Use of nomograms to calculate risk of lung metastases have been proposed based on tumour size, clinical stage and presence of systemic symptoms [123, 124]. These are based on large, retrospective datasets, and suggest that chest CT may be omitted in patients with cT1a and cN0, and without systemic symptoms, anaemia or thrombocythemia, due to the low incidence of lung metastases (< 1%) in this group of patients. There is a consensus that most bone metastases are symptomatic at diagnosis; thus, routine bone imaging is not generally indicated [120, 125, 126] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [125, 127, 128] (LE: 3). A recent prospective comparative blinded study involving 92 consecutive mRCC patients treated with first-line VEGFR-TKI (median follow-up 35 months) found that whole-body DWI/MRI detected a statistically significant higher number of bony metastases compared with conventional thoraco-abdomino-pelvic contrast-enhanced CT, with higher number of metastases being an independent prognostic factor for progression-free survival (PFS) and OS [129].

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 [130, 131] (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

[70]; however, it requires further validation. The management of cystic renal tumours is also discussed in Section 3.4.7.

Table 5.1: Bosniak classification of renal cysts [130]

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

*5.3.1 **Indications and rationale***

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 [132-137] (LE: 3).

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 [138].

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).

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) [132, 135, 139] (LE: 2b/3).

*5.3.2 **Technique***

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 [135, 140] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [132, 136, 141] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [132, 136] (LE: 3).

Core biopsies are preferred for the characterisation of solid renal masses while a combination with FNA can provide complimentary results and improve accuracy for complex cystic lesions [139, 142, 143] (LE: 2a). A systematic review and meta-analysis of the diagnostic performance and complications of renal tumour biopsy was performed by the Panel, including 57 publications and a total of 5,228 patients. Needle core biopsies were found to have better accuracy for the diagnosis of malignancy compared with FNA [139]. Other studies showed that solid pattern, larger tumour size and exophytic location are predictors of a diagnostic core biopsy [132, 135, 140] (LE: 2b).

5.3.3 *Diagnostic yield and accuracy*

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 [139] (LE: 2b). However, 0–22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [133-137, 140, 141, 144] (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%) [132, 145-147].

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 [139].

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) [139] (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 [132, 135, 148, 149] (LE: 2b). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [150] (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 [151].

5.3.4 *Morbidity*

Overall, percutaneous biopsies have a low morbidity [139]. 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 [152]. 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 [152].

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 [139].

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 [153].

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.	2a
Magnetic resonance imaging has a slightly higher sensitivity and specificity for small cystic renal masses and tumour thrombi as compared to CT.	2a
Contrast enhanced ultrasound has a high sensitivity and specificity for characterisation of renal masses.	2a
Renal mass biopsies are associated with reduced over-treatment of benign masses and offers patients additional information (i.e. grade, subtype) for an informed decision regarding optimal management.	3
Ultrasound, power-Doppler US and positron-emission tomography CT have a low sensitivity and specificity for detection and characterisation of RCC.	2a

Recommendations	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Omit chest CT in patients with incidentally noted cT1a disease due to the low risk of lung metastases in this cohort.	Weak
Use magnetic resonance imaging (MRI) to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, including MRI and contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses, if the results of contrast-enhanced CT are indeterminate.	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 and extension, collecting system invasion, perinephric- and sinus fat invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system [154, 155] (Table 4.1).

6.3 Histological factors

Histological factors include tumour grade, RCC subtype, lymphovascular invasion, tumour necrosis, and invasion of the collecting system [156, 157]. Tumour grade is considered one of the most important histological prognostic factors. Fuhrman nuclear grade is based on simultaneous investigation of nuclear size, nuclear shape and nucleolar prominence [158]. It has been the most widely accepted grading system for several decades, but has now been largely replaced by the WHO/ISUP grading classification [159]. This relies solely on nucleolar prominence for grade 1-3 tumours, allowing for less inter-observer variation [160]. It has been shown that the WHO/ISUP grading provides superior prognostic information compared to Fuhrman grading, especially for grade 2 and grade 3 tumours [161]. Rhabdoid and sarcomatoid changes can be found in all RCC types and are equivalent to grade 4 tumours. Sarcomatoid changes are more often found in chRCC than other subtypes [162]. The percentage of the sarcomatoid component appears to be prognostic as well, with a larger percentage of involvement being associated with worse survival. However, there is no agreement on the optimal prognostic cut-off for sub-classifying sarcomatoid changes [163, 164]. The WHO/ISUP grading system is applicable to both ccRCC and pRCC. It is currently not recommended to grade chRCC. However, a recent study suggested a two-tiered chRCC grading system (low vs. high grade) based on the presence of sarcomatoid differentiation and/or tumour necrosis, which was statistically significant on multivariable analysis [165]. Both the WHO/ISUP and chRCC grading systems need to be validated for prognostic systems and nomograms [159].

Renal cell carcinoma subtype is regarded as another important prognostic factor. On univariable analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [166, 167] (Table 6.1). However, prognostic information provided by the RCC type is lost when stratified according to tumour stage [167, 168] (LE: 3).

In a recent cohort study of 1,943 patients with ccRCC and pRCC significant survival differences were only shown between pRCC type I and ccRCC [169]. Papillary RCC has been traditionally divided into type 1 and 2, but a subset of tumours shows mixed features. For more details, see Section 3.2 - Histological diagnosis. Data also suggest that type 2 pRCC is a heterogeneous entity with multiple molecular subgroups [21]. Some studies suggest poorer survival for type 2 than type 1 [170], but this association is often lost in the multivariable analysis [171]. A meta-analysis did not show a significant survival difference between both types [172].

Renal cell carcinoma with Xp11.2 translocation has a poor prognosis [173]. Its incidence is low, but its presence should be systematically assessed in young patients. Renal cell carcinoma type classification has been confirmed by cytogenetic and genetic analyses [174-176] (LE: 2b). Surgically excised malignant complex cystic masses contain ccRCC in the majority of cases, and more than 80% are pT1. In a recent series, 5-year cancer-specific survival (CSS) was 98% [177]. Differences in tumour stage, grade and CSS between RCC types are illustrated in Table 6.1.

Table 6.1: Baseline characteristics and cancer-specific survival of surgically treated patients by RCC type [162]

Survival time	% RCC	% Sarcomatoid	% T3-4	% N1	% M1	% 10 year CSS (%)
clear-cell RCC	80	5	33	5	15	62
papillary RCC	15	1	11	5	3	86
chromophobe RCC	5	8	15	4	4	86

CSS = cancer-specific survival.

In all RCC types, prognosis worsens with stage and histopathological grade (Table 6.2). 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 new systemic treatments [178, 179]. Although not considered in the current N classification, the number of metastatic regional LNs is an important predictor of survival in patients without distant metastases [180].

Table 6.2: Cancer-specific survival by stage [20]

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)

CI = confidential interval. HR = hazard ratio.

6.4 Clinical factors

Clinical factors include performance status (PS), local symptoms, cachexia, anaemia, platelet count, neutrophil count, lymphocyte count, C-reactive protein (CRP), albumin, and various indices deriving from these factors such as the neutrophil-to-lymphocyte ratio (NLR) [93, 181-185] (LE: 3). As a marker of systemic inflammatory response, a high pre-operative NLR has been associated with poor prognosis [186], but there is signficant heterogeneity in the data and no agreement on the optimal prognostic cutoff. Even though obesity is an aetiological factor for RCC, it has also been observed to provide prognostic information. A high body mass index (BMI) appears to be associated with improved survival outcomes in both non-metastatic and metastatic RCC [187-189]. This association is linear with regards to cancer-specific mortality, while obese RCC patients show increasing all-cause mortality with increasing BMI [190]. There is also evolving evidence on the prognostic value of body composition indices measured on cross-sectional imaging, such as sarcopenia and fat accumulation [191, 192].

6.5 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CaIX), VEGF, hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, p21 [193], PTEN (phosphatase and tensin homolog) cell cycle, E-cadherin, osteopontin [194] CD44 (cell adhesion) [195, 196], CXCR4 [197], PD-L1 [198], miRNA, SNPs, gene mutations, and gene methylations have been investigated (LE: 3) [19]. While the majority of these markers are associated with prognosis and many improve the discrimination of current prognostic models, there has been very little emphasis on external validation studies. Furthermore, there is no conclusive evidence on the value of molecular markers for treatment selection in mRCC [199]. Their routine use in clinical practice is therefore not recommended.

Several prognostic and predictive marker signatures have been described for specific systemic treatments in mRCC. In the JAVELIN Renal 101 trial (NCT02684006), a 26-gene immunomodulatory gene signature predicted PFS in those treated with avelumab plus axitinib, while an angiogenesis gene signature was associated with PFS for sunitinib. Mutational profiles and histocompatibility leukocyte antigen (HLA) types were also associated with PFS, while PD-L1 expression and tumour mutational burden were not [200]. In IMmotion151 (NCT02420821), a T effector/IFN-γ-high or angiogenesis-low gene expression signature predicted improved PFS for atezolizumab plus bevacizumab compared to sunitinib. The angiogenesis-high gene expression signature correlated with longer PFS in patients treated with sunitinib [201]. In CheckMate 214 (NCT02231749), a higher angiogenesis gene signature score was associated with better overall response rates and PFS for sunitinib, while a lower angiogenesis score was associated with higher ORR in those treated with nivolumab plus ipilimumab. Progression-free survival ≥ 18 months was more often seen in patients with higher expression of Hallmark inflammatory response and Hallmark epithelial mesenchymal transition gene sets [202].

Urinary and plasma Kidney-Injury Molecule-1 (KIM-1) has been identified as a potential diagnostic and prognostic marker. KIM-1 concentrations were found to predict RCC up to 5 years prior to diagnosis and were associated with a shorter survival time [203]. KIM-1 is a glycoprotein marker of acute proximal tubular injury and therefore mainly expressed in RCC derived from the proximal tubules such as ccRCC and pRCC [204]. While early studies are promising, more high-quality research is required. Several retrospective studies and large molecular screening programs have identified mutated genes and chromosomal changes 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 [205-207]. These published reports suggest that patients with *BAP1*-mutant tumours have worse outcomes compared with patients with *PBRM1*-mutant tumours [206]. Loss of chromosome 9p and 14q have been consistently shown to be associated with poorer survival [208-210]. The TRACERx renal consortium has proposed a genetic classification based on RCC evolution (punctuated vs. branched vs. linear), which correlates with tumour aggressiveness and survival [209]. Additionally, a 16-gene signature was shown to predict disease-free survival (DFS) in patients with non-metastatic RCC [211]. However, these signatures have not been validated by independent researchers yet.

6.6 Prognostic models

Prognostic models combining independent prognostic factors have been developed and externally validated [212-218]. These models are more accurate than TNM stage or grade alone for predicting clinically relevant oncological outcomes (LE: 3). Before being adopted, new prognostic models should be evaluated and compared to current prognostic models with regards to discrimination, calibration and net benefit. In metastatic disease, risk groups assigned by the Memorial Sloan Kettering Cancer Center (MSKCC) (primarily created in the pre-targeted therapy, and validated in patients receiving targeted therapy) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) (initially created in the targeted therapy era) differ in 23% of cases [219]. The IMDC model has been used in the majority of recent randomised trials, including those with immune checkpoint inhibitors, and may therefore be the preferred model for clinical practice. The discrimination of the IMDC model can be improved by addition of a seventh variable, namely presence of brain, bone, and/or liver metastases [220]. For patients treated with immune checkpoint inhibitors, the monocyte-to-lymphocyte ratio, BMI, and number and site of metastases at baseline were recently used to create a four-tiered prediction model. This model showed greater discrimination than IMDC in predicting OS, but needs further validation [221].

Overall, there is no conclusive evidence that one prognostic model is superior to another for both localised and metastatic disease [19]. Tables 6.3 and 6.4 summarise the current most relevant prognostic models.

6.7 Summary of evidence and recommendations for prognostic factors

Summary of evidence	LE
In RCC patients, TNM stage, tumour size, grade, and RCC subtype provide important prognostic information.	2a

Recommendations	Strength rating
Use the current Tumour, Node, Metastasis classification system.	Strong
Use the WHO/ISUP grading system and classify renal cell carcinoma type.	Strong
Use prognostic models in localised and metastatic disease.	Strong
Do not routinely use molecular markers to assess prognosis.	Strong

Table 6.3: Prognostic models for localised RCC

Prognostic model	Subtype*	Risk factors/prognostic factors
UISS** [222]	All	1. ECOG PS 2. T classification 3. N classification (N+ classified as metastatic) 4. Grade T1N0M0G1–2, ECOG PS 0: low-risk disease T3N0M0G2–4, ECOG PS ≥ 1 OR T4N0M0: high-risk disease Any other N0M0: intermediate-risk disease
Leibovich score/model 2003 [215]	CC	1. T classification (pT1a: 0 points, pT1b: 1 point, pT2: 3 points, pT3–4: 4 points) 2. N classification (pNx/N0: 0 points, pN+: 2 points) 3. Tumour size (< 10 cm: 0 points, ≥ 10 cm: 1 point) 4. Grade (G1–2: 0 points, G3: 1 point, G4: 3 points) 5. Tumour necrosis (absent: 0 points, present: 1 point) 0–2 points: low-risk disease 3–5 points: intermediate-risk disease 6 or more points: high-risk disease
Leibovich score/model 2018 [223]	CC, P, CHR	<u>ccRCC</u> • Progression (9 factors): constitutional symptoms, grade, tumour necrosis, sarcomatoid features, tumour size, perinephric or sinus fat invasion, tumour thrombus level, extension beyond kidney, nodal involvement. • Cancer-specific survival (12 factors): age, ECOG PS, constitutional symptoms, adrenalectomy, surgical margins, grade, tumour necrosis, saromatoid features, tumour size, perinephric or sinus fat invasion, tumour thrombus, nodal involvement. • No risk groups/prognostic groups. <u>pRCC</u> • Low risk (group 1): grade 1–2, no fat invasion, no tumour thrombus. • Intermediate risk (group 2): grade 3, no fat invasion, no tumour thrombus. • High risk (group 3): grade 4 or fat invasion or any level tumour thrombus. <u>chRCC</u> • Low risk (group 1): no fat invasion, no sarcomatoid differentiation, no nodal involvement. • Intermediate risk (group 2): fat invasion and no sarcomatoid differentiation and no nodal inolvement. • High risk (group 3): sarcomatoid differentiation or nodal involvement.
VENUSS score/model*** [171]	P	1. T classification (pT1: 0 points, pT2: 1 point, pT3–4: 2 points) 2. N classification (pNx/pN0: 0 points, pN1: 3 points) 3. Tumour size (≤ 4 cm: 0 points, > 4 cm: 2 points) 4. Grade (G1/2: 0 points, G3/4: 2 points) 5. Tumour thrombus (absent: 0 points, present: 2 points) 0–2 points: low-risk disease 3–5 points: intermediate-risk disease 6 or more points: high-risk disease
GRANT score/model**** [224]	All	1. Age > 60 years 2. T classification = T3b, pT3c or pT4 3. N classification = pN1 4. (Fuhrman) grade = G3 or G4 0–1 factors: favourable-risk disease 2 or more factors: unfavourable-risk disease

* *ccRCC = clear-cell RCC; ECOG = Eastern Cooperative Oncology Group; pRCC = papillary RCC; chRCC = chromophobe RCC.*

** *University of California Integrated Staging system. Available at https://www.mdcalc.com/ucla-integrated-staging-system-uiss-renal-cell-carcinoma-rcc.*

*** *VEnous extension, NUclear grade, Size, Stage. Available at https://evidencio.com/.*

**** *GRade, Age, Nodes and Tumour.*

Table 6.4: Prognostic models for metastatic RCCC

Prognostic model	Subtype	Risk factors/prognostic factors
MSKCC [225]**	All	1. Karnofsky PS [226]* < 80% 2. Interval from diagnosis to systemic treatment < 1 year 3. Haemoglobin < Lower Limit of Normal 4. Corrected calcium >10 mg/dL/> 2.5 mmol/L 5. LDH > 1.5x Upper Limit of Normal 0 factors: favourable-risk disease 1–2 factors: intermediate-risk disease 3–5 factors: poor-risk disease
IMDC [227]***	All	1. Karnofsky PS [226]* < 80% 2. Interval from diagnosis to treatment < 1 year 3. Haemoglobin < lower limit of normal 4. Corrected calcium > upper limit of normal (i.e. > 10.2 mg/dL) 5. Neutrophil count > upper limit of normal (i.e. > 7.0×10^9/L) 6. Platelet count > upper limit of normal (i.e. > 400,000) 0 factors: favourable-risk disease 1–2 factors: intermediate-risk disease 3–6 factors: poor-risk disease

IMDC = International Metastatic Renal Cancer Database Consortium; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status.

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

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

*** *IMDC: https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-score-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 systematic review 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 in localised RCC

7.1.2.1.1 T1 RCC

Outcome 1: Cancer-specific survival

Most studies comparing the oncological outcomes of PN and RN are retrospective and include cohorts of varied and, overall, limited size [228, 229]. There is only one, prematurely closed, prospective RCT including patients with organ-confined RCCs of limited size (< 5 cm), showing comparable non-inferiority of CSS for PN vs. RN (HR: 2.06 [95% CI: 0.62–6.84]) [230].

Outcomes 2 & 3: Overall mortality and renal function

Partial nephrectomy preserved kidney function better after surgery, thereby potentially lowering the risk of development of cardiovascular disorders [228, 231-235]. When compared with a radical surgical approach, several retrospective analyses of large databases have suggested a decreased cardiovascular-specific mortality [232, 236] as well as improved OS for PN compared to RN. However, in some series this held true only for younger patients and/or patients without significant comorbidity at the time of the surgical intervention

[237, 238]. An analysis of the U.S. Medicare database [239] could not demonstrate an OS benefit for patients ≥ 75 years of age when RN or PN were compared with non-surgical management.

Conversely, another series that addressed this question and also included Medicare patients suggested an OS benefit in older patients (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 [240]. These conflicting results may be an indication that unknown statistical confounders hamper the retrospective analysis of population-based tumour registries. In the only prospectively randomised, but prematurely closed, heavily underpowered, trial, PN seems to be less effective than RN in terms of OS in the intention to treat (ITT) population (HR: 1.50 [95% CI: 1.03–2.16]). However, in the targeted RCC population of the only RCT, the trend in favour of RN was no longer significant [230]. 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 [235]. 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) [241]. 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. Huang *et al*. found that 26% of patients with newly diagnosed RCC had an GFR ≤ 60 mL/min, even though their baseline serum creatinine levels were in the normal range [96].

Outcomes 4 & 5: Peri-operative outcomes and quality of life

In terms of the intra- and peri-operative morbidity/complications associated with PN vs. RN, the European Organisation for Research and Treatment of Cancer (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 [242].

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 [242, 243].

In view of the above, and since oncological safety (CSS and RFS) of PN, so far, has been found non-differing from RN outcomes, 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. Irrespective of the available data, in frail patients, treatment decisions should be individualised, weighing the risks and benefits of PN vs. RN, the increased risk of peri-operative complications and the risk of developing or worsening CKD post-operatively.

7.1.2.1.2 T2 renal cell carcinoma

There is very limited evidence on the optimal surgical treatment for patients with larger renal masses (T2). Some retrospective comparative studies of PN vs. RN for T2 RCC have been published [244]. A trend for lower tumour recurrence- and cancer-specific mortality is reported in PN groups. The estimated blood loss is reported to be higher for PN groups, as is the likelihood of post-operative complications [244]. A recent multicentre 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 ($p = 0.04$) [245]. Overall the level of the evidence is low. These studies including T2 masses all have a high risk of selection bias due to imbalance between the PN and RN groups regarding patient's age, comorbidities, tumour size, stage, and tumour position. These imbalances in covariation factors may have a greater impact on patient outcome than the choice of PN or RN. The Panel's confidence in the results is limited and the true effects may be substantially different.

In view of the above, the risks and benefits of PN should be discussed patients with T2 RCC with a solitary kidney, bilateral renal tumours or CKD, if technically feasible, with sufficient parenchymal volume preserved to allow sufficient post-operative renal function, PN should be considered in these patients.

7.1.2.2 Associated procedures

7.1.2.2.1 Adrenalectomy

One prospective non-randomised study compared the outcomes of RN with or without, ipsilateral adrenalectomy [246]. Multivariable 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 of the 48 interventions were for benign lesions [246].

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 [247]. The clinical assessment of LN status is based on the detection of an enlargement of LNs either by CT/MRI or intra-operative palpability of enlarged nodes. Less than 20% of suspected metastatic nodes (cN+) are positive for metastatic disease at histopathological examination (pN+) [248]. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [249]. 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-mRCC were compared using a propensity score analysis. In this study LND was not significantly associated with a reduced risk of distant metastases, cancer-specific or all-cause mortality. The extent of the LND was not associated with improved oncologic outcomes [250]. 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 [249, 251-253]. 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 (eLND) on the disease-specific survival (DSS) of patients with pathologically confined negative nodes was demonstrated [254]. 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 eLND results in a significant prolongation of CSS in patients with unfavourable prognostic features (e.g., sarcomatoid differentiation, large tumour size) [255]. 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 [256].

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 LN involvement of only 4%, the risk of lymphatic spread appears to be very low. Recognising the latter, only a staging effect was attributed to LND [248]. This trial included a very high percentage of patients with pT2 tumours, which are not at increased risk for LN metastases. Only 25% of patients with pT3 tumours underwent a complete LND and the LN template used by the authors was not clearly stated.

The optimal extent of LND remains controversial. Retrospective studies suggest that an eLND 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 [249, 257, 258]. At least 15 LNs should be removed [255, 259]. Sentinel LND is an investigational technique [260, 261].

7.1.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [262, 263]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [264, 265]. 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
Retrospective studies suggest that oncological outcomes are similar following PN vs. RN in patients with larger (≥ 7 cm) RCC. Post-operative complication rates are higher in PN patients.	3b
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 radiographic 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 (PN) to patients with T1 tumours.	Strong
Offer PN to patients with T2 tumours and a solitary kidney or chronic kidney disease, if technically feasible.	Weak
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Do not offer an extended lymph node dissection to patients with organ-confined disease.	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 [266] 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 [267-269]. Based on a systematic review, less morbidity was found for laparoscopic vs. open RN [228].

Data from one RCT [268] and two non-randomised studies [270, 271] 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 [271]. 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 [268, 270, 271]. 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 [270].

Some comparative studies focused on the peri-operative outcomes of laparoscopic vs. RN for renal ≥ T2 tumours. 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 [269, 271, 272]. Intra-operative and post-operative complications were similar in the two groups and no significant differences in CSS, PFS and OS were reported [269, 271, 272] (LE: 2b). Another multicentre propensity matched analysis compared laparoscopic- and open surgery for pT3a RCC, showing no significant difference in 3-year RFS between groups [273]. The best approach for laparoscopic RN was the retroperitoneal or transperitoneal approach with similar oncological outcomes in two RTCs [274, 275] and one quasi-randomised study [276]. Quality of life variables were similar for both approaches. Hand-assisted vs. standard laparoscopic RN was compared in one quasi-randomised study [276] and one database review and estimated 5-year OS, CSS, and RFS rates were comparable [277]. 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 [276, 277]. However, the sample size was small.

Data of a large retrospective cohort study on robot-assisted laparoscopic vs. laparoscopic RN showed robotic-assisted laparoscopic RN was not associated with increased risk of any or major complications but had a longer operating time and higher hospital costs compared with laparoscopic RN [278]. A systematic review reported on robot-assisted laparoscopic vs. conventional laparoscopic RN, showing no substantial differences in local recurrence rates, nor in all-cause cancer-specific mortality [279]. Similar results were seen in observational cohort studies comparing 'portless' and 3-port laparoscopic RN, with similar peri-operative outcomes [280, 281].

7.1.3.2 Partial nephrectomy techniques

7.1.3.2.1 Open versus laparoscopic approach

Studies comparing laparoscopic and open PN found no difference in PFS [282-285] and OS [284, 285] 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 [273]. 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 [273]. The mean estimated blood loss was found to be lower with the laparoscopic approach [282, 284, 286], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events were similar [282, 284]. Operative time is generally longer with the laparoscopic approach [283-285] and warm ischaemia time is shorter with the open approach [282, 284, 286, 287]. In a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [285], but not after 3.6 years follow-up. In another comparative study, the surgical approach was not an independent predictor for post-operative CKD [287]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [288]. Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [289]. 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 [290].

7.1.3.2.2 Open versus robotic approach

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 between groups [291].

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 [292].

7.1.3.2.3 Open versus hand-assisted approach

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 vs. open PN patients, but there was no significant difference in high Clavien grade complications. Three months after the operation, GFR was lower in the HALPN than in the open PN group [293].

7.1.3.2.4 Open versus laparoscopic versus robotic approaches

In a retrospective propensity-score-matched study, comparing open-, laparoscopic- and robot-assisted PN, after 5-year of median follow-up, similar rates of local recurrence, distant metastasis and cancer-related death rates were found [294].

7.1.3.2.5 Laparoscopic versus robotic approach

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 [295].

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 differences were observed between the two groups regarding complications, change of serum creatinine after surgery, operative time, estimated blood loss and positive surgical margins [296].

7.1.3.2.6 Surgical volume

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 [297]. 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 [298]. A French study, including 1,222 RAPN patients, has shown that hospital volume is the main predictive factor of Trifecta achievement (no complications, warm ischaemia time < 25 min, and negative surgical margins) after adjustment for other variables, including surgeon volume [299]. The prospective REgistry of COnservative and Radical Surgery for cortical renal tumour Disease (RECORd-2) study including 2,076 patients showed that the hospital volume (> 60 PN/year) is an independent predictor for positive surgical margins [300].

7.1.3.3 Positive surgical margins on histopathological specimens

A positive surgical margin is encountered in about 2–8% of PNs [296]. Studies comparing surgical margins with different surgical approaches (open, laparoscopic, robotic) are inconclusive [301, 302]. Most trials showed that intra-operative frozen section analysis had no influence on the risk of definite positive surgical margins [303]. 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) [304-307]. The potential negative impact of a positive margin status on the oncologic outcome is still controversial [301].

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 [305, 306]. 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 [308].

However, only a proportion of patients with an uncertain margin status actually harbour residual malignancy [309]. Local tumour bed recurrences were found in 16% in patients with positive surgical margins compared with 3% in those with negative margins [304], Therefore, RN or re-resection of margins can result in over-treatment 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 [305, 310]. On the other hand, protection from recurrence is not ensured by negative surgical margins [311].

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
Robotic-assisted and laparoscopic PN are associated with shorter length of hospital stay and lower blood loss compared to open PN.	2b
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared to RN.	3
Hospital volume in PN might impact on surgical complications, warm ischaemia and surgical margins.	3
Radical nephrectomy after positive surgical margins can result in over-treatment in many cases.	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
Intensify follow-up in patients with a positive surgical margin.	Weak

*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 [239, 312, 313]. 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 [312]. Analyses of older patients (> 75 years) failed to show the same benefit in cancer-specific mortality for surgical treatment [314-316].

7.1.4.2 Active surveillance and watchful waiting

Elderly and comorbid patients with incidental small renal masses have a low RCC-specific mortality and significant competing-cause mortality [317, 318]. 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 [319]. 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 [320, 321].

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, at multivariate analysis, management type was not associated with OS after adjusting for age, comorbidities, and other variables [317]. No statistically significant differences 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 [322]. The prospective non-randomised multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) study 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 [323, 324].

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 [323]. 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 of small renal masses, followed, if required, by treatment for progression [319-321, 325-328].

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 [329].

7.1.4.3 Role of renal tumour biopsy before active surveillance

Histological characterisation of small renal masses by renal tumour biopsy is useful to select tumours at lower risk of progression based on grade and histotype, which can be safely managed with AS. Pathology can also help to tailor surveillance imaging schedules. In the largest cohort of biopsy-proven, small, sporadic RCCs followed with AS a significant difference in growth and progression among different RCC subtypes was observed. Clear-cell RCC small renal masses grew faster than papillary type 1 small renal masses (0.25 and 0.02 cm/year on average, respectively, p = 0.0003) [330].

7.1.4.4 Tumour ablation

7.1.4.4.1 Role of renal mass biopsy

A RMB is required prior to tumour ablation (TA) (see Sections 5.3 Renal tumour biopsy and 5.4 Summary of evidence and recommendations for the diagnostic assessment of RCC). Historically, up to 45% of patients underwent TA of a benign or non-diagnostic mass [331, 332]. A RMB in a separate session reduces over-treatment significantly, with 80% of patients with benign lesions opting not to proceed with TA [332]. Additionally, there is some evidence that the oncological outcome following TA differs according to RCC subtype which should therefore be factored into the decision-making process. In a series of 229 patients with cT1a tumours (mean size 2.5 cm) treated with RFA, the 5-year DFS rate was 90% for ccRCC and 100% for pRCC (80 months: 100% vs. 87%, p = 0.04) [333]. In another series, the total TA effectiveness rate was 90.9% for ccRCC and 100% for pRCC [334]. A study comparing RFA with surgery suggested worse outcomes of RFA vs. PN in cT1b ccRCC, while no difference was seen in those with non-ccRCC [335]. Furthermore, patients with high-grade RCC or metastasis may choose different treatments over TA. Finally, patients without biopsy or a non-diagnostic biopsy are often assumed to have RCC and will undergo potentially unnecessary radiological follow-up or further treatment.

7.1.4.4.2 Cryoablation

Cryoablation is performed using either a percutaneous- or a laparoscopic-assisted approach, with technical success rates of > 95% [336]. In comparative studies, there was no significant difference in the overall complication rates between laparoscopic- and percutaneous cryoablation [337-339]. One comparative study reported similar OS, CSS, and RFS in 145 laparoscopic patients with a longer follow-up vs. 118 patients treated percutaneously with a shorter follow-up [338]. A shorter average length of hospital stay was found with the percutaneous technique [338-340]. A systematic review including 82 articles reported complication rates ranging between 8 and 20% with most complications being minor [341]. Although a precise definition of tumour recurrence is lacking, the authors reported a lower RFS as compared to that of PN.

Oncological outcomes after cryoablation have generally been favourable for cT1a tumours. In a recently published series of 308 patients with cT1a and cT1b tumours undergoing percutaneous cryoablation, local recurrence was seen in 7.7% of cT1a tumours vs. 34.5% of cT1b tumours. Disease-free survival for the entire cohort was 92.5% at 1 year, 89.3% at 2 years, and 86.7% at 3 years. On multivariable regression, the risk of disease progression increased by 32% with each 1 cm increase in tumour size (HR: 1.32, p < 0.001). Mean decline in eGFR was 11.7 mL/min/1.73 m^2 [342]. In another large series of 220 patients with biopsy proven cT1 RCC, 5-year local RFS was 93.9%, while metastasis-free survival approached 94.4% [336].

For cT1b tumours, local tumour control rates drop significantly. One study showed local tumour control in only 60.3% at 3 years [343]. In another series, the PFS rate was 66.7% at 12 months [344].

Furthermore, recent analyses demonstrated 5-year cancer-specific mortality rates of 7.6–9% [345, 346]. On multivariable analysis, cryoablation of cT1b tumours was associated a 2.5-fold increased risk of death from RCC compared with PN [345].

Recurrence after initial cryoablation is often managed with re-cryoablation, but only 45% of patients remain disease-free at 2 years [347].

7.1.4.4.3 Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Several studies compared patients with cT1a tumours treated by laparoscopic or percutaneous RFA [348-351]. Complications occurred in up to 29% of patients but were mostly minor. Complication rates, recurrence rates and CSS were similar in patients treated laparoscopically and percutaneously.

The initial technical success rate on early (i.e. 1 month) imaging after one session of RFA is 94% for cT1a and 81% for cT1b tumours [352]. This is generally managed by re-RFA, approaching overall total technical success rates > 95% with one or more sessions [353].

Long-term outcomes with over five years of follow-up following RFA have been reported. In recent studies, the 5-year OS rate was 73–79% [352, 353], due to patient selection. Oncological outcomes for cT1a tumours have been favourable. In a recent study, the 10-year disease-free survival rate was 82%, but there was a significant drop to 68% for tumours > 3 cm [353]. In series focusing on clinical T1b tumours (4.1–7.0 cm), the 5-year DFS rate was 74.5% to 81% [352, 354]. Oncological outcomes appear to be worse than after surgery, but comparative data are severely biased (see Section 7.1.4.3.4). In general, most disease recurrences occur locally and recurrences beyond five years are rare [353, 354].

7.1.4.4.4 Tumour ablation versus surgery

The Guideline Panel performed a protocol-driven systematic review of comparative studies (including > 50 patients) of TA with PN for T1N0M0 renal masses [7]. Twenty-six non-randomised comparative studies published between 2000 and 2019 were included, recruiting a total of 16,780 patients. Four studies compared laparoscopic TA vs. laparoscopic/robotic PN; 16 studies compared laparoscopic or percutaneous TA vs. open-, laparoscopic- or robotic PN; 2 studies compared different techniques of TA and 4 studies compared TA vs. PN vs RN. In this systematic review, TA as treatment for T1 renal masses was found to be safe in terms of complications and adverse events, but its long-term oncological effectiveness compared with PN remained unclear. The primary reason for the persisting uncertainty was related to the nature of the available data; most studies were retrospective observational studies with poorly matched controls, or single-arm case series with short follow-up. Many studies were poorly described and lacked a clear comparator. There was also considerable methodological heterogeneity. Another major limitation was the absence of clearly defined primary outcome measures. Even when a clear endpoint such as OS was reported, data were difficult to interpret because of the varying length and type of follow-up amongst studies. The Panel also appraised the published systematic reviews based on the AMSTAR 2 tool which showed critically low or low ratings [7].

Tumour ablation has been demonstrated to be associated with good long-term survival in several single-arm non-comparative studies [355, 356]. Due to the lack of controls, this apparent benefit is subject to significant uncertainties. Whether such benefit is due to the favourable natural history of such tumours or due to the therapeutic efficacy of TA, as compared to PN, remains unknown. In addition, there are data from comparative studies suggesting TA may be associated with worse oncological outcomes in terms of local recurrence and metastatic progression and cancer-specific mortality [237, 345, 346, 357, 358]. However, there appears to be no clinically significant difference in 5-year cancer-specific mortality between TA and AS [313].

The Panel concluded that the current data are inadequate to reach conclusions regarding the clinical effectiveness of TA as compared with PN. Given these uncertainties in the presence of only low-quality evidence, TA can only be recommended to frail and/or comorbid patients with small renal masses.

7.1.4.4.5 Stereotactic ablative radiotherapy

Stereotactic ablative radiotherapy (SABR) has been emerging as a treatment option for medically inoperable patients with localised cT1a and cT1b tumours. Patients usually receive 26 Gy in a single fraction, three fractions of 14 Gy or five fractions of 6 Gy [359, 360]. In a systematic review or non-comparative single-arm studies, the local control rate was 97.2% and the mean change in eGFR was 7.7 mL/min/1.73 m^2. Grade 3 or 4 toxicities occurred in 1.5% of patients. However, viable tumour cells are often seen in post-SABR biopsies, although their clinical significance remains unclear [360]. Although early results of SABR are encouraging, more evidence from randomised trials is needed.

7.1.4.4.6 Other ablative techniques

Some studies have shown the feasibility of other ablative techniques, such as microwave ablation, high-intensity focused US ablation and non-thermal irreversible electroporation. However, these techniques are still considered experimental. The best evidence base for these techniques exists for percutaneous microwave ablation. In a study of 185 patients with a median follow-up of 40 months, the 5-year local progression rate was 3.2%, while 4.3% developed distant metastases [361]. Results appear to be favourable for cT1b tumours as well [362]. Overall, current data on cryoablation, RFA and microwave ablation of cT1a renal tumours indicate short-term equivalence with regards to complications, oncological and renal functional outcomes [363].

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

Summary of evidence	LE
Most population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management.	3
In AS cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1–2%).	3
Low quality studies suggest high disease recurrence rates after RFA of tumours > 3 cm and after cryoablation of tumours > 4 cm.	3
Low quality studies suggest a higher local recurrence rate for TA therapies compared to PN, but the quality of data does not allow definitive conclusions.	3

Recommendation	Strength rating
Offer active surveillance (AS) or thermal ablation (TA) to frail and/or comorbid patients with small renal masses.	Weak
Perform a percutaneous renal mass biopsy prior to, and not concomitantly with, TA.	Strong
When TA or AS are offered, discuss with patients about the harms/benefits with regards to oncological outcomes and complications.	Strong
Do not routinely offer TA for tumours > 3 cm and cryoablation for tumours > 4 cm.	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 Role of lymph node invasion in locally advanced RCC

In locally advanced RCC, the role of LND is still controversial. The only available RCT demonstrated no survival benefit for patients undergoing LND but this trial mainly included organ-confined disease cases [248]. In the setting of locally advanced disease, several papers addressed the topic with contradictory results, as did several systematic reviews. Bhindi *et al*. could not confirm any survival benefit in patients at high risk of progression treated with LND [364]. More recently, Luo *et al*. reported a systematic review and meta-analyses showing a survival benefit in patients with locally advanced disease treated with LND [365]. More specifically, thirteen studies on patients with LND and non-LND were identified and included in the analysis. In the subgroup of locally advanced RCC (cT3-T4NxM0), LND showed a significantly better OS rate in patients who had undergone LND compared to those without LND (HR: 0.73, 95% CI: 0.60–0.90, p = 0.003).

7.2.2.1 Management of clinically negative lymph nodes (cN-) in locally advanced RCC

In case of cN-, the probability of finding pathologically confirmed LN metastases ranges between 0 and 25%, depending mainly on primary tumour size and the presence of distant metastases [366]. In case of clinically negative LNs (cN-) at imaging, removal of LNs is justified only if visible or palpable during surgery [367], at least for staging, prognosis and follow-up implications although a benefit in terms of cancer control has not yet been demonstrated [250, 364]. Whether to extend the LND also to retroperitoneal areas without cN+ remains controversial [249].

7.2.2.2 Management of clinically positive lymph nodes (cN+) in locally advanced RCC

In case of cN+, the probability to find pathologically confirmed LN metastases ranges between 10.3% (cT1 tumours) up to 54.5% in case of locally advanced disease. In cN+, removal of visible and palpable nodes during lymphadenectomy is always justified [367], at least for staging, prognosis and follow-up implications, although a benefit in terms of cancer control has not yet been demonstrated [250, 364].

7.2.3 *Management of locally advanced unresectable RCC*

In case of locally advanced unresectable RCC, a multidisciplinary evaluation, including urologists, medical oncologists and radiation therapists is suggested to maximise cancer control, pain control and the best supportive care. In patients with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [264, 265, 368]. 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 [369-377].

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 [374]. Therefore, 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 [378, 379]. Only 5 studies were eligible for final inclusion, with a high risk of bias across all studies.

Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [380, 381]. 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 [382].

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 [378, 380-382]. 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, the survival benefit of LN dissection is unproven but LN dissection has significant staging, prognosis and follow-up implications.	3
Low quality data suggest that tumour thrombus excision in non-metastatic disease may be beneficial.	3

Recommendations	Strength rating
In patients with clinically enlarged lymph nodes (LNs), perform LN dissection for staging, prognosis and follow-up implications.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong
In case of metastatic disease, discuss surgery within the context of a multidisciplinary team.	Weak

7.2.5 *Neoadjuvant and adjuvant therapy*

Neoadjuvant therapy is currently under investigation and available in clinical trials.

There is currently no evidence from a recent systematic review (including ten retrospective studies and two RCTs) that adjuvant radiation therapy increases survival [383].

Similarly, there is currently no evidence from randomised phase III trials that medical 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 [384-388] (LE: 1b). Results from prior adjuvant trials studying interferon-alpha (IFN-α) and interleukin-2 (IL-2) did not show a survival benefit [389]. A similar observation was made in an adjuvant trial of girentuximab, a monoclonal antibody against carboanhydrase IX (CAIX) (ARISER Study) [390].

At present, there is no OS data supporting the use of adjuvant VEGFR or mTOR inhibitors. Thus far, several 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 [391]. 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, for 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 [392].

The PROTECT study included 1,135 patients treated with pazopanib (n = 571) vs. placebo (n = 564) in a 1:1 randomisation [393]. The primary endpoint was amended after 403 patients received a starting dose of 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: 0.51–0.94, 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 [394, 395].

The ATLAS study, a randomised, double-blind phase III trial including patients receiving (1:1) oral twice-daily axitinib 5 mg or placebo for ≤ 3 years, for a minimum of one year unless patients experienced a recurrence, had a second primary malignancy, significant toxicity, or withdrew consent. The primary endpoint was DFS. A total of 724 patients (363 vs. 361, for axitinib vs. placebo) were randomised. The trial was stopped due to futility at a preplanned interim analysis at 203 DFS events. There was no significant difference in DFS per independent review committee (IRC) (HR: 0.870, 95% CI: 0.660–1.147, p=0.3211). In the highest-risk subpopulation, a 36% and 27% reduction in risk of a DFS event (HR; 95% CI) was observed per investigator (HR: 0.641, 95% CI: 0.468–0.879, p = 0.0051) and by IRC (HR: 0.735, 95% CI: 0.525–1.028, p = 0.0704), respectively. Overall survival data were not mature. Similar adverse events (AEs; 99% vs. 92%) and serious AEs (19% vs. 14%), but more grade 3/4 AEs (61% vs. 30%) were reported for axitinib vs. placebo [396].

In contrast, the S-TRAC study included 615 patients randomised to either sunitinib or placebo [397]. The results showed a benefit of sunitinib over placebo for DFS (HR: 0.76, 95% CI: 0.59–0.98, p = 0.03). 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).

To date, the results of two RCTs on the role of adjuvant sorafenib (SORCE) and everolimus (EVEREST) in patients with RCC are still awaited. Their findings may provide additional insight into the role of adjuvant targeted therapy in RCC.

A recent meta-analysis of phase III randomised clinical trials on adjuvant TKIs in ccRCC was published [398]. In the overall population, the pooled HR of OS and DFS was 0.89 (95% CI: 0.76–1.04) and 0.84 (95% CI: 0.76–0.93), respectively. In the low- and high-risk populations, the pooled DFS HR was 0.98 (95% CI: 0.82–1.17) and 0.85 (95% CI: 0.75–0.97), respectively. Adjuvant use of TKIs does not appear to provide a statistically significant OS benefit. However, a benefit in DFS has been observed in overall and high-risk populations, suggesting that better selection of patients might be important for the evaluation of adjuvant therapies in RCC, although these results must be balanced against significant toxicity.

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.

Immune checkpoint inhibitors, designed to restore and enhance immune activity against cancer cells, have shown impressive efficacy in the metastatic setting. Several trials have tested these agents in metastatic RCC, leading to a still-ongoing revolution in the treatment pathway. The inclusion of these drugs in clinical practice has led to a third generation of adjuvant studies on immune checkpoint inhibitors. These include the programmed death receptor-1 inhibitors nivolumab (PROSPER; NCT03055013), pembrolizumab (KEYNOTE-564; NCT03142334), as well as the programmed death ligand-1 inhibitors atezolizumab (IMmotion010; NCT03024996) and durvalumab (RAMPART [Renal Adjuvant MultiPle Arm Randomised Trial]; NCT03288532). Recruitment for most of these studies is still ongoing and results are awaited as of 2022.

7.2.5.1 *Summary of evidence and recommendations for adjuvant therapy*

Summary of evidence	LE
Adjuvant therapy does not improve survival after nephrectomy.	1b
In one single RCT, in selected high-risk patients, adjuvant sunitinib improved disease-free survival (DFS) but not overall survival (OS).	1b
Adjuvant sorafenib, pazopanib, everolimus, girentuximab or axitinib does not improve DFS or OS after nephrectomy.	1b
Adjuvant RCTs are ongoing to evaluate the benefit of adjuvant immunotherapy after nephrectomy in high-risk patients.	1b

Recommendations	Strength rating
Do not offer adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab 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 combined analysis of two RCTs comparing CN+ IFN-based immunotherapy vs. IFN-based immunotherapy only, increased long-term survival was found in patients treated with CN [399].

However, IFN-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 [400, 401] and a narrative systematic review were identified [402]. The narrative systematic review included both RCTs and 10 non-randomised studies. 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 [403]. 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: 0.88, 95% CI: 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: 0.57, 95% CI: 0.34–0.95, p = 0.032). The deferred CN approach appears to select out patients with inherent resistance to systemic therapy [404]. This confirms previous findings from single-arm phase II studies [404, 405]. Moreover, deferred CN and surgery appear safe after sunitinib which supports the findings, with some caution, of the only available RCT.

In patients with poor PS or IMDC poor risk, small primaries and high metastatic volume and/or a sarcomatoid tumour, CN is not recommended [406]. These data are confirmed by CARMENA [403] and upfront pre-surgical VEGFR-targeted therapy followed by CN seems to be beneficial [407].

Meanwhile first-line therapy recommendations for patients with their primary tumour in place have changed to immune checkpoint inhibitor combination therapy (see Section 7.4.2.4) with sunitinib and other VEGFR-TKI monotherapies reserved for those who cannot tolerate immune checkpoint inhibitor (ICI) combination or have no access to these drugs. High level evidence regarding CN is not available for ICI combinations but up to 30% of patients with primary metastatic disease, treated with their tumour in place, were included in the pivotal ICI combination trials (Table 7.1). The subgroup HRs, where available, suggest better outcomes for the ICI combination compared to sunitinib monotherapy. In mRCC patients without a need for immediate drug treatment, a recent systematic review evaluating effects of CN demonstrated an OS advantage of CN [402]. These data were supported by a nation-wide registry study showing that patients selected for primary CN had a significant OS advantage across all age groups [408].

Table 7.1: Key trails on immune checkpoint inhibitor combinations for primary metastatic disease

Trial	Drug combination	Number and % of patients treated with primary tumour in place	Number of patients treated with the primary tumour in place (ICI combination vs. sunitinib)		Subgroup analyses (HR with 95% CIs)	
			ICI combination	sunitinib	PFS	OS
CheckMate 214 [409]	ipilimumab + nivolumab	187/847 (22%)	84	103	NA	0.63 (0.42–0.94)
CheckMate 9ER [410]	cabozantinib + nivolumab	196/651 (30.1%)	101	95	0.63 (0.43–0.92)	0.79 (0.48–1.29)
Javelin 101 [411]	axitinib + avelumab	179/886 (20.2%)	90	89	0.75 (0.48–1.65)	NA
KEYNOTE-426 [412]	axitinib + pembrolizumab	143/861 (16.6%)	73	70	0.68 (0.45–1.03)	0.57 (0.36–0.89)

CI = confidence interval; HR = hazard ratio; ICI = immune checkpoint inhibitor; NA = not available; PFS = profession-free survival; OS = overall survival.

The results of CARMENA and SURTIME demonstrated that patients who require systemic therapy benefit from immediate drug treatment. While randomised trials to investigate deferred vs. no cytoreductive nephrectomy with ICI and ICI combinations are ongoing, the exploratory results from the ICI combination trials demonstrate that the respective IO+IO or TKI+IO combinations have a superior effect on the primary tumour and metastatic sites when compared to sunitinib alone (Table 7.1). In accordance with the CARMENA and SURTIME data this suggests that mRCC patients and IMDC intermediate- and poor-risk groups with their primary tumour in place should be treated with upfront IO-based combinations. In patients with a clinical response to IO-based combinations, a subsequent CN may be considered.

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 [264, 265, 368] (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 in 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
Patients with their primary tumour in place treated with ICI-based combination therapy have better PFS and OS in exploratory subgroup analyses compared to treatment with sunitinib.	2b

Recommendations	Strength rating
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform immediate CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Start systemic therapy without CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Discuss delayed CN with patients who derive clinical benefit from systemic therapy.	Weak
Perform immediate CN in patients with a good performance status 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 systematic review of the local treatment of metastases from RCC in any organ was undertaken [413]. 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 [414]. 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 [415-422]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC metastases in bone, including the spine [423-425], two in the brain [426, 427] and one each in the liver [428] lung [429] and pancreas [430]. Three studies were published as abstracts only [418, 420, 429]. 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

A systematic review, including only 8 studies, compared complete vs. no and/or incomplete metastasectomy of RCC metastases in various organs [415-422]. In one study complete resection was achieved in only 45% of the metastasectomy cohort, which was compared with no metastasectomy [422]. Non-surgical modalities were not applied. Six studies [416-418, 420-422] 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 [415] showed no significant difference in CSS between complete and no metastasectomy, and one [419] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases in the lung [429], liver [428], and pancreas [430], respectively. The lung study reported a significantly higher median OS for metastasectomy vs. medical therapy only for both targeted 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 [425]. 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 [423]. A significantly higher 5-year CSS rate was observed in the intervention group. After adjusting for prior nephrectomy, gender and age, multi-variable 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 [424]. Pain, 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 compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS and WBRT [426]. 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 [427]. 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 [431]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [432] (see recommendation Section 7.1.2.2.4).

7.3.2.5 Adjuvant treatment in cM0 patients after metastasectomy

Patients after metastasectomy and no evidence of disease (cM0) have a high risk of relapse. Recent attempts to reduce RFS by offering adjuvant TKI treatment after metastasectomy did not demonstrate an improvement in RFS. In a recent phase II trial 129 patients were randomised to either pazopanib 800 mg daily vs. placebo for 52 weeks. The primary study endpoint of a 42% DFS improvement from 25% to 45% at three years was not met. Hazard ratio for DFS in pazopanib vs. placebo-treated patients was 0.85 (0.55–1.31), p = 0.47 [433]. A second phase II trial randomised 69 ccRCC patients after metastasectomy and no evidence of disease to either sorafenib (400 mg twice daily) or observation. The study was terminated early due to slow accrual and the availability of new agents and multimodal treatment options, including surgery or a locoregional approach. The primary endpoint of RFS was not reached with a RFS of 21 months in the sorafenib arms vs. 37 months in the observation arm (p = 0.404) [434].

7.3.2.6 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
Tyrosine kinase inhibitors treatment after metastasectomy in patients with no evidence of disease did not improve RFS when compared to placebo or observation.	1b

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
Do not offer tyrosine kinase inhibitor treatment to mRCC patients after metastasectomy and no evidence of disease.	Strong

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 [435].

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 [436-439]. Interferon-α has been superseded by targeted therapy in cc-mRCC.

Table 7.2: The Metastatic Renal Cancer Database Consortium (IMDC) risk model [440]*

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 [225].*

***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% [439, 441, 442]. 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 [443]. 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 for mRCC with a clear cell component (CheckMate 025, NCT01668784) reported a longer OS, better QoL and fewer grade 3 or 4 adverse events with nivolumab than with everolimus [444]. 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 with a 5-year OS probability of 26% vs. 18% [445] (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-naive 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 [446]. 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) [447]. 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 [409] 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 pre-defined endpoint. The exploratory analysis of OS data in the PD-L1-positive population was 0.45 (95% CI: 0.29–0.41).

A recent update with 48-month data shows ongoing benefits for the immune combination with independently assessed complete response rates of 10% and a HR for OS in the IMDC intermediate- and poor-risk group of 0.65 (0.54–0.78). The 48-months OS propability was 50% for ipilimumab plus nivolumab vs. 39% for sunitinib, respectively [448]. The IMDC good-risk group continues to perform better with sunitinib although this appears less marked than in earlier analyses (HR for OS: 0.93 [95% CI: 0.62–1.40]) [448].

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. For these reasons the Panel continues to recommend ipilimumab and nivolumab in the intermediate- and poor-risk population.

The KEYNOTE-426 trial (NCT02853331 reported results for the combination of axitinib plus pembrolizumab vs. sunitinib in 861 treatment-naive cc-mRCC patients [449]. 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.

A recent update of KEYNOTE-426 with a minimum follow-up of 23.4 months (median 30.6 months) demonstrated an ongoing OS benefit for axitinib plus pembrolizumab in the ITT population (HR: 0.68, 95% CI: 0.55–0.85, p < 0.001) and PFS benefit (HR: 0.71, 95% CI: 0.60–0.84, p < 0.0001 which was across all IMDC subgoups for PFS, while OS was similar between axitinib plus pembrolizumab vs. sunitinib in the favourable subgroup with an OS benefit in the IMDC intermediate- and poor-risk groups. The complete response rate by independent review was 9% in the pembrolizumab plus axitinib arm and 3% in the sunitinib arm [450].

The phase III CheckMate 9ER trial randomised 651 patients to nivolumab plus cabozantinib (n = 323) or vs. sunitinib (n = 328) in treatment-naive cc-mRCC patients. The primary endpoint of PFS assessed by central independent review in the ITT population was siginifcantly prolonged for nivolumab plus cabozantinib (16.6 months) vs. sunitinib (8.3 months, HR: 0.51, 95% CI: 0.41–0.64, p < 0.0001). The nivolumab/cabozantinib combination also demonstrated a significant OS benefit in the secondary endpoint compared with sunitinib (HR: 0.60, CI: 0.40–0.89, p = 0.0010) after a median follow-up of 18.1 months. The independantly assessed ORR was 55.7% vs. 27.1% with a complete response rate of 8% for nivolumab plus cabozantinib vs. 4.6% with sunitinib. The efficacy was observed independent of IMDC group and PD-L1 status. Treatment-related AEs (≥ grade 3) occurred in 61% of patients receiving cabozantinib and nivolumab vs. 51% of patients receiving sunitinib. Treatment-related deaths occurred in one patient in the nivolumab/cabozantinib arm and in two patients in the sunitinib arm.

Recently, the randomised phase III trial CLEAR (Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab Versus Sunitinib Alone as Treatment of Advanced Renal Cell Carcinoma) was published [451]. CLEAR randomised a total of 1,069 patients (in a 1:1:1 ratio) to lenvatinib plus pembrolizumab (n = 355) vs. lenvatinib plus everolimus (n = 357) vs. sunitinib (n = 357). The trial reached its primary endpoint of independently assessed PFS at a median of 23.9 vs. 9.2 months, for lenvatinib plus pembrolizumab vs. sunitinib, respectively (HR: 0.39, 95% CI: 0.32–0.49, p < 0.001). Overall survival siginificantly improved with lenvatinib plus pembrolizumab vs. sunitinib (HR: 0.66, 95% CI: 0.49–0.88, p = 0.005). Objective response for lenvatinib plus pembrolizumab was 71% with 16% of the patients having a complete remission. Efficacy was observed across all IMDC risk groups, independently of PD-L1 status. Treatment-related AEs of grade 3 and higher with lenvatinib plus pembrolizumab were 72%. Treatment-related death occurred in four patients in the lenvatinib plus pembrolizumab arm and in one patient in the sunitinib arm.

The JAVELIN trial investigated 886 patients in a phase III RCT of avelumab plus axitinib vs. sunitinib [411]. The trial met one of its co-primary endpoints (PFS in the PD-L1-positive population at first interim analysis [median follow up 11.5 months]). Hazard ratios for PFS and OS in the ITT population were 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) [452]. Final OS results are awaited and the combination cannot currently be recommended.

Table 7.3: First line immune checkpoint inhibitor combination trials for clear-cell RCC
Cross trial comparison is not recommended and should occur with caution

Study	N	Experimental arm	Primary endpoint	Risk groups	PFS (mo) Median (95% CI) HR	OS (mo) Median (95% CI) HR
KEYNOTE-426 **NCT02853331** Median follow-up 30.6 months [449, 450]	861	Pembrolizumab 200 mg. IV Q3W plus axitinib 5 mg. PO BID vs. sunitinib 50 mg PO QD 4/2 wk	PFS and OS in the ITT by BICR	**IMDC** FAV 31% IMD 56% POOR 13% **MSKCC** Not determined	(ITT) PEMBRO + AXI: 15.4 (12.7-18.9) SUN: 11.1 (9.1-12.5) HR: 0.71 (95% CI: 0.60, 0.84) p < 0.0001	(ITT) PEMBRO + AXI: NR SUN: 35.7 (33.3-NE) HR: 0.68 (95% CI: 0.55-0.85) p = 0.0003
JAVELIN 101 **NCT02684006** Median follow-up 19 months [411, 453]	886	Avelumab 10 mg/kg IV Q2W plus axitinib, 5 mg PO BID vs. sunitinib 50 mg PO QD 4/2 wk	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 (10.1-20.7) SUN: 7.0 (5.7-9.6) HR: 0.62 (95% CI: 0.49, 0.78) p < 0.0001	(PD-L1+) AVE + AXI: NR SUN: 28.6 (27.4-NE) HR: 0.83 (95% CI: 0.60-1.15) p = 0.1301
Immotion 151 **NCT02420821** Median follow-up 24 months [452]	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 wk	PFS in the PD-L1+ population and OS in the ITT by IR	**IMDC** Not determined **MSKCC** FAV 20% IMD 69% POOR 12%	(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 = 0.0217	(ITT) ATEZO + BEV: 33.6 (29.0-NE) SUN: 34.9 (27.8-NE) HR: 0.93 (95% CI: 0.76-1.14) p 0.4751
Checkmate 214 **NCT02231749** Median follow-up 48 months [409, 448]	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 wk	PFS and OS in the IMDC inter-mediate and poor population by BICR	**IMDC** FAV 23% IMD 61% POOR 17% **MSKCC** Not determined	(IMDC IMD/poor) NIVO + IPI: 11.2 (8.4-16.1) SUN: 8.3 (7.0-10.8) HR: 0.74 (95% CI: 0.62, 0.88)	(IMDC IMD/poor) NIVO + IPI: 48.1 (35.6-NE) SUN: 26.6 (22.1-33.5) HR: 0.65 (0.54-0.78) p < 0.0001
CheckMate 9ER **NCT03141177** Median follow-up 18.1 months [410]	651	Nivolumab 240 mg fixed dose IV every 2 wk plus cabozantinib 40 mg PO daily vs. sunitinib 50 mg PO QD 4/2 wk	PFS in the ITT by BICR	**IMDC** FAV 22% IMD 58% POOR 20% **MSKCC** Not determined	(ITT) NIVO + CABO: 16.6 (12.5-24.9) SUN: 8.3 (7.0-9.7) HR: 0.51 (95% CI: 0.41-0.64) p < 0.0001	(ITT) NIVO + CABO: NR (NE) SUN: NR (22.6-NE) HR: 0.60 (98.9% CI: 0.40-0.89) p = 0.0010

CLEAR **NCT02811861** Median follow-up 26.6 months [451]	712	Pembrolizumab 200 mg IV Q3W plus lenvatinib 20 mg PO QD vs. sunitinib 50 mg PO QD 4/2 wk	PFS in the ITT by BIRC	**IMDC** FAV 31% IMD 59% POOR 9% NE 1% **MSKCC** FAV 27% IMD 64% POOR 9%	(ITT) PEMBRO + LEN: 23.9 (20.8-27.7) SUN: 9.2 (6.0-11.0) HR: 0.39 (95% CI: 0.32-0.49) p > 0.001	(ITT) PEMBRO + LEN: NR (33.6-NE) SUN: NR (NE-NE) HR: 0.66 (95% CI: 0.49-0.88) p = 0.005

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; BID = twice a day; CABO = cabozantinib; CI = confidence interval; FAV = favourable; R = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; LEN = lenvatinib; mo = months; MSKCC = Memorial Sloan Kettering Cancer Center; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = profession-free survival; PO = by mouth; BID = twice a day; QD = once a day; Q2W = every 2 weeks; Q3W = every 3 weeks; SUN = sunitinib; wk = weeks.

Patients who stop nivolumab plus ipilimumab because of toxicity require expert guidance and support from a multidisciplinary team before re-challenge can occur (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 [454, 455] (LE: 1).

Patients who stop TKI and IO due to immune-related toxicity can receive single-agent TKI 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 plus pembrolizumab or nivolumab plus cabozantinib 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, pembrolizumab plus axitinib and nivolumab plus cabozantinib 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-naive 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 plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naive patients with cc-mRCC across all IMDC risk group demonstrated PFS, OS and ORR benefits compared to sunitinib.	1b
Currently, PD-L1 expression is not used for patient selection.	2b
Axitinib, cabozantinib or lenvatinib can be continued if immune-related adverse events result in cessation of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus 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, pembrolizumab plus axitinib, nivolumab plus cabozantinib and lenvatinib plus pembrolizumab 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 plus ipilimumab in the IMDC intermediate- and poor-risk population of treatment-naive patients with cc-mRCC leads to superior survival compared to sunitinib while OS was higher in IMDC good-risk patients with sunitinib.	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, lenvatinib plus pembrolizumab or nivolumab plus cabozantinib to treatment-naive patients in clear-cell metastatic renal cell carcinoma (cc-mRCC).	Strong
Offer ipilimumab plus nivolumab to treatment-naive patients with IMDC intermediate- and poor-risk cc-mRCC.	Strong
Administer nivolumab plus ipilimumab, pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab and cabozantinib 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, cabozantinib or lenvatinib as subsequent treatment to patients who experience treatment-limiting immune-related adverse events after treatment with the combination of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus 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 sunitinib or pazopanib to treatment-naive patients with IMDC favourable-, intermediate-, and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to treatment-naive 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 overexpression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis [456-458]. 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 7.2) [227].

Table 7.4: 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 [227]; ** based on [440].*
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, $p < 0.01$) [459]. Overall survival improved in patients initially assigned to placebo who were censored at crossover [460].

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 or 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. IFN-α (21.8 months) despite crossover [461].

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 [462]. 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 [463, 464].

7.4.3.1.3 Pazopanib

Pazopanib is an oral angiogenesis inhibitor. In a trial of pazopanib vs. placebo in treatment-naive mRCC patients and cytokine-treated patients, a significant improvement in PFS and tumour response was observed [465].

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 [466]. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%, $p < 0.05$) due to symptomatic toxicity [467]. 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) [468].

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 [469, 470]. In a randomised phase III trial of axitinib vs. sorafenib in first-line treatment-naive 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 [471]. 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 [197]. Based on these results an RCT investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapies (METEOR) [472, 473]. Cabozantinib delayed PFS compared to everolimus in VEGF-targeted therapy refractory disease (HR: 0.58, 95% CI: 0.45–0.75) [472] (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, $p = 0.0003$) [473]. 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 [474, 475]. 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 for discussion of results) [476].

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 [477, 478]. Tivozanib was approved by the EMA in front-line mRCC. While it was 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 considers there is too much uncertainty, and too many attractive alternatives, to support its use in this front-line 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 IFN-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) [479].

An open-label trial (CALGB 90206) of bevacizumab plus IFN-α vs. IFN-α showed a higher median PFS for the combination group [480, 481]. 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 [482]. 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) [483]. The data showed a median PFS of 4 vs. 1.9 months for everolimus and placebo, respectively [483].

The 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 lenvatinib 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 plus axitinib as well as nivolumab plus cabozantinib and lenvatinib plus pembrolizumab is the standard of care in all IMDC-risk patients and ipilimumab plus nivolumab in 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 [444, 472, 476]. Pembrolizumab plus axitinib, nivolumab plus cabozantinib, lenvatinib plus pembrolizumab and nivolumab plus ipilimumab are the new standard of care in 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 TKI plus IO in a first-line setting are lacking, and available cohorts are limited [484]. Prospective data on cabozantinib and axitinib are available for patients progressing on immunotherapy, but these studies do not focus solely on the front-line setting, involve subset analyses, and are too small for definitive conclusions [472, 485].

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 over another after immunotherapy/immunotherapy or immunotherapy/VEGFR combination (Figure 7.2). After the axitinib plus pembrolizumab combination, changing the VEGFR-TKI at progression to cabozantinib or any other TKI not previously used is recommended.

The Panel do not support the use of mTOR inhibitors unless VEGF-targeted therapy is contraindicated as they have been outperformed by other VEGF-targeted therapies in mRCC [486]. 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 RCT data showing a survival advantage and should be used preferentially [468]. 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 [486]. The lenvatinib plus 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 [476]. As shown in a study which also included patients on immune checkpoint inhibitors tivozinib provides PFS superiority over sorafenib in VEGF-refractory disease [487].

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 analyses 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 pembrolizumab [438, 488-490].

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 [490-493]. A trial of both types of pRCC treated with everolimus (RAPTOR), showed a median PFS of 3.7 months per central review in the ITT population with a median OS of 21.0 months [493]. In a non-randomised phase II trial, type 2 papillary RCC associated to HLRCC, a familial cancer syndrome caused by germline mutations in the fumarate hydratase enzyme (FH) gene, the combination of bevacizumab 10 mg/kg IV every 2 weeks and erlotinib 150 mg orally daily has been evaluated [494]. The combination regimen reports interesting activity with an ORR of 64% (27/42; 95% CI: 49–77) in the HLRCC cohort, with a median PFS of 21.1 months (95% CI: 15.6–26.6). Grade ≥ 3 treatment-related AEs occurred in 47% of patients, including hypertension (34%) and proteinuria (13%).

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 [495]. The final results showed a non-significant trend favouring sunitinib (6.1 vs. 4.1 months). Based on a systematic review including subgroup analyses of the ESPN, RECORD-3 and another phase II trial (ASPEN), sunitinib and everolimus remain options in this population, with a preference for sunitinib [8, 144, 496]. 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 [447]. Pembrolizumab can be conceded in this setting due to the high unmet need.

Subset analyses have 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 EAU Guidelines recommendations for the first-line treatment of metastatic clear-cell RCC

	Standard of Care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b]	sunitinib* [1b] pazopanib* [1b]
IMDC intermediate and poor risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b] nivolumab/ipilimumab [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 a well-designed study without randomisation, or a subgroup analysis of a randomised controlled trial.

Figure 7.2: EAU Guidelines recommendations for later-line therapy

	Standard of care	Alternative
Prior IO	Any VEGF-targeted therapy that has not been used previously 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.

*7.4.7 **Summary of evidence and recommendations for targeted therapy in metastatic RCC***

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-naive 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) after one or two lines of therapy.	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 or cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Offer cabozantinib after VEGF-targeted therapy in cc-mRCC.	Strong
Sequence systemic therapy in treating mRCC.	Strong

7.5 Locally recurrent RCC after treatment of localised disease

Locally recurrent disease can either affect the tumour-bearing kidney after PN or focal ablative therapy such as RFA and cryotherapy. Local relapse may be due to the incomplete resection of the primary tumour (type A), in a minority of the cases to the local spread of the tumour by microvascular embolisation (type B), or true multifocality (type C) [497]. 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. In the existing literature the topic is poorly investigated and available data are mainly related to positive surgical margins only [498, 499].

The prognosis of recurrent disease not due to multifocality (type A and B) is poor, despite salvage nephrectomy [497]. Recurrent tumour growth in the regional LNs or ipsilateral adrenal gland may reflect metachronous metastatic spread (see Section 7.3). After PN for pT1 disease, recurrences within the remaining kidney occur in 0.5–2% of patients [500, 501].

Following thermal ablation or cryotherapy generally intra-renal, but also peri-renal, recurrences have been reported in up to 14% of cases [502]. 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.

Isolated local recurrence is associated with worse survival [503, 504]. Based on retrospective and non-comparative data only, several approaches such as surgical excision, radiotherapy, systemic treatment and observation have been suggested for the treatment of isolated local recurrence [505-507]. Among these alternatives, surgical resection with negative margins remains the only therapeutic option shown to be associated with improved survival [503] 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 [505]. Another recent series identified 33 patients with isolated local recurrences and 30 local recurrences with synchronous metastases within a cohort of 2,502 surgically treated patients, confirming the efficacy of locally directed treatment vs. conservative approaches (observation, systemic therapy) [508]. 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 [506].

Open surgery has been successfully reported in studies [509, 510]. However, minimaly invasive approaches, including standard and hand-assisted laparoscopic- and robotic approaches for the resection of isolated RCC recurrences have been occasionally reported. Ablative therapies including cryoablation, radiofrequency and microwave ablation, may also have a role in managing recurrent RCC patients, but further validation will be needed [511].

In summary, the limited available evidence suggests that in selected patients surgical removal of locally recurrent disease can induce durable tumour control, although with expected high risk of complications. Johnson *et al*. published on 51 planned repeat PNs in 47 patients with locally recurrent disease, reporting a total of 40 peri-operative complications, with temporary urinary extravasation being the most prevalent [512]. Since local recurrences develop early, with a median time interval of 10–20 months after treatment of the primary tumour [513], a guideline-adapted follow-up scheme for early detection is recommended (see Chapter 8 - Follow-up) even though benefit in terms of cancer control has not yet been demonstrated [514].

Adverse prognostic parameters are a short time interval since treatment of the primary tumour (< 3–12 months) [515], sarcomatoid differentiation of the recurrent lesion and incomplete surgical resection [505]. 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 on locally recurrent RCC after treatment of localised disease

Summary of evidence	LE
Isolated recurrence is a rare entity (< 2%).	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, treatment of local recurrences can induce durable local control.	3
The most optimal modality of local treatment for locally recurrent RCC is still under debate.	3

Recommendation	Strength rating
Offer local treatment of locally recurrent disease when technically 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;
- distant metastases;
- cardiovascular events.

There is no consensus on follow-up strategies after RCC treatment, with limited evidence suggesting that more frequent post-operative imaging intervals do not provide any improvement for early detection of recurrence that would lead to improved survival [514]. As such, intensive radiological surveillance may not be necessary for all patients. Follow-up is also important to assess functional outcomes and to limit long-term sequelae such as renal function impairment, end-stage renal disease and cardiovascular events [516].

Currently, the key question is whether any recurrence detection during follow-up and subsequent treatment will lead to any meaningful change in survival outcome for these patients.

In contrast to high-grade and/or locally advanced disease, 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 each different RCC to develop a local or distant recurrence. Although there is no randomised evidence, large studies have examined prognostic factors with long follow-up [168, 517, 518] (LE: 4). One study has shown a survival benefit in patients who were followed within a structured surveillance protocol vs. patients who were not [519]; patients undergoing follow-up seem to have a longer OS when compared to patients not undergoing routine follow-up [519].

Furthermore, an individualised and risk-based approach to RCC follow-up has recently been proposed. The authors used 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 [520]. 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 consortium, initiated by this Panel, collects similar data with the aim to provide comparators for guideline recommendations. Recently published RECUR data support a risk-based approach; more specifically a competing-risk analysis showed that for low-risk patients, the risk of non-RCC related death exceeded the risk of RCC recurrence shortly after the intial surgery. For intermediate-risk patients, the corresponding time point was reached around four to five years after surgery. In high-risk patients, the risk of RCC recurrence continously exceeded the risk of non-RCC related death [10]. In the near future, genetic profiling may refine the existing prognostic scores and external validation in datasets from adjuvant trials have been promising in improving stratification of patient's risk of recurrence [10, 521].

Recurrence after PN is rare, but early diagnosis is relevant, as the most effective treatment is surgery [509, 522]. Recurrence in the contralateral kidney is rare (1–2%) and can occur late (median 5–6 years) [523] (LE: 3). Follow-up 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 imaging investigations for which patients, and when?

- The sensitivity of chest radiography and US for detection of small RCC metastases is poor. The sensitivity of chest radiography is significantly lower than CT-scans, as proven in comparative studies including histological evaluation [524-526]. Therefore, follow-up for recurrence detection with chest radiography and US are less sensitive [527].
- Positron-emission tomography and PET-CT as well as bone scintigraphy should not be used routinely in RCC follow-up, due to their limited specificity and sensitivity [6, 119].
- Surveillance should also include evaluation of renal function and cardiovascular risk factors [516].
- Outside the scope of regular follow-up imaging of the chest and abdomen, targeted imaging should be considered in patients with organ-specific symptoms, e.g. CT or MRI imaging of the brain in patients experiencing neurological symptoms [528].

Controversy exists on the optimal duration of follow-up. Some authors 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. Several authors have designed scoring systems and nomograms to quantify the likelihood of patients to develop tumour recurrences, metastases, and subsequent death [215, 217, 529, 530]. These models, of which the most utilised are summarised in Chapter 6 - Prognosis, have been compared and validated [531] (LE: 2). Using prognostic variables, several stage-based follow-up regimens have been proposed, although, none propose follow-up strategies after ablative therapies [532, 533]. A post-operative nomogram is available to estimate the likelihood of freedom from recurrence at five years [212]. Recently, a pre-operative prognostic model based on age, symptoms and TNM staging has been published and validated [534] (LE: 3).

A follow-up algorithm for monitoring patients after treatment for RCC is needed, recognising not only the patient's risk of recurrence profile, but also the efficacy of the treatment given (Table 8.1). These prognostic systems can be used to adapt the follow-up schedule according to predicted risk of recurrence. Ancillary to the above, life-expectancy calculations based on comorbidity and age at diagnosis may be useful in counselling patients on duration of follow-up [535].

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

Risk profile (*)	Oncological follow-up after date of surgery								
	3 mo	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**30 mo**	**36 mo**	**> 3 yr (**) (***)**	**> 5 yr (**) (***)**
Low risk of recurrence For ccRCC: Leibovich Score 0-2 For non-ccRCC: pT1a-T1b pNx-0 M0 and histological grade 1 or 2.	-	CT	-	CT	-	CT	-	CT once every two yrs	-
Intermediate risk of recurrence For ccRCC: Leibovich Score 3-5 For non-ccRCC: pT1b pNx-0 and/or histological grade 3 or 4.	-	CT	CT	-	CT	-	CT	CT once yr	CT once every two yrs
High risk of recurrence For ccRCC: Leibovich Score ≥ 6 For non-ccRCC: pT2-pT4 with any histological grade or pT any, pN1 cM0 with any histological grade	CT	CT	CT	CT	CT	-	CT	CT once yr	CT once every two yrs

ccRCC = clear cell renal cell carcinoma, CT = computed tomography, mo = months, non-ccRCC = non clear cell renal cell carcinoma; yr = years.

The table above provides recommendations on follow-up strategies for low, intermediate and high risk of recurrence in patients curatively treated for localised RCC either with NSS or RN. Computed tomography in the table refers to imaging of both chest and abdomen. Alternatively, MRI of the abdomen can be performed instead of a CT-scan.

* *Risk of recurrence profiles should be based on validated prognostic models. The EAU RCC Guidelines Panel recommends the 2003 Leibovich model for ccRCC [215]. However, other validated models can be used by physicians based on their own national/regional recommendations. In a similar fashion, for curatively treated localised non-ccRCC, the Panel recommends the use of the University of California Los Angeles integrated staging system (UISS) to determine risk of recurrence [216].*

** *for all risk of recurrence profiles, functional follow-up, mainly monitoring renal and cardiovascular function, may continue according to specific clinical needs irrespective of the length of the oncological follow-up.*

*** *For low-risk profiles at > 3 years and intermediate-risk at > 5 years of follow-up respectively, consider counselling patients about terminating oncological follow-up imaging based on assessment of comorbidities, age, life expectancy and/or patient wishes.*

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

Summary of evidence	LE
Functional follow-up after curative treatment for RCC is useful to prevent renal and cardiovascular deterioration.	4
Oncological follow-up can detect local recurrence or metastatic disease while the patient may still be 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 follow-up have a better overall survival than patients not undergoing surveillance.	3
Prognostic models provide stratification of RCC risk of recurrence based on TNM and histological features.	3
In competing-risk models, risk of non-RCC-related death exceeds that of RCC recurrence or related death in low-risk patients.	3
Life expectancy estimation is feasible and may support counselling of patients on duration of follow-up.	4

Recommendations	Strength rating
Base follow-up after treatment of localised RCC on the risk of recurrence.	Strong
Perform functional follow-up (renal function assessment and prevention of cardiovascular events) both in nephron-sparing (NSS) and radical nephrectomy patients.	Weak
Intensify follow-up in patients after nephron-sparing surgery for tumours > 7 cm or in patients with a positive surgical margin.	Weak
Consider curtailing follow-up when the risk of dying from other causes is double that of recurrence risk.	Weak
Base risk of recurrence stratification on validated subtype-specific models such as the Leibovich Score for ccRCC or the University of California Los Angeles integrated staging system (UISS) for non-ccRCC.	Weak

8.4 Research priorities

There is a clear need for future research to determine whether follow-up can optimise patient survival. Data evaluating at which time point follow-up has the highest chance to detect recurrence will be most valuable for clinical practice.

Novel 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 Guidelines Panel 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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