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 when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and references/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 EAU Guidelines Panel on RCC consists of an international multidisciplinary group of clinicians, including 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 Available publications

A quick reference document, the Pocket Guidelines, is available in print. This is an abridged version which may require consultation together with the full text version. Several scientific publications are available and all documents are accessible through the EAU website Uroweb: http://uroweb.org/guideline/renal-cell-carcinoma/.

A EAU Guidelines App for iOS and Android devices is also available containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, guidelines cheat sheets and links to the extended guidelines.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU RCC Guidelines were first published in 2000. This 2025 RCC Guidelines document presents a limited update of the 2024 publication.

*1.4.2 **Summary of changes***

All chapters of the 2025 RCC Guidelines have been updated, based on the 2024 version of the Guidelines. References have been added throughout the document. Other key changes incorporated in this publication includes:

- A new summary of evidence (SoE) in section 5.4 on lung metastises in cT1a, cN0 patients.
- A new figure 7.1 on the treatment of locally advanced RCC and update on Figure 7.2.
- A new subchapter and recommendation regarding smoking cessation in chapter 7.1.2
- A new SoE and recommendation on stereotactic body radiotherapy (SBRT) in section 7.2.4.4.8
- Inclusion of arm B data for Checkmate 914 in table 7.1
- A new subchapter 7.3.5.5 on the progression after adjuvant PD-1 therapy.
- Update on the SoE and recommendations in section 7.3.5.6 for neoadjuvant and adjuvant therapy.
- Update on the SoE in chapter 7.5.2.5 regarding belzutifan.
- Update of table 7.5 regarding RENOTORCH data and update of the SoE and recommendations in section 7.5.4.1.2
- Update on the SoE and recommendations in section 7.5.4.2.4 for systematic therapy in chromophobe and unclassified RCC.
- A new subchapter 8 including Table 8.1 on hereditary and syndrome specific RCC.

2. METHODS

2.1 Data identification

For the 2025 RCC Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. A broad and comprehensive scoping exercise covering all areas of the RCC Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between May 1st, 2023 and May 1st, 2024. Databases covered included Medline, EMBASE, and the Cochrane Library. After de-duplication, a total of 1,781 unique records were identified, retrieved and screened for relevance. A search strategy is published online: https://uroweb.org/guidelines/renal-cell-carcinoma/publications-appendices.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. 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 the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [1];
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 and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [2].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found in the online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

All publications ensuing from systematic reviews (SR)s have been peer reviewed. The 2025 print of the RCC Guidelines was also peer-reviewed prior to publication.

2.3 Future goals

The RCC Guideline Panel supports the focus on patient-reported outcomes as well as the development of clinical quality indicators. A number of key quality indicators for this patient group have been selected:

- the proportion of patients undergoing 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 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.

In addition, the panel has collected data from various European datasets on atypical recurrences following minimally invasive renal surgery to establish incidence and insight on potential causes, their management and outcome.

Further, a registry for Bosniak IV cysts with single nodularity will be established to investigate if diameter of the cyst or nodule is leading in clinical management.

The panel plan to perform a survey investigating the decision factors and the rate of urologists performing NSS in patients with T1a N0M0.

Finally the panel seeks to establish surveillance recommendation for biopsy proven but untreated oncocytomas (oncocytic tumours).

The results of ongoing and new SRs will be included in future updates of the RCC Guidelines:

- Systematic review of individual, unit and hospital surgical volume for radical and partial nephrectomy and their impact on outcomes;
- Systematic review of the treatment modalities in Oligometastatic Renal Cell Carcinoma with and without systemic therapy.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Renal cell carcinoma ranks 14th on the list of cancers, representing around 2% of all cancers, with the highest incidence occurring in Western countries [3-5]. In 2022, there were an estimated 434,840 [5] new cases of RCC globally with 155,953 deaths worldwide [6]. Incidence and mortality are the highest in Europe and Asia whereas age standardised incidence rate per 100,000 person/years (age-standardized rate [ASR] World) is the highest in Northern America and mortality in Eastern Europe. There is predominance in men over women ASR 13.7 and 6.4 respectively with a higher incidence in the older population [7].

In Europe incidence of RCC was 145,721 in 2022 with mortality of 52,347 [7], with ASR (European 2013) 18.9 and 6.9 in 27 European union (EU) countries [8, 9]. In 2022, Belarus, Latvia and Czechia reported the highest overall rate of RCC in Europe [9], with estimated age-standardised rates (ASR Europe 2013) for Czechia and Latvia for males being 41.3 and 37.8, respectively while being the lowest in Cyprus, Luxembourg and Bulgaria 13.9-15.4 [10].

Mortality was the lowest amongst 27 EU countries in males In Luxembourg, Cyprus and Finland ASR (European 2013) 4.6, 6.9 and 7.3, respectively. In contrary, the highest mortality rates were reported in the Baltics following Czechia and Slovakia 15.5-16.2, 14.7 and 14.4, respectively [10].

Overall, there is ongoing rise in incidence of RCC, however mortality trends vary. In Europe, 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 [11].

3.2 Aetiology

Established risk factors include lifestyle factors such as smoking (hazard ratio [HR]: 1.23–1.58), obesity body mass index (BMI) (> 35 vs. < 25), (HR: 1.71 [1.06-2.79]), hypertension (HR: 1.70 [1.30-2.22]) and metabolic syndrome (relative risk [RR] 1.62 [1.41-1.87]) [4, 8, 12-16]. A total of 50.2% of patients with RCC are current or former smokers. By histology, the proportions of current or former smokers range from 38% in patients with chromophobe renal cell carcinoma (chRCC) to 61.9% in those with collecting duct/medullary carcinoma [17]. In a SR, diabetes was also found to be detrimental [18]. Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC [19]. Among RCC patients, 3.1% have one or more FDR (first-degree relative—parents and siblings). Having one or more FDR with RCC approximately doubles the risk of RCC with a higher risk increase for women than for men [20]. Moderate alcohol consumption appears to have a protective effect for reasons as yet unknown, while any physical activity level also seems to have some protective effect [4, 8, 18, 21, 22]. 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 no high-quality evidence level exists [12, 23]. The most effective prophylaxis is to avoid cigarette smoking and reduce obesity [4, 8, 12, 13]. Genetic risk factors are known to play a role in the development of RCC (see Section 8 – Hereditary and syndrome specific RCC).

3.3 Screening

Despite a growing interest from both patients and clinicians in RCC screening programmes, there is a relative lack of studies reporting the efficacy, cost-effectiveness, and optimal modality for RCC screening. Urinary dipstick is an inadequate screening tool due to low sensitivity and specificity. Also incidence of RCC with non-visible hematuria is low; 0.58% [24]. No clinically validated urinary or serum biomarkers have as yet been identified. Computed tomography cannot be recommended due to cost, radiation dose and the increased potential for other incidental findings. Ultrasound (US) could be used and has acceptable sensitivity and specificity, although it is tumour size and operator dependant. Major barriers to population screening include

the relatively low prevalence of the disease, the potential for false positives and over-diagnosis of slow-growing kidney tumours. Targeting high-risk individuals and/or combining detection of RCC with other routine health screenings may represent pragmatic options to improve the cost-effectiveness and reduce the potential harms of RCC screening [25-28]. Targeting of high-risk patient groups e.g., those with end-stage renal disease (ESRD) which is associated with a ten-fold increased risk of developing RCC may also be a valid approach (see Section 3.5.2) [29]. People with two FDRs with RCC constitute a small high-risk group that may benefit from screening [20].There is currently no evidence to support primary screening in the general population.

3.3.1 Summary of evidence and recommendations for epidemiology, aetiology and screening

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
There is no evidence to support primary screening for RCC.	4

Recommendations	**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
Do not routinely screen people for primary RCC.	Weak

3.4 Histological diagnosis

Renal cell carcinomas and other renal tumours comprise a broad spectrum of histopathological entities described in the 5th edition of the World Health Organization (WHO) classification of urogenital tumours published in 2022 [30-32]. The 5th edition presents standard morphologic diagnostic criteria, combined with immunohistochemistry and relevant molecular tests was significantly revised as compared to the 2016 classification [33]. The global application of next-generation sequencing (NGS) will result in a diagnostic shift from morphology to molecular analyses. Therefore, a molecular-driven renal tumour classification has been introduced in addition to morphology-based renal tumours (Table 3.1). Examples of molecularly-defined epithelial renal tumours include *SMARCB1*-deficient renal medullary carcinoma, *TFE3*- and *TFEB*-rearranged RCC, *ALK*-rearranged RCC, and elongin *C (ELOC)*-mutated RCC. The most profound changes in the 2022 WHO classification mainly relate to rare kidney tumours.

There are three main RCC types: clear cell (ccRCC), papillary (pRCC no longer divided into type I and II) and chRCC. The RCC type classification has been confirmed by cytogenetic and genetic analyses [33, 34] (LE: 2b). The five-year overall survival (OS) for non-metastatic (including N0-N1) chromophobe, papillary, clear-cell and collecting duct RCC is 91%, 82%, 81% and 44%, respectively [35]. Sarcomatoid RCC is not a specific subtype, but essentially represents a pattern of de-differentiation associated with adverse outcome and poor cancer-specific survival (CSS), irrespective of the underlying RCC subtype; it should be graded as WHO/ISUP (International Society of Urological Pathology) grade IV. At the time of diagnosis of sarcomatoid RCC, only 15.3% are localised, 28.9% locally advanced and 55.8% metastatic. The overall five-year survival was 18.1% and 27.1% in patients who underwent surgery [36]. Multilocular cystic renal neoplasm of low malignant potential is a new subtype of ccRCC in the 2022 classification. A new group “oncocytic and chromophobe tumours” encompass oncocytoma together with chRCC and other oncocytic tumours. Other oncocytic tumours include tumours that do not strictly fit into either the oncocytoma or chRCC subtypes [30, 37].

Histological diagnosis includes, besides RCC type; evaluation of international society of urological pathology (ISUP) 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 grading system has replaced the Fuhrman grading system [30, 33].

Table 3.1 World Health Organization classification of renal tumours 2022 [30, 31]

WHO classification of renal tumours 2022	
1. Renal Cell Tumours	
01.I	Clear cell renal tumours
	Clear cell RCC
	Multilocular cystic renal neoplasm of low malignant potential
01.II	Papillary renal tumours
	Papillary adenoma
	Papillary RCC
01.III	Oncocytic and chromophobe renal tumours
	Oncocytoma of the kidney
	Chromophobe RCC
	Other oncocytic tumours of the kidney
01.IV	Collecting duct tumours
	Collecting duct carcinoma
01.V	Other renal tumours
	Clear cell papillary renal cell tumour
	Mucinous tubular and spindle cell carcinoma
	Tubulocystic RCC
	Acquired cystic disease-associated RCC
	Eosinophilic solid and cystic (ESC) RCC
	RCC NOS (Not Otherwise Specified)
01.VI	Molecularly defined renal tumours
	TFE3-rearranged RCCs
	TFEB-altered RCC (*TFEB*-rearranged RCC and *TFEB* amplified RCC)
	ELOC (formerly *TCEB1*)-mutated RCC
	Fumarate hydratase-deficient RCC
	Succinate dehydrogenase-deficient RCC
	ALK-rearranged RCCs
	SMARCB1-deficient renal medullary carcinoma
2. Metanephric tumours	
	Metanephric adenoma
	Metanephric adenofibroma
	Metanephric stromal tumour
3. Mixed epithelial and stromal tumour family	
	Mixed epithelial and stromal tumour
	Adult cystic nephroma
4. Renal mesenchymal tumours	
04.I	Adult renal mesenchymal tumours
	Classic angiomyolipoma/PEComa of the kidney
	Epitheloid angiomyolipoma/epithelioid PEComa of the kidney
	Renal haemangioblastoma
	Juxtaglomerular cell tumour
	Renomedullary interstitial cell tumour

04.II	Paediatric renal mesenchymal tumours
	Ossifying renal tumour of infancy
	Congenial mesoblastic nephroma
	Rhabdoid tumour of kidney
	Clear cell sarcoma of kidney
5. Embryonal neoplasms of the kidney	
Nephroblastic tumours	
	Nephrogenic rests
	Pediatric cystic nephroma
	Cystic partially differentiated nephroblastoma
	Nephroblastoma
6. Miscellaneous tumours	
Germ cell tumours of the kidney	

3.4.1 ***Clear-cell RCC***

Overall, ccRCC representing about 70% of RCC [31], is well circumscribed with a pseudocapsule. 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 VHL protein function contributes to tumour initiation, progression, and metastases. The *3p* locus harbours additional ccRCC tumour suppressor genes *(UTX, JARID1C, SETD2, PBRM1, BAP1)* [30]. For details about prognosis, see Section 6.3.

3.4.1.1 Multilocular cystic renal neoplasm of low malignant potential (MCNLMP)

Indolent, exclusively cystic, multiloculated renal tumour devoid of any expansile solid growth, with clear cells lining and low grade nuclei. Detection of small solid expansive nodules and tumour necrosis are incompatible with MCNLMP. It represents 0.5-2.5% of all renal tumours and is a benign lesion. There are no reports of progression, metastases or cancer-related death with long-term follow-up [30, 31].

3.4.2 ***Papillary RCC***

Papillary RCC is the second-most encountered morphotype of RCC accounting for 13-20% of renal epithelial tumours. It is usually circumscribed and characterised by papillary or tubulopapillary architecture, without specific features of other RCCs with papillary architecture [30, 31]. Papillary RCC has traditionally been subdivided into two types; Type I and II pRCC [33]. However, in the new 2022 WHO classification, the former pRCC type I is now referred to as "pRCC of classic pattern". Three additional morphologic patterns of pRCC have been introduced including: a) bi-phasic (alveolo-squamoid) pattern exhibiting mostly solid growth; b) papillary neoplasm with reverse nuclear polarity, previously described as "oncocytic low-grade pRCC"; and c) Warthin-like pRCC that exhibits brisk inflammation mimicking Warthin tumour of the salivary gland.

Genetic changes of pRCC include trisomies and tetrasomies of chromosomes 7 and 17 and loss of Y-chromosome. Mesenchymal-epithelial Transition (MET) gene mutations are more frequent in low-grade pRCC.

The typical histology of classical pattern pRCC, formerlly type I pRCC, (narrow papillae without any binding, and only microcapillaries in papillae) explains its typical clinical signs. Narrow papillae without any binding and a tough pseudo-capsule 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 explains the minimal post-contrast attenuation on CT. Classical pattern pRCC can imitate a pathologically changed cyst (Bosniak IIF or III). The typical signs of classical pattern pRCC are an ochre colour, frequently exophytic, extra-renal growth and low grade. A risk of renal tumour biopsy tract seeding exists, probably due to the fragility of the tumour papillae [38, 39].

3.4.3 ***Chromophobe RCC***

Chromophobe RCC is now grouped in "Oncocytic and chromophobe tumours". Most chRCC are discovered incidentally in asymptomatic patients [30, 31]. Overall, chRCC presents as a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Most tumours are sporadic. Rare hereditary forms include Birt-Hogg-Dubé (BHD) syndrome with mutations in folliculin and Cowden syndrome with mutations in phosphatase and tensin homolog (PTEN) see Section 8 for further information [30, 31]. Chromophobe RCC cannot be graded by the WHO/ISUP (formerly Fuhrman) grading system because of its innate nuclear atypia.

An alternative grading system has been proposed but has yet to be validated and broadly accepted [30, 31, 40]. Loss of chromosomes-Y, 1, 2, 6, 10, 13, 17 and 21 are typical genetic changes [30, 31]. The prognosis is relatively good, with high five-year recurrence-free survival (RFS), and ten-year CSS. The five- and ten-year RFS rates were 94.3% and 89.2%, respectively. Recurrent disease developed in 5.7% of patients, and 76.5% presented with distant metastases with 54% of metastatic disease diagnoses involving a single organ, most commonly bone. Recurrence and death after surgically resected chRCC are rare. For completely excised lesions < pT2a without coagulative necrosis or sarcomatoid features, the prognosis is excellent [41].

3.5 Other renal tumours

Other renal tumours constitute the remaining renal cortical tumours. These include a variety of uncommon, sporadic, and familial carcinomas/tumours, some only recently described, as well as a group of unclassified carcinomas. A summary of these tumours are provided in Table 3.1, but some clinically relevant tumours and extremely rare entities are mentioned below, and in Table 3.2, including a summary on their management. About 15% of excised renal masses are benign [42]. For hereditary and syndrom-specific RCC see Chapter 8.

Table 3.2: Other renal cortical tumours and recommendations for treatment (strength rating: weak)

Entity	Clinical relevant notes	Malignant potential	Treatment
Collecting duct carcinoma	Formerly Bellini duct carcinoma. No hemoglobinopathy or *SMARCB1* abnormality. Rare, often presenting at an advanced stage (N+ 44% and M1, 33% at diagnosis). The HR CSS in comparison with ccRCC is 4.49 [30, 31, 43].	High, very aggressive. Median survival 30 months [44].	Surgery. Systemic therapy and surgery in metastatic disease [45].
Clear-cell papillary renal cell tumour	Patient with ACKD, 100 times greater risk compared with general population [31].	Indolent	Surgery, NSS, discuss active surveilance.
Mucinous tubular and spindle cell carcinoma	Tumour is associated with the loop of Henle. < 1% of renal neoplasm. Female predilection (3–4:1) [31].	Intermediate	Surgery, NSS.
Tubulocystic RCC	Rare (< 1%). Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS.
Eosinophilic solid and cystic RCC (ESC RCC)	Usually alteration of TCS genes. Predominantly in adult women. Some with TSC (tuberous sclerosis complex) syndrome.	Rarely metastatic.	NSS
TFE3 re-arranged RCC	Gene fusions involving TFE3 with one of many different partner genes. Formerly translocation RCC (TRCC) Xp11.2. Appr. 40 % of paediatric RCC and 1.6–4% of adult RCC [24].	Survival similar to clear cell RCC.	Surgery. Systemic therapy in metastatic disease.
TFEB altered (re-arranged and amplified) RCC	Gene fusions involving the *TFEB* transcription factor, typically via a t(6;11)(p21;q12) translocation resulting in a *MALAT1-TFEB* gene fusion. Formerly translocation RCC t(6;11). Less common than *TFE3*-re-arranged RCC. Appr. 100 cases in the literature [31]. *TFEB*-amplified in older patient and has a worse prognosis.	More indolent than the TFE3-rearranged RCC, with fewer than 10% of cases resulting in patient death.	Surgery. Systemic therapy in metastatic.

ELOC (formerly *TCBE1*)-mutated RCC	Twenty cases described in literature [30, 31]. Typically T1.	Indolent. Only two metastatic cases described.	NSS
Fumarate hydratase-deficient RCC [For more information, please review Chapter 8 on Hereditary kidney tumours]	Formerly hereditary leiomyomatosis and RCC-associated RCC. Alterations in the *FH* gene. Autosomal dominant. 21–30% lifetime risk of RCC [46]. Cutaneous leiomyomas, female uterine leiomyoma or leiomyosarcoma. More common in males. Median age 44 years [30, 37, 47].	Often aggressive.	Immediate surgery. No data about treatment of metastatic disease. Genetic counselling in the family. Imaging screening in relatives [46].
Succinate dehydrogenase--deficient RCC (SDH-deficient RCC) [For more information, please review Chapter 8 on Hereditary kidney tumours.]	Rare. 0.05–0.2 % of all RCCs.	A metastatic rate of 11%.	Surgery, NSS. Long-term follow-up and surveillance for other SDH-deficient neoplasms (i.e. paraganglioma, SDH-deficient gastrointestinal stromal tumour, and pituitary adenoma) is indicated for cases associated with germline mutation [23].
ALK-rearranged RCC	Gene fusions involving anaplastic lymphoma kinase gene *(ALK)* at chromosome 2p23. Less than 100 cases described. [30, 31].	Low (90% indolent)	Surgery, NSS.
Metanephric tumours	Divided into metanephric adenoma, adenofibroma, and metanephric stromal tumours.	Benign	NSS
Mixed epithelial and stromal renal tumour	It encompasses 2 benign leasions - mixed epithelial and stromal tumour (MEST) of the kidney (MEST) and adult cystic nephroma. Imaging – Bosniak type III or IIF/IV. Overwhelmingly in women (7:1).	Benign	Active surveillance. NSS.
Renal cysts/cystic lesions	Simple cysts are frequently occurring, while occurring septa, calcifications and solid components require follow-up and/or management.	Mostly benign	Treatment or follow-up recommendation based on Bosniak classification.

ACKD: Acquired Cystic Kidney Disease; ALK: Anaplastic Lymphoma Kinase; NSS: Nephron-Sparing Surgery SMARCB1: SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1; TCS: Tuberous Sclerosis Complex; TFEB: Transcription Factor EB.

3.5.1 ***Renal medullary carcinoma (SMARCB1-deficient renal medullary carcinoma)***

Renal medullary carcinoma (RMC) (referred to as *SMARCB1*-deficient RMC in the 2022 WHO Classification) is a very rare tumour, comprising < 0.5% of all RCCs [48], predominantly diagnosed in young adults of African ancestry (median age 28 years) with sickle haemoglobinopathies (including sickle cell trait). It has a male predominance of 2:1 and is mainly centrally located with ill-defined borders. Renal medullary carcinoma is one of the most aggressive RCCs [49, 50] and most patients (~67%) will present with metastatic disease [49, 51]. Even patients who present with seemingly localised disease may develop unequivocal metastases shortly (within weeks) after diagnosis (for treatment see Chapter 7). Apart from the RMC described above, some patients present with identical tumours without haemoglobinopathy. Such tumours have been described as "unclassified RCC with medullary phenotype" [30].

3.5.2 *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 ESRD. Renal cell carcinomas of native end-stage kidneys are found in approximately 4% of patients with ESRD. 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 like that of sporadic RCC; pRCC occur relatively more frequently [37, 52]. A specific subtype of RCC occurring only in end-stage kidneys has been described as "acquired cystic disease-associated RCC" (ACD-RCC). Tumours present exclusively in patients with ACKD, usually after long-term dialysis. The vast majority occur in men. Tumours are often multiple and bilateral and, in most cases, have an indolent clinical behaviour; although, aggressive courses have been documented [30].

3.5.3 *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, according to the 2022 WHO classification [30].

3.5.4 *Renal oncocytoma*

Oncocytoma is a benign tumour representing 4-7% of all solid renal tumours and 30% of benign surgically removed kidney masses are contributed to oncocytomas [33, 53, 54]. The diagnostic accuracy of imaging modalities (CT, magnetic resonance imaging [MRI]) in renal oncocytoma is limited and histopathology remains the only reliable diagnostic modality [33, 53]. However, ^{99m}Tc-sestamibi (SestaMIBI, MIBI) SPECT/CT has shown promising initial results for the differentiation between benign and low-grade RCC [55-58]. Standard treatment for renal oncocytoma is similar to that of other renal tumours; surgical excision by partial- or radical nephrectomy (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) [30, 31], other RCCs (12.5%), and other benign lesions (4.2%) [59, 60]. The 2022 WHO classification strictly excludes that a definitive diagnosis of oncocytoma be done on a needle-core biopsy. The majority of oncocytomas slowly progress in size with an annual growth rate of approximately 2 mm [53]. Preliminary data show that active surveilnace (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 [61, 62].

3.5.5 *Other oncocytic tumours of the kidney*

Other oncocytic tumours of the kidney are a heterogeneous group of oncocytic tumours not classifiable as oncocytoma, chRCC, or other tumour types with eosinophilic features. These tumours are typically indolent, so it is important to distinguish such low-grade tumours from the high-grade unclassified RCCs that typically behave aggressively. In the setting of Birt–Hogg–Dubé syndrome (see Section 8), tumours with such intermediate features (hybrid oncocytic tumours) also exist, typically being multifocal and bilateral. As this is a heterogeneous tumour group, it is likely that new subtypes of renal neoplasia will emerge. There are already two emerging entities: eosinophilic vacuolated tumour (EVT) and low-grade oncocytic tumour (LOT) [30].

3.5.6 *Classical Angiomyolipoma*

Classical angiomyolipoma (AML)/PEComa of the kidney is a benign mesenchymal tumour, which can occur sporadically or as part of tuberous sclerosis complex [63]. 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 [64]. 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 even metastasize, while classic AMLs are completely benign [33, 65, 66]. Ultrasound, CT, and 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 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 (IVC) 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 and with mean age of onset

of 50 years (range 30-80 years), without gender predilection [65, 66]. Epithelioid AMLs are potentially malignant with a variable proportion of cases with aggressive behaviour [67]. Criteria to predict the biological behaviour in epithelioid AML were proposed by the WHO 2022 [30, 31]. Angiomyolipoma, in general, has a slow and consistent growth rate, and minimal morbidity [68]. Subtypes of AML are oncocytic AML and AML with epithelial cysts [30].

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 [68]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of tuberous sclerosis.

3.5.6.1 Treatment of angiomyolipoma

Active surveillance (AS) 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 [68] (LE: 3). The association between AML size and the risk of bleeding remains unclear and the traditionally used 4cm cut-off should not per se trigger active treatment [68]. 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 [68].

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 randomised controlled trials (RCTs) [69, 70]. 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 four and six months was demonstrated in 55.6% and 71.4% of patients, respectively. However, 20% of patients were withdrawn due to toxicities and 40% self-withdrew from the study due to side effects [71].

*3.5.7 **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 [72]. Bosniak IV cysts are mostly (83%) malignant tumours with pseudo-cystic changes only [73]. 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 US (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) [74]. Surgical and radiological cohorts pooled estimates show a prevalence of malignancy of 0.51 (0.44-0.58) in Bosniak III and 0.89 (0.83-0.92) in Bosniak IV cysts, respectively. In a SR, less than 1% of stable Bosniak IIF cysts showed malignancy during follow-up. Twelve percent of Bosniak IIF cysts had to be reclassified to Bosniak III/IV during radiological follow-up, with 85% of these showing malignancy, which is comparable to the malignancy rates of Bosniak IV cysts [72]. The updated Bosniak classification strengthens the classification and includes also MRI [75] and even CEUS diagnostic criteria [76].

The most common histological types for Bosniak III cysts are ccRCC with pseudo-cystic changes and low malignant potential [77, 78]; multilocular cystic renal neoplasm of low malignant potential, see Section 3.4.1.1; classical pattern pRCC (very low malignant potential); benign multilocular cyst; benign group of mixed epithelial and stromal renal tumour (mixed epithelial and stromal tumour of the kidney and adult cystic nephroma); 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 [72, 75, 79, 80].

3.6 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.	3
The most common renal tumours are three malignant types of RCC (clear cell, papillary and chromophobe) and two benign renal tumours: oncocytoma and angiomyolipoma.	3
A definitive histopathological diagnosis of oncocytoma cannot be made on a needle-core biopsy, because chRCC can show intratumoural heterogeneity with areas very similar to oncocytoma.	3
Histological work up and results of AS of Bosniak III cysts shows low risk of malignant potential/ course.	2

Recommendations	Strength rating
Manage Bosniak type III cysts the same as localised RCC, or offer active surveillance (AS).	Weak
Manage Bosniak type IV cysts the same as localised RCC.	Strong
Offer AS to patients with biopsy-proven oncocytoma or other oncocytic renal tumours as an acceptable alternative to surgery or ablation.	Weak
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 (everolimus) to patients with surgically unresectable AMLs which are not amenable to embolisation and require therapy	Weak

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Staging

The Tumour Node Metastasis (TNM) classification system is recommended for clinical and scientific use [81]. A supplement was published in 2012, and the latter's prognostic value was confirmed in single- and multi-institution studies [82, 83]. Tumour size, venous invasion, renal capsular invasion, adrenal involvement, 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 [84];
- The value of size stratification of T2 tumours has been questioned [85];
- Renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion but is nevertheless included in the same pT3a stage group [86-89] (LE: 3);
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [83];
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [90, 91] (LE: 4).

A proposed imaging analysis of Tumour Contour Irregularity might be a valuable tool to enhance the preoperative staging between T1 and T3a RCCs for treatment decisions [92].

The TNM classification should not be considered the only criterion for clinical decision-making, but patient's condition, comorbidities and wishes are of fundamental importance to select the most optimal treatment. A clinically-guided RCC staging classification was proposed in 2022 by the EAU panel, based on changes observed in the management of small renal masses (SRM), locally advanced and metastatic disease [84].

Table 4.1: 2017 TNM classification system [93]

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 [94].*

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 [95-97]. 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. Increasing tumour shape irregularity on imaging is associated with an increased risk of pT3a upgrading and grade 3-4 disease, but the positive marign rate was similar [98].

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. The majority of RCCs are detected incidentally by non-invasive imaging investigating various non-specific symptoms and other abdominal diseases [99, 100] (LE: 3). In a retrospective observational cohort study, 60% of patients overall, 87% of patients with stage T1a renal tumours and 39% of patients with stage III or IV disease presented incidentally [101]. The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare (0.6%) [101]. Patients, who have tumours with local symptoms or systemic symptoms correlates with aggressive histology, advanced disease, and poorer outcomes [102, 103] (LE: 3). The increasing detection of incidental tumours is found in females and older patients with a better prognosis and lower stage [103]. Paraneoplastic syndromes (PNS) are found in approximately 33% of patients with symptomatic RCCs, but resolution of PNS occurred in 52% of patients after nephrectomy [104, 105] (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [106] (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, estimated glomerular filtration rate (e-GFR), complete cell blood count, C-reactive protein (CRP) or erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase (LDH) [107], 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 [108, 109] (LE: 2b):

- when renal function is compromised, as indicated by increased serum creatinine or significantly decreased e-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 [101] (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 [110] (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 parenchymal phase with intravenous contrast material to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield units (HU) before, and after, contrast administration. A change of fifteen HU, or more, in the solid tumour parts demonstrates enhancement and thus vital tumour parts [111] (LE: 3). Computed tomography or MRI allows accurate diagnosis of RCC but cannot reliably distinguish oncocytoma and fat-free AML from malignant renal neoplasms [112-115] (LE: 3). Abdominal CT with contrast provides information on [116]:

- function and morphology of the contralateral kidney [117] (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 [118, 119]. If the results of CT are indeterminate, CEUS is a valuable alternative to further characterise renal lesions [120-123] (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 [124, 125] (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 IVC. The T2-weighted image with its intrinsic contrast allows a good delineation [125].

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [125, 126] (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 [127]. Recently, the use of multiparametric MRI (mpMRI) to diagnose ccRCC via a clear cell likelihood score (ccLS) in SRMs was reported [128]. 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 [129], and ccLS was found to be an independent prognostic factor for identifying ccRCC.

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) [74].

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 [130].

A SR and meta-analysis [131] compared the diagnostic performance of CEUS vs. contrast-enhanced CT (CECT) and contrast-enhanced MRI (CEMRI) in the assessment of benign and malignant cystic and solid renal masses. Sixteen studies were included in the pooled analysis. The results suggested comparable diagnostic performance of CEUS compared with CECT (pooled sensitivity 0.96 [95% CI: 0.94-0.98], vs. 0.90 [95% CI: 0.86-0.93], for studies with a final diagnosis of benign or malignant renal masses by pathology), and CEUS vs. CEMRI (pooled sensitivity 0.98 [95% CI: 0.94-1.0], vs. 0.78 [95% CI: 0.66-0.91], for studies with final diagnosis by pathology report or reaffirmed diagnosis by follow-up imaging without pathology report). However, there were significant limitations in the data, including very few studies for CEMRI, clinical and statistical heterogeneity and inconsistency, as well as high risks of confounding.

*5.2.3 **Other investigations and emerging technologies***

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 [108, 109] (LE: 2a). ^{18}FDG-Positron-emission tomography (PET) is not recommended in primary staging [120, 132] (LE: 1b).

Emerging technologies have a growing body of evidence with regard to prostate-specific membrane antigen (PSMA) positron emission tomography (PET)-CT [133-135], ^{99}TC sestamibi SPECT/CT [55-58, 136] and ^{89}Zr-DFO-Girentuximab PET-CT [137] for differentiation of RCC subtypes, differentiation between benign tumours and RCC, and differentiation between high grade from low grade tumours. Additionally some of these modalities are being evaluated for staging purposes [57, 135]. Currently, the level of published evidence is not sufficient in terms of external validation to allow any guideline recommedation to be made.

*5.2.4 **Radiographic investigations to evaluate RCC metastases***

Chest CT is accurate for chest staging [90, 91, 138-140] (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 [141, 142]. 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 [138, 143, 144] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and

symptoms [143, 145, 146] (LE: 3). A prospective comparative blinded study involving 92 consecutive mRCC patients treated with first-line vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (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 overall survival (OS) [147].

The incidence of brain metastasis without neurological symptoms was retrospectively evaluated in 1,689 mRCC patients, selected to be included in 68 clinical trials between 2001-2013 [148]. All patients had a mandatory brain screening by CT/MRI. Seventy-two patients (4.3%) were diagnosed with occult brain metastases, of whom 39% multi-focal. Most patients (61%) were International Metastatic Renal Cancer Database Consortium (IMDC) intermediate risk and 26% were favourable risk. A majority (86%) of the patients had > 2 extracranial metastatic sites, including lung metastases in 92%. After predominantly radiotherapy, performed in 93% of patients, a median OS of 10.3 months (range 7.0–17.9 months) was observed.

*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 [149, 150] (LE: 3), and also advocates treatment for each category (Table 5.1). An updated Bosniak classification (2019) strengthened the classification and included MRI diagnostic criteria [75]; however, it requires further validation. According to a Meta-analysis based on 471 patients, the risk of maliganacy of Bosniak IIF-III, may be higher than with the old classification [151]. Until further validation, the imaging report should therefore identify which classification has been used. Lastly, the management of cystic renal tumours is also discussed in Section 3.5.7.

Table 5.1: Bosniak classification of renal cysts updated 2019 [75]

Bosniak classification / Imaging modality	**CT**	**MRI**
1 (Benign)	Well-defined, thin (≤ 2 mm) smooth wall; homogeneous simple fluid (-9 to 20 HU); no septa or calcifications; the wall may enhance	Well-defined, thin (≤ 2 mm) smooth wall; homogeneous simple fluid (signal intensity similar to CSF); no septa or calcifications; the wall may enhance
2 (Benign)	1. Cystic masses with thin (≤ 2 mm) and few (1–3) septa; septa and wall may enhance; may have calcification of any type 2. Homogeneous hyperattenuating (≥ 70 HU) masses at non-contrast CT 3. Homogeneous non-enhancing masses. 20 HU at renal mass protocol CT, may have calcification of any type† 4. Homogeneous masses -9 to 20 HU at non-contrast CT 5. Homogeneous masses 21 to 30 HU at portal venous phase CT 6. Homogeneous low-attenuation masses that are too small to characterise	1. Cystic masses with thin (≤ 2 mm) and few (1-3) enhancing septa; any non-enhancing septa; may have calcification of any type 2. Homogeneous masses markedly hyperintense at T2-weighted imaging (similar to CSF) at non-contrast MRI 3. Homogeneous masses markedly hyperintense at T1-weighted imaging (approximately 32.5 normal parenchymal signal intensity) at non-contrast MRI

2F (Follow-up, up to five years. Some are malignant.)	Cystic masses with a smooth minimally thickened (3 mm) enhancing wall, or smooth minimal thickening (3 mm) of one or more enhancing septa, or many (≥ 4 mm) smooth thin (≤ 2 mm) enhancing septa	1. Cystic masses with a smooth minimally thickened (3 mm) enhancing wall, or smooth minimal thickening (3 mm) of one or more enhancing septa, or many (≥ 4 mm) smooth thin (≤ 2 mm) enhancing septa 2. Cystic masses that are heterogeneously hyperintense at unenhanced fat-saturated T1-weighted imaging
3 (Surgery or AS – see Chapter 7. Over 50% are malignant.)	One or more enhancing thick (≥ 4 mm width) or enhancing irregular (displaying ≤ 3 mm obtusely margined convex protrusion[s]) walls or septa	One or more enhancing thick (≥ 4 mm width) or enhancing irregular (displaying ≤ 3 mm obtusely margined convex protrusion[s]) walls or septa
4 (Surgery. Most are malignant.)	One or more enhancing nodule(s) (≥ 4 mm convex protrusion with obtuse margins, or a convex protrusion of any size that has acute margins	One or more enhancing nodule(s) (≥ 4 mm convex protrusion with obtuse margins, or a convex protrusion of any size that has acute margins)

AS: Active Surveillance; CSF: Cerebrospinal Fluid; CT: Computed Tomography; HU: Hounsfield Units; MRI: Magnetic Resonance Imaging

5.3 Renal tumour biopsy

*5.3.1 **Indications and rationale***

Percutaneous 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 [152-157] (LE: 3).

A multicentre study assessing 542 surgically removed SRMs 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 [158]. In a recent series of patients who underwent a percutaneous biopsy for a SRM, active treatment (surgery or cryotherapy) was avoided in 50/182 patients (27.5%) because of a benign diagnosis at biopsy [159].

Renal biopsy is not indicated in 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, unless areas with a solid pattern are present (Bosniak IV cysts) [152, 155, 160] (LE: 2b/3). Histological characterisation by percutaneous biopsy of undefined retroperitoneal masses at imaging may be useful for decision making, especially in the younger patient population.

*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 [155, 161] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [152, 156, 162] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [152, 156] (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 [160, 163, 164] (LE: 2a). A SR 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 [160]. Other studies showed that solid pattern, larger tumour size and exophytic location are predictors of a diagnostic core biopsy [152, 155, 161] (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 [160] (LE: 2b). However, 0-22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [153-157, 161, 162, 165] (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%) [152, 166-168].

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 [160]. A recent study assessing the diagnostic performance of 151 renal tumour biopsies performed before robotic PN or RN confirmed that pathology on RTBs is highly concordant with the presence/absence of malignancy (147/151= 97%) and the histotype on surgical specimens (141/151=93%) [169].

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) [160] (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 [152, 155, 170, 171] (LE: 2b). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [172] (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 [173].

5.3.4 ***Morbidity***

Overall, percutaneous biopsies have a low morbidity [160]. 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 seven patients in whom tumour seeding was identified on histological examination of the resection specimen after surgical resection of RCC following diagnostic percutaneous biopsy [174]. Six of the seven 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 [174].

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 [160].

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 [175].

5.3.5 ***Genetic assessment***

Renal cancer can be related to an inherited or *de novo* monogenic germline alteration and this recognition has significant implications [176]. Hereditary kidney cancer is thought to account for 5-8% of all kidney cancer cases, although this number is likely an underestimation since a more recent study found germline mutations in up to 38% of all metastatic kidney cancer patients [177] (see Section 8 - Hereditary kidney tumours). Patients with a germline predisposition to kidney cancer often require multidisciplinary approaches, it is critical for clinicians to be familiar with how and when referral for counselling is warranted, methods of genetic testing, implications of the findings, screening of at-risk (non-renal) organs, and the screening protocol for family members. Well-defined renal cancer management strategies exist, and specific therapeutic strategies are available or in development (see Section 8). Lack of a syndromic manifestation does not exclude a genetic contribution to cancer development. Moreover, other genetic components or polymorphisms are heritable and may confer a mildly increased risk. When several risk alleles are present, they can significantly increase cancer risk.

Many factors are associated with an increased risk of hereditary renal cancer syndromes. For instance, even in the absence of clinical manifestations and personal/family history, an age of onset of 46 years or younger should trigger consideration for genetic counselling/germline mutation testing [178]. Moreover, presence of bilateral or multifocal tumours/cysts and/or a first- or second-degree relative with RCC and/or a close blood relative with a known pathogenic variant significantly increases the risk to detect hereditary cancer. The presence of renal cysts can be associated with BHD and VHL, and form part of the clinical diagnostic spectrum. Moreover, specific histologic characteristics can support differential diagnosis of a particular RCC syndrome

(e.g., multifocal papillary histology, hereditary fumarate hydratase-deficient RCC, RCC with fumarate hydratase deficiency, multiple chromophobe, oncocytoma or oncocytic hybrid, succinate dehydrogenase-deficient RCC histology). Finally, additional tuberous sclerosis complex criteria should be assessed in individuals with AML [178-187].

If additional risk factors are established in a patient, referral to a comprehensive clinical care centre, or a hospital with demonstrated expertise in managing hereditary cancer syndromes, will provide a dedicated working team, tailored clinical decisions, research translational programme, appropriate patient psychosocial support, and prospective collection of clinical data and biological samples. This can contribute to a better patient's care and further improvements in cancer care.

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
The incidence of lung metastises in cT1a, cN0, without systemic symptoms and normal heamoglobin and thrombocystes is neglicable.	3
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 US has a high sensitivity and specificity for characterisation of renal masses.	2a
Renal mass biopsies are associated with reduced overtreatment 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 PET- 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, in case the results of contrast-enhanced CT are indeterminate.	Strong
Offer brain CT/MRI in metastatic patients when systemic therapy or cytoreductive nephrectomy is considered.	Weak
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 unless a significant solid component is visible at imaging.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation of solid renal tumours.	Strong

5.5 Summary of evidence and recommendations for genetic assessment of RCC

Summary of evidence	LE
Hereditary kidney cancer is thought to account for 5-8% of all kidney cancer cases, though that number is likely an underestimate.	3
In case of renal cancer, if patient's age is 46 years or younger, and/or with bilateral or multifocal tumours and/or with a first or second-degree relative with RCC and/or with a close blood relative with a known pathogenic variant and/or with specific histologic characteristics (see text), the risk of hereditary cancer is significantly higher.	3
Hereditary RCC detection has unique implications for decision-making and follow-up.	3

Recommendations	Strength rating
Perform a genetic evaluation in patients aged ≤ 46 years, with bilateral or multifocal tumours and/or a first- or second-degree relative with RCC and/or a close blood relative with a known pathogenic variant and/or specific histologic characteristics which suggest the presence of a hereditary form of RCC.	Strong
Refer patients to a cancer geneticist or to a comprehensive clinical care centre in case of suspected hereditary RCC.	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 [81, 94] (Table 4.1).

6.3 Histological factors

Histological factors include tumour grade, RCC subtype, lymphovascular invasion, tumour necrosis, and invasion of the collecting system [188, 189]. Tumour grade is considered one of the most important histological prognostic factors. Fuhrman nuclear grade [190] has now been replaced by the WHO/ISUP grading classification [191]. This relies solely on nucleolar prominence for grade 1-3 tumours, allowing for less inter-observer variation [192]. 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 [193]. 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 [194]. The percentage of the sarcomatoid component appears to be prognostic as well, with a larger percentage of involvement being associated with worse survival. There is no agreement on the optimal prognostic cut-off for sub-classifying sarcomatoid changes [195, 196], although 20% has been suggested to distinguish focal and extensive amount of sarcomatoid features [197]. 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 [198]. Both the WHO/ISUP and chRCC grading systems need to be validated for prognostic systems and nomograms [191].

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 [199, 200] (Table 6.1). However, prognostic information provided by the RCC type is lost when stratified according to tumour stage [200, 201] (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 [202]. 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 [203]. Some studies suggest poorer survival for type 2 than type 1 [204], but this association is often lost in the multivariable analysis [205]. A meta-analysis did not show a significant survival difference between both types [206, 207].

TFE3 re-arranged RCC (formerly called RCC with Xp11.2 translocation) has a poor prognosis [208]. 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 [209-211] (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, five-year CSS was 98% [212]. 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 [199]

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 five-year 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 [209, 210]. 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 [211].

Table 6.2: Cancer-specific survival by stage [199]

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 = confidence interval; HR = hazard ratio.

6.4 Clinical factors

Clinical factors include performance status (PS), local symptoms, cachexia, anaemia, platelet count, neutrophil count, lymphocyte count, CRP [216], albumin, and various indices deriving from these factors such as the neutrophil-to-lymphocyte ratio (NLR) [106, 217-222] (LE: 3). As a marker of systemic inflammatory response, a high pre-operative NLR has been associated with poor prognosis [223], but there is significant heterogeneity in the data and no agreement on the optimal prognostic cut-off. 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 [224-226]. This association is linear with regards to cancer-specific mortality (CSM), while obese RCC patients show increasing all-cause mortality with increasing BMI [227]. There is also evidence on the prognostic value of body composition indices measured on cross-sectional imaging, such as sarcopenia and fat accumulation [222, 228, 229]. Health-related quality of life (HRQoL) at baseline and during treatment of mRCC may also be prognostic. In CheckMate 214, HRQol measured by the Functional Assessment of Cancer Therapy-Kidney Symptom Index-19 at baseline and during follow-up was associated with improved OS in both the ipilimumab+nivolumab and the sunitinib arm [230]. Perioperative blood transfusion is linked to worse cancer-specific and overall mortality, as well as a higher risk of recurrence. However, receiving 1 to 2 units of packed red blood cells does not significantly impact outcomes compared to receiving 3 or more units. Notably, intraoperative transfusion is associated with higher cancer-specific mortality and recurrence, while postoperative transfusion is not [231].

6.5 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CaIX), VEGF, HIF, Ki67 (proliferation), p53, p21 [232], PTEN (phosphatase and tensin homolog) cell cycle [233], E-cadherin, osteopontin [234] CD44 (cell adhesion) [235, 236], CXCR4 [237], PD-L1 [238], miRNA, SNPs, gene mutations, and gene methylations have been investigated (LE: 3) [239]. 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 [216, 238, 240]. 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 programmed death-ligand 1 (PD-L1) expression and tumour mutational burden were not [241]. 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 [242]. In CheckMate214 (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 [222].

Urinary and plasma Kidney-Injury Molecule-1 (KIM-1) has been identified as a potential diagnostic and prognostic marker. Kidney-Injury Molecule-1 concentrations are elevated in RCC patients at least up to five years before diagnosis and were associated with a shorter survival time [243]. Kidney-Injury Molecule-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 [244]. While early studies are promising, more high-quality research is required. Several retrospective studies and large molecular screening programmes 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 [245-248]. These published reports suggest that patients with BAP1- mutant tumours have worse outcomes compared with patients with PBRM1-mutant tumours [246]. Loss of chromosome 9p and 14q have been consistently shown to be associated with poorer survival [249-251]. 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 [250]. Additionally, a 16-gene signature was shown to predict disease-free survival (DFS) in patients with non-metastatic RCC [252]. 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 [253-260]. 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. Pathological prognostic factors are used in the Leibovich 2003 score/groups for clear cell [256]. There are prognostic models for non-clear cell RCC, like the VENUSS score for papillary RCC [205]. Although both were validated in several studies and showed superior discrimination to other prognostic models, molecular markers are needed [261-264]. In metastatic disease, risk groups assigned by the Memorial Sloan Kettering Cancer Centre (MSKCC) (primarily created in the pre-targeted therapy era and validated in patients receiving targeted therapy) and the IMDC (initially created in the targeted therapy era) differ in 23% of cases [265]. The IMDC model has been used in most of the recent RCTs, including those with immune checkpoint inhibitors (ICIs), and may therefore be the preferred model for clinical practice. It has recently been shown to continues to risk stratify patients with mRCC treated with first-line immune checkpoint inhibitor combination therapies [266].

The discrimination of the IMDC models improves by additional variables, such as presence of brain metastasis, bone metastasis, liver metastasis, NLR and platelet count [267-270]. 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
The 2003 Leibovich score is a validated prognostic model to predict the short- and long-term risk of metastasis in individual patients with sporadic, unilateral pT1-4 N0/+ M0 clear cell renal cell carcinoma.	2b
The VENUSS score is a validated prognostic model to predict the short- and long-term risk of disease recurrence in individual patients with sporadic, unilateral pT1-4 N0/+ M0 papillary renal cell carcinoma.	2b

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
Use the 2003 Leibovich scoring model for risk stratification of localised and locally advanced clear cell renal cell carcinoma.	Weak
Use the VENUSS scoring model for risk stratification of localised and locally advanced papillary renal cell carcinoma.	Weak
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** [271]	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 [256]	CC	1. T classification (pT1a: 0, pT1b: 2, pT2:3, pT3-4: 4 points) 2. N classification (pNx/N0: 0, pN+: 2 points) 3. Tumour size (< 10 cm: 0, ≥ 10 cm: 1 point) 4. Grade (G1-2: 0, G3: 1, G4: 3 points) 5. Tumour necrosis (absent: 0, 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 [272]	CC, P, CH	ccRCC • 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, sarcomatoid features, tumour size, perinephric or sinus fat invasion, tumour thrombus, nodal involvement. • No risk groups /prognostic groups. pRCC • 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. chRCC • 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 involvement. • High risk (group 3): sarcomatoid differentiation or nodal involvement.
VENUSS score/ model*** [205, 261]	P	1. T classification (pT1: 0, pT2: 1, pT3-4: 2 points) 2. N classification (pNx/pN0: 0, pN1: 3 points) 3. Tumour size (≤ 4 cm: 0, > 4 cm: 2 points) 4. Grade (G1/2: 0, G3/4: 2 points) 5. Tumour thrombus (absent: 0, 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**** [273]	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; PS = performance status.*

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

*** *Venous extension, Nuclear grade, Size, Stage. Available at https://www.evidencio.com/models/show/2369.*

**** *Grade, Age, Nodes and Tumour.*

Table 6.4: Prognostic models for metastatic RCC

Prognostic model	Subtype	Risk factors/prognostic factors
MSKCC [274]**	All	1. Karnofsky PS [275]* < 80% 2. Interval from diagnosis to systemic treatment < 1 year 3. Haemoglobin < Lower Limit of Normal 4. Corrected calcium >10mg/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 [276]***	All	1. Karnofsky PS [275]* < 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. > 7.0×10⁹/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-etastaticrenal-cell-carcinoma-rcc.*

*** *IMDC: https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-score-rcc.*

7. DISEASE MANAGEMENT

7.1 Patient involvement in kidney cancer treatment

A large-scale global survey of patients with RCC, identified geographic variations in patient education, experience, awareness, access to care, best practices, QoL, and unmet psychosocial needs [277]. A total of 1,983 patients from 43 countries revealed that at diagnosis, 43% of all respondents had no understanding of their RCC subtype, 29% of all patients reported no involvement in their treatment decision and 96% of respondents reported psychosocial impacts, with only 50% disclosing it to their health care team, with 90% indicated they would be interested in participating in clinical trails. Furthermore, an effort should be made to increase diversity in clinical trial participants, ensuring representation of the target population.

One RCT has indicated that patient involvement in reporting their symptoms during management of a variety of metastatic solid tumours, can improve clinical outcomes, including OS [278].

*7.1.1 **Recommendation on patient involvement and shared decision making***

Recommendation	Strength rating
Employ a shared decision-making approach when deciding on appropriate treatment for RCC	Strong

*7.1.2 **Smoking cessation***

A prospective study on 212 patients with RCC investigated the impact of smoking cessation on the risk of tumour recurrence/progression, RCC-specific and all-cause mortality. Quitting smoking was associated with lower all-cause mortality, lower cancer-specific mortality and a lower risk of recurrence/progression.

The beneficial effect of quitting smoking was evident across all RCC stages and all levels of smoking [279].

7.1.2.1 Recommendation on smoking cessation.

Recommendation	Strength rating
Counsel RCC patients to stop smoking.	Strong

7.2 Treatment of localised RCC

*7.2.1 **Introduction***

Section 7.2.2 is underpinned by a SR which includes all relevant published literature comparing surgical management of localised RCC (T1-2N0M0). Randomised or quasi-RCTs were included. However, due to the very limited number of RCTs, non-randomised studies, prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from the databases of well-defined registries were also included. A recent SR highlights the heterogeneity of outcome reporting and definitions in studies in localised RCC, supporting the development of a core outcome set to enable robust evaluation of evidence [280]. Historically, surgery has been the benchmark for the treatment of localised RCC.

*7.2.2 **Surgical treatment***

7.2.2.1 Nephron-sparing surgery versus radical nephrectomy in localised RCC

7.2.2.1.1 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 [281, 282]. There is only one, prematurely closed, prospective RCT including patients with organ-confined RCCs of limited size (< 5 cm) published, showing comparable non-inferiority of CSS for PN vs. RN (HR: 2.06 [95% CI: 0.62-6.84]) [283].

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 [281, 284-288]. When compared with a radical surgical approach, several retrospective analyses of large databases have suggested a decreased cardiovascular-specific mortality [285, 289] 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 [290, 291]. An analysis of the U.S. Medicare database [292] 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 included Medicare patients, suggested an OS benefit in older patients (75-80 years) when subjected to surgery rather than non-surgical management. A retrospective database analysis was conducted to compare patients who underwent PN for RCC with a non-cancer healthy control group, demonstrating an OS benefit for the cancer cohort [293]. 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 [283]. 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 [288]. 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) [294]. 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. A retrospective cohort study 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 [109].

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 [295].

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 [295, 296].

In view of the above, and since the oncological outcomes (CSS and RFS) of PNare comparable to those of RN, PN is the treatment of choice for T1 RCC since it better preserves kidney function and potentially limits the long-term incidence of cardiovascular disorders and ESRD. In frail patients, treatment decisions should be individualised, weighing the risks and benefits of PN vs. RN, the increased risk of peri-operative complications with PN, and the increased risk of developing or worsening CKD with RN.

7.2.2.1.2 T2 RCC

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 [297]. A trend for lower tumour recurrence- and CSM 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 [297]. A 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) [298]. Retrospective comparative studies of cT1 and cT2 RCC patients upstaged to pT3a RCC show contradictory results: some reports suggest similar oncologic outcomes between PN and RN [299], whilst another recent report suggests that PN of clinical T1 in pathologically upstaged pT3a of cT1 RCC is associated with a significantly shorter RFS than RN [300]. 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 with patients with T2 tumours. In this setting PN should be considered, if technically feasible, in patients with a solitary kidney, bilateral renal tumours or CKD with sufficient parenchymal volume preserved to allow sufficient post-operative renal function.

7.2.2.1.3 T3 RCC

A meta-analysis of nine articles including 1,278 patients with PN and 2,113 patients with RN for pT3a RCC showed no difference in CSS, OS, CSM and RFS, indicating that PN techniques can be used for functional benefits and if technically feasible [301].

7.2.2.2 Associated procedures

7.2.2.2.1 Adrenalectomy

One prospective non-randomised study compared the outcomes of RN with, or without, ipsilateral adrenalectomy [302]. Multivariable analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at five or ten years was seen with, or without, adrenalectomy. Adrenalectomy was justified using criteria based on radiographic- and intra-operative findings. Only 48 of 2,065 patients underwent concurrent ipsilateral adrenalectomy of which 42 of the 48 interventions were for benign lesions [302].

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

The indication for LN dissection (LND) together with PN or RN is still controversial [303]. 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+) [304]. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [305]. 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 [306]. The number of LN metastases (</> 4) as well as the intra- and extra-capsular extension of intra-nodal metastasis correlated with the patients´ clinical prognosis in some studies [305, 307-309]. Better survival outcomes were seen in patients with a low number of positive LNs (< 4) and no extra-nodal extension. Based on 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 [310]. However, in patients with pathologically proven lymphogenic spread (pN+), an increase of ten for the number of nodes dissected resulted in a 10% absolute increase in DSS.

In addition, a larger cohort of 1,983 patients demonstrated that eLND results in a significant prolongation of CSS in patients with unfavourable prognostic features (e.g., sarcomatoid differentiation, large tumour size) [311]. As to morbidity related to eLND, a 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 [312].

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 [304]. 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 [305, 313, 314]. At least fifteen LNs should be removed [311, 315]. Sentinel LND is an investigational technique [316, 317].

7.2.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [318, 319]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [320]. These indications will be revisited in Sections 7.2 and 7.3 with cross reference to the summary of evidence and recommendations below.

7.2.2.2.4 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 RCTs.	1b
Retrospective studies suggest a clinical benefit associated with LND 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

*7.2.3 **Radical and partial nephrectomy techniques***

7.2.3.1 Radical nephrectomy techniques

7.2.3.1.1 Open versus laparoscopic or robotic approach

No RCTs have assessed the oncological outcomes of laparoscopic vs. open RN. A retrospective comparative study with data retrieved from a national database studying the OS of open vs. minimally-invasive RN (laparoscopic RN or robotic assisted RN) showed an OS benefit in the minimally invasive RN group, as well as in hospital stay, re-admission rate, and 30-day and 90-day mortality rate [321]. However, a SR did not demonstrate any survival difference in laproscopic RN and open RN [322].

Data from one SR [322] and two non randomised studies [323, 324] 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 [324]. 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. Quality of life and perioperative outcomes were inconsistently defined, measured, or reported [281, 322] (LE: 2b, based on 1 low quality SR).

7.2.3.1.2 Laparoscopic versus robotic approach

Data of a large retrospective cohort study on robot-assisted laparoscopic vs. laparoscopic RN showed robot-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 [325]. A SR and meta-analysis of seven studies including 1,832 patients showed no difference between the two approaches in peri-operative outcomes, including operative time, blood loss, conversion rates and complications [326]. A SR reported on robot-assisted laparoscopic vs. conventional laparoscopic RN, showing no substantial differences in local recurrence rates, nor in all-cause CSM [327].

7.2.3.1.3 Laparoscopic single port versus laparoscopic multiport approach

Similar results were seen in observational cohort studies comparing 'portless' and 3-port laparoscopic RN, with similar peri-operative outcomes [328, 329].

7.2.3.2 Partial nephrectomy techniques

7.2.3.2.1 Open versus laparoscopic approach

Studies comparing laparoscopic and open PN found no difference in PFS [330-333] and OS [332, 333] 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 [334]. 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 [334]. The mean estimated blood loss was found to be lower with the laparoscopic approach [330, 332, 335], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events were similar [330, 332]. Operative time is generally longer with the laparoscopic approach [331, 333] and warm ischaemia time is shorter with the open approach [330, 332, 335, 336]. The results for GFR decline are debatable, an RCT reported greater three to twelve months kidney function reduction in the open group [337] whilst in a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [333], but not after 3.6 years follow-up. In another comparative study, the surgical approach was not an independent predictor for post-operative CKD [336]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [338]. Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [339]. 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 [340].

7.2.3.2.2 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 [341].

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 robot-assisted PN group with less overall complications, less major complications, less transfusions and a much shorter hospital stay [342].

A SR and meta-analysis comparing robot-assisted PN and open PN demonstrated similar short-term functional outcomes, however results are inconsistent [343].

OPERA, a prospective RCT comparing open vs. robotic PN in intermediate/high complexity renal tumours (RENAL Score > = 7) prematurely closed due to poor accrual and data have not been fully published [344].

The single-Centre, open-label feasibility ROBOCOP II RCT enrolled patients with suspected localized RCC referred for PN and randomized them at a 1:1 ratio to either robot-assisted PN or open PN [345]. The primary outcome was the feasibility of recruitment, assessed as the accrual rate. Secondary outcomes included perioperative and postoperative data. Overall, 50 patients underwent robot-assisted PN or open PN (accrual rate 65%). In comparison to open PN, robot-assisted PN had lower blood loss, less need for opioids, and fewer complications according to the mean Comprehensive Complication Index. Open PN has a shorter operative time and warm ischemia time. There were no differences between robot-assisted PN and open PN regarding postoperative functional outcomes. Considering the limitations of both prospective trials, the clinical impact of robot-assisted PN is still controversial.

7.2.3.2.3 Open versus hand-assisted approach

Hand-assisted laparoscopic PN (HALPN) is rarely performed. A 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 [346].

7.2.3.2.4 Open versus laparoscopic versus robotic approaches

In a retrospective propensity-score-matched study, comparing open-, laparoscopic- and robot-assisted PN, after five years of median follow-up, similar rates of local recurrence, distant metastasis and cancer-related death rates were found [347]. A recent SR comparing the three approaches included 31 studies with a combined 769 patients. There was no difference in ischaemia time, inra-operative complications, positive surgical margins (PSM), operative time or trifecta rate. The estimated blood loss, post-operative complications and length of stay were all significantly reduced with robot-assisted PN and laparoscopic PN compared to open surgery, with robot-assisted PN superior to laparoscopic PN in terms of reduced EBL [348].

7.2.3.2.5 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 robitic-assisted PN, respectively, at the beginning of the study. Peri-operative and short-term oncological and functional outcomes appeared broadly comparable between robitic-assisted PN and laparoscopic PN when performed by highly experienced surgeons [349].

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 PSMs [350].

A multi-institutional prospective study of 105 patients with hilar tumours demonstrated a reduced warm ischaemia time (20.2 min vs. 27.7 min) and a comparable rate of 1.9% when compared with a historical laparoscopic control group which was defined by literature research and meta-analysis for warm ischaemia time and PSM, respectively [351].

7.2.3.2.6 Laparoscopic transperitoneal versus retroperitoneal approach

Data from the Italian RECORD 2 project, a multi-institutional prospective observational project, compared the transperitoneal vs. the retroperitoneal approach for laparoscopic PN. After propensity score matching (each group n = 413) no differences in post-operative complications (surgical and medical), PSMs, early and late eGFR levels were observed. Intra-operative and surgical complications were slightly higher and operative times lower in the transperitoneal vs. the retroperitoneal approach [352]. In terms of peri-operative complications, retroperitoneal and transperitoneal PN have similar outcomes [338].

A SR assessed the outcomes of retroperitoneal vs. transperitoneal robotic-asssited PN. Seventeen studies, published between 2013 and 2021, were retrieved; none of which an RCT. Among the 6,266 patients included 2,261 (36.1%) and 4,005 (63.9%) underwent retroperitoneal vs. transperitoneal robotic-asssited PN, respectively. Both retroperitoneal and transperitoneal robotic-asssited PN offered similar surgical outcomes, while retroperitoneal robotic-asssited PN was associated with shorter surgical time and length of hospital stay [353].

7.2.3.2.7 Tumour enucleation, standard partial nephrectomy and single-port approach

Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [339]. 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 [340].

The only prospective multi-centre study available to date assessing the impact of resection technique (enucleation vs. enucleoresection vs. resection) during PN using a standardised reporting score to classify the resection technique after surgery found that the resection technique significantly impacts surgical complications, early functional outcomes and positive surgical margins after PN of localized renal masses [354].

A SR and pooled analysis found heterogeneity in the reporting of resection techniques across robotic PN series [355]. Out of twenty studies retrieved, nine compared "standard" resection versus enucleation. A pooled analysis did not reveal significant differences in terms of operative time, ischemia time, blood loss, transfusions, or positive margins. Significant differences favoring enucleation were found for clamping management (odds ratio [OR] for renal artery clamping 3.51, 95% confidence interval [CI] 1.13-10.88; p = 0.03), overall complications (OR for occurrence 0.55, 95% CI 0.34-0.87; p = 0.01) major complications (OR for occurrence 0.39, 95% CI 0.19-0.79; p = 0.009), length of stay (weighted mean difference [WMD] -0.72 d, 95% CI -0.99 to -0.45; p < 0.001), and decrease in estimated glomerular filtration rate (WMD -2.64 ml/min, 95% CI -5.15 to -0.12; p = 0.04).

7.2.3.2.8 Off-clamp versus On-clamp PN

The use of a off-clamp and selective-clamping approaches for PN has increased in recent years with the aim to minimize/avoid warm ischemia time and improve functional outcomes. One RCT (CLOCK study) showed a comparable safety profile of off-clamp vs. on-clamp PN in terms of intra- and peri-operative complications as well as comparable absolute eGFR variation and split renal function at six months from surgery in patients with regular baseline function and two kidneys. However, 40% of the patients randomized in the off-clamp group, were intraoperatively shifted to on-clamp (median ischemia time of fifteen minutes) [356, 357]. Due to the selective inclusion criteria of the RCT, off-clamp techniques may still be indicated in patients with chronic kidney disease, single kidney or multifocal disease [358, 359].

In a contemporary cohort of 1359 patients from the prospectively maintained database of the French national network of research on kidney cancer (UROCCR), PSM rate was not statistically different between the off-clamp group (5.6%) and the on-clamp group (11%) (p = 0.1). With short median follow-up, no statistical differences between the two groups were seen in OS, local RFS and metastasis-free survival [360].

7.2.3.2.9 Surgical volume

In a 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 35-40 cases per year overall, and 18-20 cases for the robotic approach [361]. 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 showed that undergoing robot-assisted PN at higher-volume hospitals may have better peri-operative outcomes (conversion to open and length of hospital stay) and lower PSM rates [362]. A French study, including 1,222 robot-assisted PN 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 [363]. 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 PSMs [364].

7.2.3.2.10 Pre-operative embolisation prior to partial nephrectomy

A SR and meta-analysis of 270 patients demonstrated significantly reduced blood loss in patients with selective renal artery embolisation (n = 222; 154 ± 22.6 mL vs. n = 48; 353.4 ± 69.6 mL) prior to PN [365].

7.2.3.3 Positive surgical margins on histopathological specimens

A PSM is encountered in about 2-8% of T1 PNs [366]. Studies comparing surgical margins with different surgical approaches (open, laparoscopic, robotic) are inconclusive [367-369]. Most trials showed that intra-operative frozen section analysis had no influence on the risk of definite PSMs [370]. A PSM 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) [371-374].

The majority of retrospective analyses reported so far indicated that PSMs do not translate into a higher risk of metastases or a decreased CSS [372, 373]. On the other hand, another retrospective study of a large single-institutional series showed that PSMs are an independent predictor of PFS due to a higher incidence of distant and local relapses [375]. Another retrospective study of 42,114 PN patients with 2,823 PSM patients (6.7%) showed an increased presence of PSM in upstaged pT3a tumours (14.1%), increased all-cause mortality in PSM patients and a decreased five-year OS rate in pT3a tumours (PSM: 69% vs. NSM: 90.9 %) [376].

However, only a proportion of patients with an uncertain margin status actually harbour residual malignancy. Local tumour bed recurrences were found in 16% in patients with PSMs compared with 3% in those with negative margins [371], Therefore, RN or re-resection of margins can result in over-treatment in many cases. Patients with PSMs 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 [372, 377]. On the other hand, protection

from recurrence is not ensured by negative surgical margins [378] as it is reported in up to 1.5% of cases in this category of patients [366].

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

Summary of evidence	LE
Laparoscopic RN has lower morbidity than open RN.	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
Robot-assisted and laparoscopic PN are associated with shorter length of hospital stay and lower blood loss compared to open PN.	2b
Transperitoneal and retroperitoneal laparoscopic PN do not differ in post-operative surgical and medical complications, PSMs, and kidney function.	2a
Hospital volume for PN might impact on surgical complications, warm ischaemia time and surgical margins.	3
Immediate completion nephrectomy for PSMs can result in over-treatment in many cases.	3
Off-clamp partial nephrectomy does not improve renal function outcomes in patients with baseline normal renal function.	1b

Recommendations	Strength rating
Offer laparoscopic or robotic 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, especially in upstaged pT3a patients.	Weak
Do not attempt off-clamp partial nephrectomy unless indicated.	Weak

7.2.4 Therapeutic approaches as alternatives to surgery

7.2.4.1 Watchful waiting

Elderly and comorbid patients with incidental SRMs have a low RCC-specific mortality and significant competing-cause mortality [379, 380].

Frailty is a geriatric syndrome characterized by a decline in individuals' resilience and physiological functional reserve across multiple body systems, resulting in increased vulnerability to external stressors [381]. The Comprehensive Geriatric Assessment is considered the gold standard of care for older patients in several settings, given its ability to identify frailty and risk of geriatric syndromes and the positive impact on patients' outcomes [382].

Beyond age and comorbidities, frailty has been increasingly recognized as a major risk factor for adverse perioperative and oncological outcomes in patients with genitourinary malignancies [381].

In this sense, watchful waiting is employed in cases where RCC is not expected to significantly impact the patient's remaining life expectancy, and when the focus is on managing symptoms rather than attempting a cure.

7.2.4.2 Active surveillance

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 [383]. The concept of AS differs from the concept of 'Watchful Waiting'; watchful waiting is reserved for patients whose comorbidities contra-indicate any subsequent active treatment and who do not require follow-up imaging, unless clinically indicated.

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 CSM in patients treated with surgery [292, 384, 385]. 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 [384]. Analyses of older patients (> 75 years) failed to show the same benefit in CSM for surgical treatment [291, 386, 387].

Growth rate and metastasis

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 [388, 389]. A SR of eighteen AS cohorts comprising 2,066 patients (cT1-2 N0M0) with a pooled mean follow-up of 53 months, showed that 2.1% (95% CI: 1.0-3.6) of patients developed metastatic disease during follow-up [390]. For patients with SRMs (nine studies, n = 987), the pooled metastasis rate was 1.8% (95% CI: 0.5-3.7).

In 136 biopsy-proven SRMs managed by AS, median follow-up of patients who remained on AS was 5.8 years (interquartile range 3.4-7.5 years). Clear-cell RCC grew faster than papillary type 1 SRMs (0.25 and 0.02 cm/year on average, respectively, p = 0.0003). Overall, 60 (44.1 %) of the malignant SRMs progressed; 49 (82%) by rapid growth (volume doubling), seven (12%) increasing to ≥ 4 cm, and four (6.7%) by both criteria. Six patients developed metastases, and all were of ccRCC histology [391].

Overall- and cancer-specific survival

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 [379]. 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 [392].

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 SRM 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 [393, 394].

Overall survival for primary intervention and AS was 98% and 96% at two years, and 92% and 75% at five years, respectively (p = 0.06). At five years, CSS was 99% and 100%, respectively (p = 0.3). Active surveillance was not predictive of OS or CSS in regression modelling with relatively short follow-up [393]. In the previously mentioned large SR of eighteen AS cohorts 1.0% (95% CI: 0.3-2.1) died from RCC and 22.6% (95% CI: 15.8-30.2) died from any cause. For patients with SRMs RCC-specific mortality was 0.6% (95% CI: 0-2.1), and all-cause mortality was 28.5% (95% CI: 17.4-41.4) [390].

A study using data from the DISSRM Registry investigated the outcomes of active surveillance in a cohort of patients aged 60 or younger at diagnosis [395]. Of 224 patients with median follow-up of 4.9 years, 30.4% chose surveillance. There were 20 (29.4%) surveillance progression events, including four elective crossovers, and 13 (19.1%) patients underwent delayed intervention. Among patients with initial tumour size ≤ 2 cm, 15.1% crossed over, compared to 33.3% with initial tumour size 2-4 cm. Overall survival was similar in primary intervention and surveillance at seven years (94.0% vs. 90.8%, log-rank p = 0.2). The CSS remained at 100% for both groups and RFS at five years was 96.0% and 100% for primary and delayed intervention, respectively (log-rank p = 0.6).

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 SRMs, followed, if required, by treatment for progression [383, 388, 389, 396-399].

Quality of life

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 [400].

7.2.4.3 Role of renal tumour biopsy before active surveillance

Histological characterisation of SRMs 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 SRMs grew faster than papillary type 1 SRMs (0.25 and 0.02 cm/year on average, respectively, p = 0.0003) [391].

7.2.4.4 Tumour ablation

7.2.4.4.1 Role of renal mass biopsy

A RMB is required prior to tumour ablation (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 tumour ablation of a benign or non-diagnostic mass [401, 402]. An analysis of the European multi-national prospective EuRECA registry (871 patients undergoing cryoablation) showed that the use of pre-cryoablation biopsy has significantly increased from 42% (65/156) in 2015 to 72% (88/122) in 2019 (p < 0.001), making treatment for a benign or an unknown histology significantly less likely (OR: 0.64, p < 0.001 and OR 0.31, p = 0.044, respectively) [403]. A RMB in a separate session reduces over-treatment significantly, with 80% of patients with benign lesions opting not to proceed with TA [402]. 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 five-year DFS rate was 90% for ccRCC and 100% for pRCC (80 months: 100% vs. 87%, p = 0.04) [404]. In another series, the total tumour ablation effectiveness rate was 90.9% for ccRCC and 100% for pRCC [405]. 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 [406]. Furthermore, patients with high-grade RCC or metastasis may choose different treatments over tumour ablation. 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.

7.2.4.4.2 Cryoablation

Cryoablation is performed using either a percutaneous- or a laparoscopic-assisted approach, with technical success rates of > 95% [407]. In comparative studies, there was no significant difference in the overall complication rates between laparoscopic- and percutaneous cryoablation [408-410]. 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 [409]. A shorter average length of hospital stay was found with the percutaneous technique [409-411]. A SR including 82 articles reported complication rates ranging between 8-20% with most complications being minor [412]. Although a precise definition of tumour recurrence is lacking, the athors reported a lower RFS as compared to that of PN.

Oncological outcomes after cryoablation have generally been favourable for cT1a tumours. In a 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. 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 m2 [413]. In another large series of 220 patients with biopsy-proven cT1 RCC, five-year local RFS was 93.9%, while metastasis-free survival approached 94.4% [407]. A series of 134 patients with T1 RCC (median tumour size 2.8 cm) submitted to percutaneous cryoablation yielded a ten-year DSF of 94% [414].

For cT1b tumours, local tumour control rates drop significantly. One study showed local tumour control in only 60.3% at three years [415]. In another series, the PFS rate was 66.7% at twelve months [416]. Furthermore, recent analyses demonstrated five-year cancer-specific mortality rates of 7.6-9% [417, 418]. On multivariable analysis, cryoablation of cT1b tumours was associated a 2.5-fold increased risk of death from RCC compared with PN [417]

Recurrence after initial cryoablation is often managed with re-cryoablation, but only 45% of patients remain disease-free at two years [419].

7.2.4.4.3 Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Several studies compared patients with cT1a tumours treated by laparoscopic or percutaneous radiofrequency ablation (RFA) [420-423]. 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., one month) imaging after one session of RFA is 94% for cT1a and 81% for cT1b tumours [424]. This is generally managed by re-RFA, approaching overall total technical success rates > 95% with one or more sessions [425].

Long-term outcomes with over five years of follow-up following RFA have been reported. Some studies reported that the five-year OS rate was 73-79% [424, 425], due to patient selection. While oncological outcomes have been favourable for cT1a tumours, it's important to note that within the T1a 3-4 cm subpopulation, these outcomes are less encouraging [426]. A study involving 106 patients treated with radiofrequency ablation, and with a median follow-up of 79 months, the ten-year DFS rate was 82%, but a notable decline was observed to 68% for tumours larger than 3 cm [425]. In series focusing on clinical T1b tumours (4.1-7.0 cm), the five-year DFS rate was 74.5% to 81% [424, 427]. Oncological outcomes appear to be worse than after surgery, but comparative data are severely biased (see Section 7.2.4.4.4). In general, most disease recurrences occur locally and recurrences beyond five years are rare [425, 427].

7.2.4.4.4 Microwave ablation

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 five-year local progression rate was 3.2%, while 4.3% developed distant metastases [428]. Results appear to be favourable for cT1b tumours as well [429]. 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 [430, 431].

7.2.4.4.5 Tumour ablation versus surgery

The Guideline Panel performed a protocol-driven SR of comparative studies (including > 50 patients) of tumour ablation (TA) with PN for T1N0M0 renal masses [432]. 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; sixteen studies compared laparoscopic or percutaneous TA vs. open-, laparoscopic- or robotic PN; two studies compared different techniques of TA and four studies compared TA vs. PN vs. RN. In this SR, 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 SRs based on the AMSTAR 2 tool which showed "Critically Low" or "Low" ratings [432].

Tumour ablation has been demonstrated to be associated with good long-term survival in several single-arm non-comparative studies [433, 434]. 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 CSM [290, 417, 418, 435-438]. However, there appears to be no clinically significant difference in five-year CSM between TA and AS [385]. A retrosepctive multicentre study, including 86 partial nephrectomies and 104 TA, matched for complexities, has shown that PN and cryoablation are comparable regarding complications within 90 days after treatment [439].

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 SRMs.

7.2.4.4.6 Stereotactic ablative radiotherapy

Stereotactic ablative radiotherapy (SABR) has been emerging as a treatment option for medically inoperable patients with localised cT1a and cT1b tumours [440, 441].

A variety of dose-fractionation schedules have been reported (26-60Gy; single, three and five fractions) [441]. The international society of stereotactic radiosurgery guidelines suggest the optimal dose fractionation is 25-26 Gy in one fraction for tumours < 4-5 cm , or 42-48 Gy in three fractions for larger tumours [442]. Published single-arm studies, mainly including cT1 RCC, with a median follow-up range of 16.4-34.3 months, reported local control rates of 90-97.2% [441, 443-450]. However, viable tumour cells are often seen in post-SABR biopsies, although their clinical significance remains unclear [445]. Grade 3 or 4 toxicities were reported in 0-9.1% of the patients across studies [441]. Even though early reported results of SABR look encouraging, more evidence from well conducted prospective studies with longer follow-up is needed [442].

7.2.4.4.7 Other ablative techniques

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

7.2.4.4.8 Summary of evidence and recommendations 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 SRMs is low in most cases and progression to metastatic disease is rare (1-2%).	3
Low quality studies suggest higher 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 quality of data does not allow definitive conclusions.	3
Stereotactic ablative radiotherapy in patients with non-metastatic RCC who where unfit for or declined surgery, demonstrated short term safety and efficacy but long term and comparative data are lacking.	3

Recommendations	Strength rating
Offer active surveillance (AS) or tumour 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
Discuss the harms/benefits with regards to oncological outcomes and complications when TA or AS is offered.	Strong
Offer stereotactic ablative radiotherapy for patients with non metastatic growing biopsy proven RCC, unfit for surgery.	Weak
Do not routinely offer radiofrequency ablation for tumours > 3 cm and cryoablation for tumours > 4 cm.	Weak

7.3 Treatment of locally advanced RCC

*7.3.1 **Introduction***

In addition to the summary of evidence and recommendations outlined in Section 7.2 for localised RCC, certain therapeutic strategies arise in specific situations for locally-advanced disease.

*7.3.2 **Role of lymph node dissection 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 [304]. In the setting of locally-advanced disease, several retrospective papers and SRs addressed the topic with contradictory results. A SR and meta-analyses could not confirm any survival benefit in patients at high risk of progression treated with LND [451]. A More recent SR and meta-analyses showing a survival benefit in patients with locally-advanced disease treated with LND [452]. 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).

7.3.2.1 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 0-25%, depending mainly on primary tumour size and the presence of distant metastases [453]. In case of clinically-negative LNs (cN-) at imaging, removal of LNs is justified only if visible or palpable during surgery [454], at least for staging, prognosis, adjuvant therapy and follow-up implications, although a benefit in terms of cancer control has not yet been demonstrated [306, 451].

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

In case of cN+, the probability to identify pathologically-confirmed LN metastases ranges between 10.3% (cT1 tumours) and up to 54.5% in case of locally-advanced disease. In cN+, removal of visible and palpable nodes during LND is justified [454], at least for staging, prognosis, adjuvant therapy and follow-up implications, although a benefit in terms of cancer control has not yet been demonstrated [306, 451]. Whether to extend the LND in case of lymphadenopathy (cN1) remains controversial. Retrospective data showed for resected isolated macroscopical lymphnode metastasis (pN1) that the time to systemic progression was a median of 4.2 months [455], suggesting that systemic therapy should always be discussed in presence of lymph node invasion.

*7.3.3 **Management of RCC with venous tumour thrombus***

Tumour thrombus formation in RCC patients accounts for 4-10% of RCC and may involve renal vein (pT3a, 78.3%), subdiaphragmatic inferior vena cava (pT3b, 16.4%) or supradiaphragmatic inferior vena cava (pT3c, 5.3%) [456]. This is a significant adverse prognostic factor with a five-year survival rate of 36% to 57% for patients without metastatic disease to other organs [457-460]. The majority are clear cell RCC and sarcomatoid differenciation are frequent (58%) [461].

Magnetic resonance imaging has been established as the imaging method of choice to determine the upper extent of the tumour thrombus, the degree of IVC occlusion, and to predict IVC wall invasion [125]. However, with the advent of the multidetector CT (MDCT), it may replace MRI.

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, although the associated surgical mortality is 2-10% [456, 457, 462-464] [459, 460]. A pre-operative imaging within one to two weeks of surgery is recommended given the propensity for tumour thrombus to progress rapidly [465]. Complete surgical excision should always be attempted because positive vascular wall margins increase local recurrence rates [466].

The role of neoadjuvant treatment with targeted agents has also been investigated in downstaging of tumour thrombus within the IVC with limited and controversial results [458, 467, 468]. Further investigations are needed to better identifying which patients with RCC and tumour venous might benefit from neoadjuvant therapy (See also section 7.3.5).

Several scores and tools have been proposed to estimate surgical complexity and the risk of complications, although an external validation is needed [469, 470].

In the largest published study, OS was higher in patients with a level of thrombus in the renal vein compared to inferior caval vein [471]. Survival was also associated with tumour size, grade, perinephric fat extension, sarcomatoid features, Eastern Cooperative Oncology Group PS and regional- and distant metastases in multivariate analysis [458, 471]. 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 (open vs. laparoscopic vs. robotic) for each case should be selected based on patients' characteristics, surgeon and hospital volumes and the extent of tumour thrombus and the grade of occlusion of the IVC [467, 472-474].

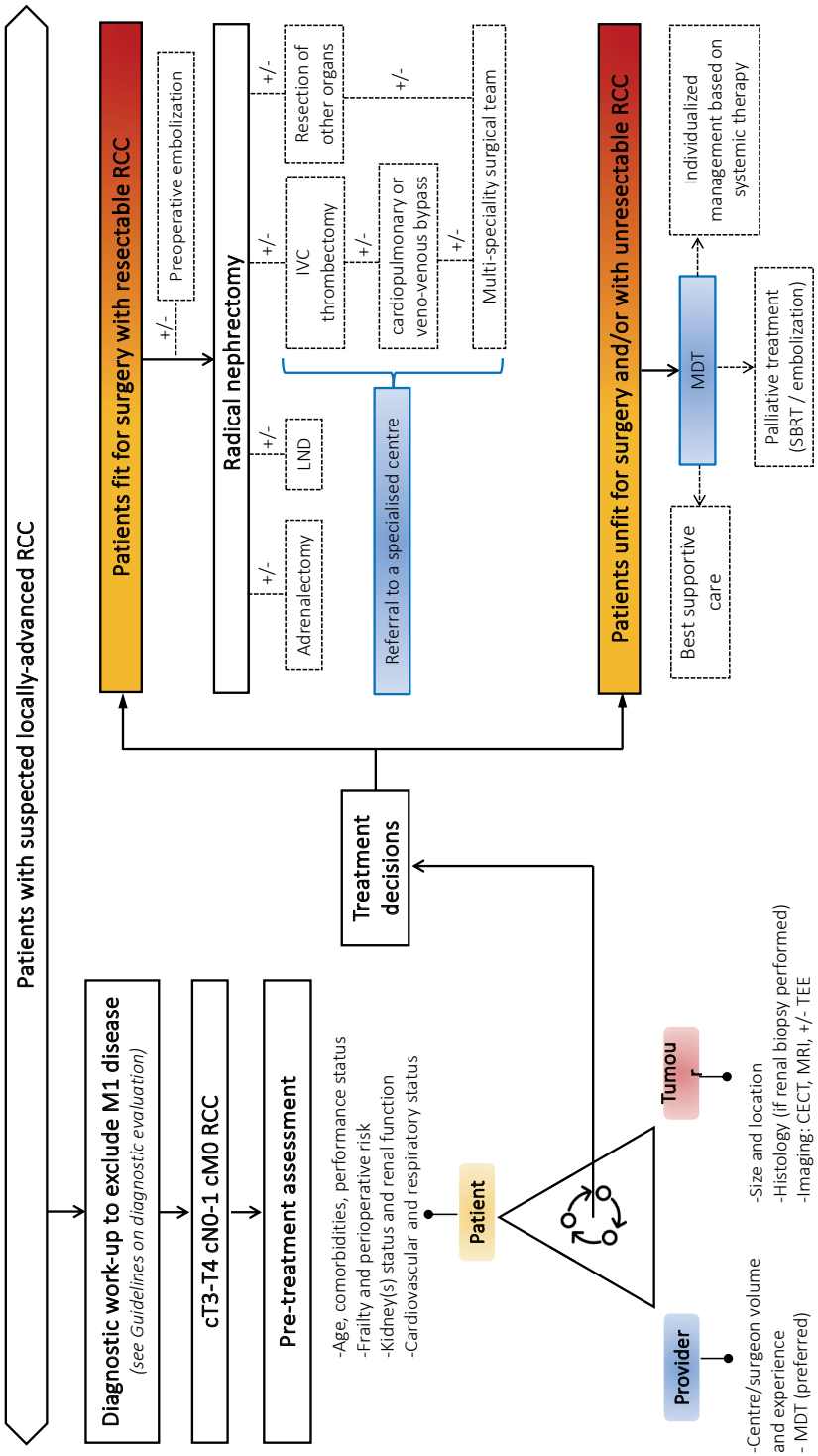
A SR and meta-analyses regarding surgical approach included 1,375 patients, out of which 329 patients were in single-arm studies and 1,046 patients were in comparative studies [475]. Of the 329 patients who underwent robotic, 14.7% were level I, 60.9% level II, 20.4% level III and 2.5% level IV thrombus. Compared with open thrombectomy, robotic approach was associated with a lower blood transfusion rate and fewer overall complications. Major complication and 30-day mortality rates were similar in both groups.
In a propensity-matched retrospective cohort containing 324 patients with renal tumour and venous thrombus, robotic approach was associated with a shorter operative time, a lower blood loss and transfusion rate, and a lower complication rate and postoperative hospital stay after matching, while there was no significant difference in survival [476]. In experienced hands with carefully selected patients, robotic thrombectomy can be considered; however, an emphasised selection bias limits definitive inference of these results, and optimal patient selection criteria remain to be elucidated.

In case of venous thrombus, referral to a tertiary care center/speciailsed centre is recommended to guarantee a multidisciplinary evaluation and treatment, especially in case of caval thrombus.

7.3.4 Management of locally-advanced unresectable RCC

The management of locally-advanced unresectable RCC should be based around systemic therapy [477]. 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 [320, 478-480].

Figure 7.1: Treatment of locally advanced RCC



CECT = contrast-enhanced computed tomography; IVC = inferior vena cava; LND = lymph node dissection; MDT = multidisciplinary team; MRI = magnetic resonance imaging; TEE = transesophageal echocardiogram.

7.3.4.1 *Summary of evidence and recommendations for lymph node dissection, the management of RCC* with venous tumour thrombus and unresectable tumours

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, adjuvant therapy and follow-up implications.	3
Low quality data suggest that tumour thrombus excision in non-metastatic disease may be beneficial.	3

Recommendations	Strength rating
During nephrectomy, remove clinically enlarged lymph nodes for staging, prognosis and follow-up implications.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong
Discuss treatment options in patients with locally-advanced unresectable RCC (biopsy and/or systemic therapy/deferred resection, or palliative management) within a multidisciplinary team to determine treatment goal.	Strong

7.3.5 ***Neoadjuvant and adjuvant therapy***

Neoadjuvant therapy is currently under investigation and available in clinical trials. In the pre-surgical setting neoadjuvant TKI and immune checkpoint therapy demonstrated varying response rates between 7-59% in retrospective series and some phase II trials [467, 481, 482].

In a presurgical phase II trial in patients with vascular thrombus treatment with axitinib demonstrated a reduction in the level of tumour thrombus in 35% of patients (7/20) [481]. Another presurgical phase II trial with axitinib showed a median shrinkage of tumour diameter of 1.3cm in complex renal tumours (RENAL Score 10-12) [483] and presurgical nivolumab did not show any primary tumour response in a prospective single arm trial [484]. There is currently no evidence of a prolonged OS by neoadjuvant treatment and at present, the data do not support its use outside clinical trials.

There is currently no evidence from a SR (including ten retrospective studies and two RCTs) that adjuvant radiation therapy increases survival [485]. The impact on OS of adjuvant tumour vaccination in selected patients undergoing nephrectomy for T3 renal carcinomas remains unconfirmed [486-490] (LE: 1b). A similar observation was made in an adjuvant trial of girentuximab, a monoclonal antibody against carbonic anhydrase IX (CAIX) (ARISER Study) [491].

At present, there is no OS data supporting the use of adjuvant VEGFR or mTOR inhibitors. Thus far, several RCTs comparing VEGFR-TKI or mTOR vs. placebo have been published [492-500]. Only S-TRAC, a trial of adjuvant sunitinib vs. placebo demonstrated a DFS benefit which was not reproduced in ASSURE, a trial of sunitinib and sorafenib vs. placebo. Due to an unfavourable AE profile and no survival advantage, none of these drugs are recommended [501].

7.3.5.1 *PD-1 Inhibition: Keynote-564*

The Keynote-564 trial is the first trial to report positive primary endpoint data on DFS [502, 503] and OS. Keynote-564 evaluated pembrolizumab (17 cycles of three-weekly therapy) vs. placebo as adjuvant therapy in 994 patients with intermediate (pT2, grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0) or high risk (pT4, any grade, N0, M0; or pT any stage, and grade, or N+, M0), or M1 (no evidence of disease [NED] after primary tumour plus soft tissue metastases completely resected < one year from nephrectomy) disease. The median follow-up, defined as time from randomisation to data cut-off, was 24.1 months. The primary endpoint of DFS per investigator assessment was significantly improved in the pembrolizumab group vs. (at the primary analysis HR: 0.68, 95% CI: 0.53-0.87, p = 0.001). The estimated 48-month DFS rate was 64.9% vs. 56.6% for pembrolizumab and placebo, respectively. Benefit occurred across broad subgroups of patients including those with M1/NED disease post-surgery (n = 58 [6%]). Investigator assessed DFS was considered preferable to DFS by central review due to its clinical applicability. Overall survival was statistically significant with a benefit in the pembrolizumab arm (HR: 0.62, 95% CI: 0.44-0.87, p = 0.005) and a consistant DFS advantage (HR 0.72) after median follow-up of 57.2 months. The estimated overall survival 91.2% in the pembrolizumab group vs. 86.0% in the placebo group at 48 months. Grade III-V all-cause adverse events occurred in 32% vs. 18% of patients for pembrolizumab and placebo, respectively. Quality of life assessment by FKSI-DRS and QLQ30 did not show a statistically significant or clinically meaningful deterioration in health-related QoL or symptom scores for either adjuvant pembrolizumab or placebo.

7.3.5.2 PD-L1 inhibition: IMmotion010

The IMmotion010 phase III trial was the first adjuvant ICI trial to be developed in RCC to investigate the effect of a PD-L1 inhibitor on DFS [504]. IMmotion010 evaluated atezolizumab 1200 mg (once every three weeks for sixteen cycles or one year) vs. placebo as adjuvant therapy in 778 patients with increased risk of recurrence defined as: pT2, grade 4 or sarcomatoid, N0, M0; or pT3, grade 3-4, N0, M0; or pT3b/c/T4, any grade, N0, M0; or pT any stage and grade, pN1, M0, or M1 no NED after primary tumour plus soft tissue metastases completely resected either synchronous or if metachronous, > 12 months from nephrectomy.

The minimum follow-up, defined as time from randomisation to data cut-off, was 38.6 months. The primary endpoint of DFS per investigator assessment was not met in the atezolizumab group vs. placebo (HR: 0.93, 95% CI: 0.75-1.15, p = 0.4950) with a median DFS of 57.2 months (95% CI: 44.6, NE) for atezolizumab vs. 49.5 months for placebo (47.4, NE). None of the exploratory subgroups suggested a DFS benefit with atezolizumab, most notably the M1 NED subgroup (n = 108/13.9%) which was larger than in Keynote-564 (5.8%), the sarcomatoid subgroup and the subgroup expressing > 1% PD-L1 had a HR of 0.93 (0.58-1.49), 0.77 (0.44-1.36) and 0.83 (0.63-1.10), respectively.

There were no OS differences. Grade 3-4 all-cause and treatment-related adverse events occurred in 27.2% and 14.1% vs. 21.1% and 4.7% of patients for atezolizumab and placebo, respectively. There were no treatment-related grade 5 adverse events.

7.3.5.3 PD-1 and CTLA-4 inhibition: CheckMate 914

CheckMate 914 was the first phase III trial to investigate a combination of nivolumab plus ipilimumab vs. placebo as adjuvant treatment in RCC (part A) [505]. Subsequently, a nivolumab monotherapy arm was also added to the trial (part B). The following results relate to part A which evaluated nivolumab 240 mg every two weeks (Q2W) for twelve cycles or six months plus ipilimumab 1 mg/kg Q6W for four cycles vs. placebo in 816 patients with recurrence risk defined as pT2a, grade 3 or 4, N0, M0; pT2b/T3/T4, any grade, N0, M0, or pT any stage, any grade, pN1, M0. The median time of follow-up, defined as time from randomisation to data cut-off, was 37 months. The primary endpoint of DFS per investigator assessment was not met in the nivolumab plus ipilimumab group vs. placebo (HR 0.92 [0.71-1.19], p = 0.5347). Of the exploratory subgroups, patients with sarcomatoid tumours (n = 40) and those with > 1% PD-L1 expression (n = 107) had a HR of 0.29 (0.09-0.91) and 0.46 (0.23-0.94) in favour of the ICI combination, respectively.

All-cause treatment discontinuation due to study drug occurred in 43% and 33% in the nivolumab plus ipilimumab group vs. 11% and 1% in the placebo group. Treatment-related adverse events grade > III were 29% in the nivolumab plus ipilimumab group and 2% in the placebo group with four deaths (1%) considered related to combination therapy. The high adverse event profile may have contributed to the lack of efficacy and patient retention. The results of the nivolumab arm are awaited.

Results from Part B, which studied the efficacy and safety of NIVO monotherapy versus placebo in this setting were reported at GU ASCO 2024. The primary endpoint, DFS of NIVO versus placebo per blinded independent central review (BICR), was not met (HR (95% CI), 0.87 (0.62-1.21) p = 0.3962 with median DFS not reached in both arms) [506].

7.3.5.4 Perioperative PD-1 inhibition: PROSPER

PROSPER is a peri-operative trial of neoadjuvant nivolumab (one cycle) followed by radical or partial nephrectomy and adjuvant nivolumab (480 mg IV q4 weeks) for nine doses compared to surgery followed by surveillance without a placebo [507, 508]. Patients with clinical stage > T2 or T any N+ RCC or patients with selected oligometastatic disease were included if they had no evidence of disease within twelve-weeks post surgery. A total of 819 patients with clear cell (87%) and non-ccRCC were included, a biopsy in the nivolumab arm was mandatory. The primary endpoint of RFS was similar between the arms (HR: 0.97; 95% CI: 0.74-1.28; p = 0.43) and the trial was stopped by the data and safety monitoring committee. The OS was not statistically different (HR: 1.48; 95% CI: 0.89-2.48; p = 0.93), although not mature. Grade III-IV adverse events occurred in 20% (nivolumab arm) and 6% (control arm) of patients, respectively. Fifteen (4%) patients died in the nivolumab arm and eighteen (4%) in the surgery alone arm.

The panel reached consensus and issued a strong recommendation for adjuvant pembrolizumab for patients with high-risk (defined as per study) operable ccRCC as final OS data is now available [509, 510]. This decision was taken as immune checkpoint inhibitor therapy has a different mode of action than VEGFR-TKI resulting in complete responses in up to 16% of patients in PD-1 unselected populations in metastatic disease [511]. Despite immature OS data with the early OS signal potentially driven by the M1 population the Panel cannot exclude that a survival benefit will emerge. This was not the case in the adjuvant sunitinib trial (S-TRAC) [505, 512]. The Panel recommends for adjuvant pembrolizumab, but the following topics should be considered:

- A high proportion of patients, cured by surgery, are receiving unnecessary treatment.
- The tolerability profile is acceptable but treatment related grade III-V adverse events were higher with 18.6% in the pembrolizumab arm vs. 1.2% in the placebo arm (occurring in approximately one-third of patients, all cause). Approximately 21% of patients required treatment discontinuation for adverse events. There is a risk of life-changing toxicity.
- Other ICI trials have not shown consistent results.
- Biomarker analysis to predict outcome and adverse events are not available.

The results of IMmotion010, CheckMate 914 and PROSPER need to be discussed with patients [504, 505, 507]. Meta-analysis with these data sets is not recommended due to heterogeneity across the ICI studies. It is likely that there are several reasons behind these inconsistent results, including study population with potential heterogeneity independent of TNM risk groups, selection criteria and trial design. To date pembrolizumab is the only positive trial [512].

While the results of IMmotion010 may reflect the non-significant OS results seen in the metastatic setting with PD-L1 inhibitors (IMmotion151, Javelin 101), the results of CheckMate 914 and PROSPER are more difficult to interpret. Nivolumab and ipilimumab leads to durable remission and long-term OS in metastatic disease and nivolumab has a similar mode of action as pembrolizumab (anti PD-1).

The high treatment discontinuation rate of 33% in CheckMate 914 is of concern and may have had an impact on the trial effectivity (20% in Keynote-564). The Panel strongly feels that biomarker work on all of these trials should occur to identify patients that do respond to therapy and to give a better explanation for the inconsistent results with KIM-1 as a potential prognostic factor as shown in IMmotion010 [513]. Treatment of unselected patients in the adjuvant setting based on the Keynote-564 criteria will result in a large proportion of patients receiving unnecessary therapy. In the absence of OS data or appropriate biomarkers, the patient preference should be leading in a shared decision-making process. Patients considering adjuvant therapy should be aware of all trials and not be presented with only one data set.

7.3.5.5 Progression after adjuvant PD-1 therapy

Currently, uncertainty exists regarding further treatment of patients who receive adjuvant therapy with pembrolizumab and develop a recurrence. Due to the relatively recent approval and recommendation no phase III prospective trial data exist in this setting. The Guideline panel thinks that there are different patient categories for patient progressing on or after pembrolizumab:

1. IO-Refractory patients: Progressing within the first three months of adjuvant pembro.
2. Early progressors: Patient progressing during pembrolizumab therapy.
3. Intermediate progressors: Patient progressing within the first six months after finishing adjuvant pembrolizumab treatment.
4. Late progressors: Patient progressing more than twelve months after finishing adjuvant pembrolizumab treatment.

The CONTACT-03 [514] and TiNivo [515] trial in mRCC patients showed no additional benefit of TKI+IO combinations over single agent TKI in IO pretreated patients. Therefore, it is likely, that the first two groups of IO-refractory patients and early progressors after adjuvant pembro will not benefit from a subsequent TKI+IO combination and should be treated with TKI monotherapy. For late progressors and potentially intermediate progressing patients the benefit of an IO combination can not be excluded, but neither be confirmed.

Table 7.1: Overview phase III trials of PD-1 immune checkpoint inhibitors in adjuvant RCC

Phase III trial of PD-1 immune checkpoint inhibitors in adjuvant RCC						
Study	**N**	**Experimental arm**	**Primary endpoint**	**Risk groups**	**DFS (mo) Median (95% CI) HR**	**OS (mo.) Median (95% CI) HR**
Keynote-564 NCT03142334 Median follow-up of 57.2 mo. [502, 510]	994	PEMBRO 200 mg IV Q3W (17 cycles) vs. placebo	DFS in the ITT by IR	**Intermediate-high:** pT2 grade 4 or sarcomatoid; pT3 any grade **High:** pT4 any grade, pN1 **M1 NED:** cM0 after resection of oligometastatic disease < 12 mo.	(ITT) PEMBRO: NR (NE) PLACEBO: NR (NE) HR: 0.72 (95% CI: 0.59- 0.87)) P < 0.002 DFS at 48 mo.: PEMBRO: 64.9% PLACEBO: 56.6%	(ITT) PEMBRO: NR (NE) PLACEBO: NR (NE) HR: 0.62 (95% CI: 0.44- 0.87) p<0.005 alive at 48 mo.: PEMBRO: 91.2% PLACEBO: 86.0%
IMmotion010 NCT03024996 Median follow-up of 44.7 mo. [504]	778	ATEZO 1200 mg IV Q3W (16 cycles or 1 yr.) vs. placebo	DFS in the ITT by IR	**By TNM:** pT2 grade 4 or sarcomatoid; pT3 a grade 3-4; pT3b/c/T4 any grade, pN1 M1 NED: cM0 after resection of oligometastatic disease (synchronous or >/=12 mo.)	(ITT) ATEZO: 57.2 (44.6-NE) PLACEBO: 49.5 (47.4-NE) HR: 0.93 (95% CI: 0.75-1.15) p = 0.4950 DFS at 24 mo.: NR	(ITT) ATEZO : NE (59.8-NE) PLACEBO : NE (NE-NE) HR : 0.97 (95% CI: 0.67-1.42) alive at 24 mo.: NR
CheckMate 914 NCT03138512 Median follow-up of 37.0 mo. [505]	816	NIVO 240 mg IV Q2W (× 12 cycles) + ipilimumab 1 mg/kg IV Q6W (× 4 cycles vs. placebo)	DFS in the ITT by BICR	**By TNM:** pT2a grade 3-4; pT2b/T3/T4 any grade, pN1	(ITT) NIVO + IPI: NR (NE) PLACEBO: 50.7 (48.1-NE) HR: 0.92 (95% CI: 0.71-1.19) p = 0.5347 DFS at 24 mo.: NIVO + IPI: 76.4% PLACEBO: 74.0%	NR

Arm B median follow-up of 18.7months [506]	825 Arm B	Nivolumab 240 mg IV Q2W (× 12 cycles) + placebo Q6W (× 4 doses) vs. placebo IV Q2W (× 12) + placebo IV Q6W (× 4) vs Nivolumab 240 mg IV Q2W (× 12) + ipilimumab 1 mg/kg IV Q6W (× 4) 2:1:1	DFS in the ITT by BICR	**By TNM:** pT2a grade 3-4; pT2b/T3/T4 any grade, pN1	(ITT) NIVO: NR (NE) PLACEBO: NR (NE) HR: 0.87 (95% CI:0.62-1.21) p=0.3962 DFS at 18 months NIVO: 78.4% PLACEBO: 75.4% **Secondary endpoint:** NIVO: NR (NE) NIVO+IPI: (NR (NE) HR: 1.27 (95% CI: 0.92-1.76) DFS at 18 months NIVO: 78.4% NIVO+IPI: 72.3%	NR
PROSPER NCT03055013 Median follow-up: NR [508]	779	Neoadjuvant NIVO 240 mg IV Q2W (x 2 cycles) followed by adjuvant nivolumab 240 mg Q2W for 3 mo. and Q4W for 6 mo. vs. observation	RFS in the ITT by IR	**By TNM:** >/= cT2 (7 cm) or cT any cN1	(ITT), RFS: NIVO: NR (NE) Observation: NR (NE) HR: 0.94 (95% CI: 0.74-1.21) p = 0.32	(ITT) NIVO : NR (NE) Observation : NR (NE) HR: 1.28 (95% CI: 0.84-1.95) p = 0.26

ATEZO = atezolizumab; BICR = blinded independent central review; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; IPI = ipilimumab; IR = investigator review; ITT = intention-to-treat; IV = intravenous; mo = months; NE = non-estimable; NED = no evidence of disease; NIVO = nivolumab; NR = not reached; OS = overall survival; PD-1 = programmed death-receptor 1; PEMBRO = pembrolizumab; PFS = progressionfree survival; Q2W = every 2 weeks; Q3W = every 3 weeks.

7.3.5.6 Summary of evidence and recommendations for neoadjuvant and adjuvant therapy

Summary of evidence	**LE**
Neoadjuvant systemic therapy can reduce vascular thrombus and tumour size in the presurgical setting.	2a
Adjuvant sunitinib, sorafenib, pazopanib, everolimus, girentuximab, or axitinib does not improve OS after nephrectomy.	1b
Adjuvant PD1 inhibition with pembrolizumab defined by the inclusion criteria of the trial* after nephrectomy improves DFS and OS.	1b
Adjuvant PD-L1 inhibition with atezolizumab and PD1 inhibition with nivolumab did not improve DFS or OS.	1b
Adjuvant dual PD-1 and CTLA-4 inhibition with nivolumab and ipilimumab did not improve DFS.	1b
Peri-operative treatment with nivolumab did not improve RFS.	1b
There is uncertainty regarding further systemic therapy in patients who receive adjuvant pembrolizumab and develop a recurrence.	4
The lack of biomarker data is hindering progress in this field.	4

** pT2 G4 or pT3 any G; pT4 any G; pN+ any G; M1, NED after resection of metastases.*

Recommendations	Strength rating
Do not use neoadjuvant therapy outside a clinical trial setting.	Weak
Offer adjuvant pembrolizumab to ccRCC patients, preferably within 12-16 weeks post-nephrectomy, with a recurrence risk as defined in the Keynote-564 trial: Intermediate-high risk: • pT2, grade 4 or sarcomatoid, N0 M0 • pT3, any grade, N0, M0 High risk: • pT4, any grade, N0, M0 • any pT, any grade, N+, M0 M1 no evidence of disease (NED): • NED after resection of oligometastatic sites ≤ 1 year from nephrectomy.	Strong
If adjuvant therapy is planned: • Discuss the contradictory results of the available adjuvant ICI trials with the patient to facilitate shared decision making. • Inform the patient about the potential risk of overtreatment and immune related side effects if adjuvant therapy is considered.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma (ccRCC).	Weak
Offer vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) to patients developing a recurrence while receiving pembrolizumab or within the first six months after stopping pembrolizumab given for one year.	Weak
Do not offer immune checkpoint inhibitor (ICI) mono- or combination therapy in patients with recurrence during or within six months after adjuvant pembrolizumab.	Weak

7.4 Advanced/metastatic RCC

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

7.4.1.1 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+ interferon (IFN)-based immunotherapy vs. IFN-based immunotherapy only, increased long-term survival was found in patients treated with CN [516]. However, IFN-based immunotherapy is no longer relevant in contemporary clinical practice.

Two RCTs [454, 517] and a narrative SR were identified [518]. The narrative SR included both RCTs and ten non-RCTs. 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 [519]. 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 twelve 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 patients with inherent resistance to systemic therapy [520]. This confirms previous findings from single-arm phase II studies [518, 521]. 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 [522]. These data are confirmed by CARMENA [448] and upfront pre-surgical VEGFR-targeted therapy followed by CN seems to be beneficial [511].

Meanwhile first-line therapy recommendations for patients with their primary tumour in place have changed to ICI combination therapy (see Section 7.4.2.4) with sunitinib and other VEGFR-TKI monotherapies reserved for those who cannot tolerate 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 7.2). 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 SR evaluating effects of CN demonstrated an OS advantage of CN [518]. 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 [523].

Table 7.2: Key trials 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 [524]	ipilimumab + nivolumab	187/847 (22%)	84	103	NA	0.63 (0.42-0.94)
CheckMate 9ER [525]	cabozantinib + nivolumab	196/651 (30.1%)	101	95	0.63 (0.43-0.92)	0.79 (0.48-1.29)
Javelin 101 [526]	axitinib + avelumab	179/886 (20.2%)	90	89	0.75 (0.48-1.65)	NA
KEYNOTE-426 [527]	axitinib + pembrolizumab	143/861 (16.6%)	73	70	0.68 (0.45-1.03)	0.57 (0.36-0.89)
CLEAR [528]	lenvatinib + pembrolizumab	179/714 (25.1%)	97	82	0.38 (0.31-0.48)	0.52 (0.31-0.86)

CI = confidence interval; HR = hazard ratio; ICI = immune checkpoint inhibitor; NA = not available; PFS = progression-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 Immune-Oncology (IO) + IO or TKI + IO combinations have a superior effect on the primary tumour and metastatic sites when compared to sunitinib alone (Table 7.2). 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. Real-world data have demonstrated durable response and surgical safety with this strategy, however long-term surveillance is lacking [529-531]. Randomised controlled trials in this setting are ongoing but are unlikely to report soon [532].

7.4.1.1.1 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 [320, 479] (see recommendations Section 7.2.2.2.4).

7.4.1.1.2 Summary of evidence and recommendations for local therapy of advanced/metastatic renal cell carcinoma

Summary of evidence	LE
Deferred CN with pre-surgical sunitinib in intermediate-risk patients with clear cell metastatic RCC (ccmRCC) 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 do not benefit from CN.	1a
Patients with their primary tumour in place treated with IO-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 IMDC/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

*7.4.2 **Local therapy of metastases in metastatic RCC***

A SR of the local treatment of metastases from RCC in any organ was undertaken [533]. 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 [534]. Of the 2,235 studies identified only sixteen non-randomised comparative studies were included. 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. A subsequent SR did not change the quality of evidence [535].

7.4.2.1 Complete versus no/incomplete metastasectomy

A SR, including only eight studies, compared complete vs. no and/or incomplete metastasectomy of RCC metastases in various organs [536-543]. In one study complete resection was achieved in only 45% of the metastasectomy cohort, which was compared with no metastasectomy [543]. Non-surgical modalities were not applied. Six studies [537-539, 541-543] 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 [536] showed no significant difference in CSS between complete and no metastasectomy, and one [540] reported a longer median OS for metastasectomy albeit no p-value was provided.

7.4.2.2 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 [544]. Single-dose IGRT (> 24 Gy) had a significantly better three-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 [545]. A significantly higher five-year CSS rate was observed in the intervention group. After adjusting for prior nephrectomy, gender and age, multivariable analysis still favoured metastasectomy/curettage and stabilisation. A third study compared the efficacy and durability of pain relief between single- dose SBRT and conventional radiotherapy in patients with RCC bone metastases to the spine [546]. For pain the overall response rate, time-to-pain relief and duration of pain relief were similar.

7.4.2.3 Local therapies for RCC brain metastases

Two studies on RCC brain metastases were included. A three-arm study compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS and WBRT [547]. 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 two-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 [548]. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. One-, two- and three-year survival rates were higher but not significantly so for FSRT as for metastasectomy and conventional radiotherapy, or conventional radiotherapy alone. Fractionated stereotactic radiotherapy did not result in a significantly better two-year local control rate compared with metastasectomy plus conventional radiotherapy.

Stereotactic radiotherapy (SRT) with a median physical dose of 20 (18-30) Gy and a biologically effective dose (DED10) of 63.3 (45-125) Gy in a median (range) of 1 (1-6) fractions for 1-5 brain metastases were safe also during ICI and targeted therapy [479]. Targeted therapy was paused only in one-third of patients for 2-21 days. Local control at all sites, including extracranial, was 75% at one year. After one year, 62% of patients remained on the same systemic therapy as at the time of SRT, which was more frequent for ICI therapy as compared to targeted therapy (83% vs. 36%; p = 0.035). No grade IV or V toxicity was observed.

7.4.2.4 Embolisation of metastases

Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss [180]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [181] (see recommendation Section 7.2.2.2.4).

7.4.2.5 Stereotactic radiotherapy in oligo-recurrent and oligo-progressive metastases

Sterotatic radiotherapy has been used in oligoprogression (i.e. limited number of metastasis in progression, while other sites are controlled under systemic therapy) and in oligonmetastatic recurrences. Two SRs of single arm studies have been conducted [549, 550]. The non-comparative nature of the studies included in both SR does not allow to definate conclusions.

A retrospective analysis of 207 patients with oligo-recurrent and oligo-progressive lesions in mainly bones and lungs with or without systemic therapy (mainly targeted therapy) demonstrated two-year local control rate of 78.3% (95% CI: 72.5-83.0). One, two and three-year local control rates were 89.4%, 80.1% and 76.6% in oligo-recurrent patients, and 82.7%, 76.9% and 64.3% in those with oligo-progressive disease, respectively. Median applied biologically effective dose (BED) 10 was 60 Gy. Median time to subsequent systemic therapy was 13.9 months and median PFS was 37.9 months. No grade III or higher toxicities were reported [551].

Similar results in oligo-progressive mRCC has been reported in a single-arm prospective study including 37 patients with IMDC favourable- and intermediate risk where one-year local control of the irradiated lesions was 93% (95% CI: 71-98%) and median time to change in systemic TKI therapy was 12.6 months (95% CI: 9.6-17.4 months). Median therapy prior to study entry was 18.6 months and therapy was discontinued during SRT. The median BED 10 was 72 Gy, corresponding to a SRT dose of 40 Gy in five fractions. Median PFS was 9.3 months and there were no reported grade III acute or late toxicities [552].

Several RCTs with SBRT in oligometastatic setting are ongoing.

7.4.2.6 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 in randomized prospective phase II trials of sorafenib and pazopanib after metastasectomy did not demonstrate an improvement in RFS [183, 553].

KEYNOTE-564 included a small percentage of patients who were treated by nephrectomy and complete metastasectomy within one year after primary diagnosis (6% in the experimental arm and 6% in the placebo arm) [502, 503]. Patients with brain and bone metastises where not included. A metachronous interval of < 1 year for recurrences following surgery with curative intent is a poor prognostic factor by IMDC classification [274, 554]. Systemic therapy based on immune combinations has stronger levels of evidence than surgery in this intermediate/advanced disease setting [555]. Also, TKI- driven adjuvant trials after metastasectomy have shown no DFS or OS benefit [182, 183].

Results for single-agent pembrolizumab post-surgery for metastatic disease are therefore difficult to interpret due to the small subgroup. The DFS HR of 0.40 (95% CI: 0.20-0.81) and OS HR was 0.51 (95% CI 0.15-1.75) in favour of resection of M1 to NED plus pembrolizumab shows that patients with subclinical, but progressive, disease who were subjected to metastasectomy had a benefit of adjuvant systemic therapy with pembrolizumab. Based on the current data it cannot be concluded that for patients with oligo-progressive disease, metastasectomy within the first year of initial diagnosis of the primary and subsequent adjuvant pembrolizumab is superior to a period of observation and dual IO-based combination first-line therapy upon progression. Data from the TKI era suggest that patients with oligometastatic disease recurrence can be observed for up to a median of sixteen months before systemic therapy is required and that this practice is common in real-world settings (30%) [556, 557].

In addition, it is possible that metastasectomy may lead to poorer outcomes compared to systemic therapy approaches as a relapse within the first twelve months and presentation with synchronous (oligo-metastatic disease is attributed to the IMDC intermediate risk-group. The Panel therefore does not encourage metastasectomy and adjuvant pembrolizumab in this population with recurrent disease within one year after primary surgery. A careful reassessment of disease status to rule out rapid progressive disease should be performed. Data from another adjuvant ICI study with the PD-L1 inhibitor atezolizumab (IMmotion010) also included an M1 NED subgroup which showed no DFS advantage [504]. This result underscores the need for caution in the treatment of the M1 NED subgroup.

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

Summary of evidence	**LE**
Retrospective comparative studies point towards a benefit of complete metastasectomy in mRCC patients in terms of OS, CSS and delay of systemic therapy.	3
A single-arm prospective and retrospective study support that oligometastases can be observed for up to sixteen months before systemic therapy is required due to progression.	2a
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 metastatic RCC patients after metastasectomy and no evidence of disease.	Strong
Perform a confirmatory axial scan of disease status prior to metastasectomy to rule out rapid progressive metastatic disease which requires systemic treatment.	Weak
Before initiating systemic therapy for oligometastases that cannot be resected, discuss with your patient a period of observation until progression is confirmed.	Weak

7.5 Systemic therapy for advanced/metastatic RCC

*7.5.1 **Chemotherapy***

Chemotherapy has proven to be generally ineffective in the treatment of RCC but can be offered to patients with collecting duct or medullary carcinoma [184].

7.5.1.1 Recommendation for systemic therapy in advanced/metastatic RCC

Recommendation	Strength rating
Do not offer chemotherapy to patients with metastatic RCC.	Strong

*7.5.2 **Targeted therapies***

In sporadic ccRCC, HIF accumulation due to VHL-inactivation results in overexpression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis [558-560]. 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 evidencebased 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 (see chapter 6.6 on prognostic models) [276].

7.5.2.1 Tyrosine kinase inhibitors

7.5.2.1.1 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 [561].

In the EFFECT trial, sunitinib 50 mg/day (four weeks on/two weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with clear cell metastatic renal cell carcinoma (cc-mRCC) [562]. 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 (two weeks on/one week off) is being used to manage toxicity, but robust data to support its use is lacking [563, 564].

7.5.2.1.2 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 [565].

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 [566]. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%, $p < 0.05$) due to symptomatic toxicity [567]. Both studies were limited in that intermittent therapy (sunitinib) was compared with continuous therapy (pazopanib).

7.5.2.1.3 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) [568].

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 III diarrhoea in 11%, hypertension in 16%, and fatigue in 11% of patients. Final analysis of OS showed no significant differences between axitinib or sorafenib [569]. 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 [570]. As a result of this study, axitinib is not approved for first-line therapy.

7.5.2.1.4 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 [237]. Based on these results an RCT investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapies (METEOR) [571, 572]. Cabozantinib delayed PFS compared to everolimus in VEGF-targeted therapy refractory disease (HR: 0.58, 95% CI: 0.45-0.75) [571] (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) [500]. Grade III or IV 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 cabozantinib and sunitinib in first-line in 157 intermediate- and poor-risk patients favoured cabozantinib for RR and PFS, but not OS [573, 574]. 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 III or IV 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.

7.5.2.1.5 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 (PDGFRα), 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 7.5.4.1.1 for discussion of results) [575].

7.5.2.1.6 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 [576, 577]. 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.

7.5.2.2 Monoclonal VEGF antibody

Bevacizumab is a humanised monoclonal antibody. Initial first-line treatment in combination with IFN-α has been superseded by more effective therapies [578-580]. Bevacizumab in combination with atezolizumab has not been approved for treatment of mRCC (see Section 7.5.3.2) [581].

7.5.2.3 mTOR inhibitors

7.5.2.3.1 Temsirolimus

Temsirolimus is a specific inhibitor of mTOR [582]. Its use has been superseded as front-line treatment option.

7.5.2.3.2 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) [583]. The data showed a median PFS of 4 vs. 1.9 months for everolimus and placebo, respectively [583].

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.

7.5.2.4 Small molucule inhibitor.

7.5.2.4.1 Belzutifan

Belzutifan is an inhibitor of the HIF2a transcription factor with single agent activity ccRCC. Initial Phase I/II trials in 55 patients confirmed objective response rate was 25% (all partial responses), and the median PFS was 14.5 months. The most common grade ≥ 3 adverse events were anaemia (27%) and hypoxia (16%) [584]. In the randomized phase III LITESPARK 005, it shows a PFS advantage over everolimus in heavily pretreated ccRCC. It has a favourable adverse event profile. It should be considered as an attractive alternative to everolimus in this setting. There was no significant difference in OS. Results of a number of combination studies are awaited [585]. Belzutifan has also been investigated in combination with cabozantinib in a single arm phase II trial with two cohorts (treatment-naive and after immunotherapy with up to two lines) [586]. In second and third line, this combination yielded an objective response rate of 30.8% with one CR (2%).

7.5.2.4.2 Vascular endothelial growth factor (VEGF) targeted therapy

Intermittent VEGF targeted therapy is attractive for patients on long term therapy, due to the chronic toxicity associated with long term therapy such as fatigue. It has been tested with sunitinib or pazopainib in a phase III study and found to be safe [587]. Patients in the study had stable disease (or better) for at least six months after staring therapy. They were closely followed for progression with cross sectional imaging. Cessation of therapy was associated with higher rates of progression but no detrimental effect was seen on OS [587]. Intermittent therapy has not been tested with VEFG/PD-1 combinations, therefore its application in the modern first line setting is unknown, but extrapolation suggests it should be safe.

7.5.2.5 Summary of evidence and recommendations for single-agent targeted therapy in metastatic clear-cell RCC

Summary of evidence	**LE**
Single-agent VEGF-targeted therapy has been superseded by immune checkpoint-based combination therapy.	1b
Intermittent VEGF therapy can be considered in patients on long term VEGF targeted therapy.	2
Immuno-oncology-VEGFR TKI combination established a RR and PFS benefit over single agent VEGFR TKI but no OS benefit in subgroup analysis.	1a
Pazopanib is non-inferior to sunitinib as first-line management option in mRCC.	1b
Cabozantinib in intermediate- and poor-risk treatment-naive ccRCC leads to better response rates and PFS but not OS when compared to sunitinib.	2b
Tivozanib has been approved by the EMA in the first-line setting.	3
Single-agent VEGF-targeted therapies are preferentially recommended after first-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
Belzutifan has a progression free survial advantage and no OS benefit over everolimus in second and more lines pretreated ccRCC.	1b
Lenvatinib in combination with everolimus improved PFS over everolimus alone in VEGF-refractory disease. Its role after ICIs 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 metastatic RCC.	Strong
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak
Offer belzutifan as an alternative to everolimus in patients previously treated with second to fourth line therapy for clear cell RCC.	Weak
Intermittent single agent VEGFR tyrosine kinase inhibitor can be offered in case of partial response or stable disease > six months.	Weak

*7.5.3 **Immunotherapy***

7.5.3.1 Immune checkpoint inhibitors

7.5.3.1.1 Immuno-oncology monotherapy

Immune checkpoint inhibitor 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 [588]. 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 III or IV adverse events with nivolumab than with everolimus [589]. 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 five-year OS probability of 26% vs. 18% [590] (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 ICI 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 [591]. 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) [591]. 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.

In addition, several trials explored the strategy of nivolumab monotherapy in first-line ccRCC followed by a salvage strategy with nivolumab plus ipilimumab upon progression or if stable disease was the best response. Trial results do not support such a strategy which was frequently not feasible and of limited benefit [592, 593]. This was confirmed in a pooled analysis of three of these trials [594]. However, recent data suggest that nivolumab monotherapy may yield extensive treatment-free survival in the IMDC favourable risk patient population [595].

7.5.3.2 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 [524] and a paradigm shift in the treatment of mRCC [596]. 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 RR (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 median follow-up of eight years shows ongoing benefits for the immune combination with independently assessed complete response rates of 12% and a HR for OS in the IMDC intermediate- and poor-risk group of 0.73 (0.61-0.87) [597]. However, this complete RR has not been consistent across trials for this combination (the Cosmic313 study showed complete RR of 3%. However, this complete RR has not been consistent across trials for this combination (the Cosmic313 study showed complete response rates of 3% [598]).

In CheckMate 214 the 90 month OS probability was 35% for ipilimumab plus nivolumab vs. 25% for sunitinib, respectively [599]. In this update the IMDC good-risk group continues to perform better with sunitinib (HR for OS: 0.82 [95% CI: 0.60-1.13]) [599]. Nivolumab plus ipilimumab was associated with 46% grade III-IV toxicity and 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.

Subset analysis of the favorable-risk group was not a primary endpoint of the trial. Initial results were favored sunitinb over nivolumab plus ipiliumab for this population, leading to a recommendations restricted to intermediate- and poor-risk disease. In updated results, after a median follow-up of 67.7 months, ipilimumab-nivolumab was associated with an OS HR of 0.94 (95% CI 0.65-1.37),while ORR (30% versus 52%) and PFS still favored sunitinib (HR 1.60, 95% CI 1.13-2.26), and improved CR rates (13% versus 6%) and duration of response (59% versus 52% with ongoing response at five years) were observed with ipilimumab plus ivolumab. This longer term results led the Guidelines panel to change the recommendation towards nivolumab plus ipilimumab in the IMDC favourable risk patient population [597].

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 and as an alternative in the favourable 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 [600]. 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 minimum follow-up of 35.6 months (median 42.8 months) this trial demonstrated an ongoing OS benefit for axitinib plus pembrolizumab in the ITT population (HR: 0.73, 95% CI: 0.60-0.88, p < 0.001). Median OS for axitinib plus pembrolizumab was 45.7 months (95% CI: 43.6 - NR) vs. 40.1 month (95% CI: 34.3 - 44.2) for sunitinib with a PFS benefit (HR: 0.68, 95% CI: 0.58-0.80, p < 0.0001) which was shown across all IMDC subgroups 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 10% in the pembrolizumab plus axitinib arm and 4% in the sunitinib arm [601]. With an extended median follow-up of 67 months median OS was 47.2 months (43.6-54.8) vs. 40.8 months (34.3-47.5; HR 0.84 95%CI: 0.71-0.99) for sunitib, median PFS was 15.7 (13.6-20.2) vs. 11.1 (8.9-12.5) HR 0.69 (95% CI: 0.59-0.81) and ORR was 60.6% (CR 11.6%) vs. 39.6% (CR 4.0%) [602]. Treatment-related adverse events (≥ grade III) 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 [600].

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 [456]. The primary endpoint of PFS assessed by central independent review in the ITT population was significantly 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 in the initial report [603]. The independently 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 adverse events (> grade III) 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. With an extended follow-up with median 44 months the median OS was 49.5 months (40.3-not estimable) in the nivolumab plus cabozantinib patients vs. 35.5 months (29.2-42.3) in the sunitinib treated patients (HR: 0.70 [95% CI: 0.56-0.87, p = 0.0043). The updated median PFS was 16.6 months (12.8-19.5) vs. 8.4 months (7.0-9.7; HR 0.59 [95% CI: 0.49-0.71], p < 0.0001 [604].

The randomised phase III trial CLEAR (Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab vs. Sunitinib alone as treatment of advanced RCC) was published [605]. 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 significantly 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. In the final analyis with a median follow-up of 49.8 months median OS was 53.7 months (48.7-not estimable) for lenvatinib plus pembrolizumab vs. 54.3 (40.9-not estimable; HR 0.79 95% CI: 0.63-0.99) for sunitinib [606]. Efficacy was observed across all IMDC risk groups, independently of PD-L1 status. Treatment-related adverse events (> grade III) 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 [526]. 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, but with a missing significant OS improvement also with longer follow-up [607] and in the third interim analyis with a median follow-up of 34.1 months [608]. The same applies to the atezolizumab/bevacizumab combination (IMmotion151) 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 shown a significant OS advantage at final analysis (HR: 0.91 [95% CI: 0.76-1.08], p = 0.27) [581, 609]. Therefore, these combinations cannot currently be recommended [610].

A similar combination of a PD-1 inhibitor (toripalimab) with axitinib was investigated in the RENOTORCH trial in cc-mRCC patients with intermediate and poor IMDC risk. A total of 421 patients were randomized, n=210 received toripalimab plus axitinib and n=211 sunitinib. After a median follow-up of 14.6 months, toripalimab plus axitinib significantly improved PFS compared with sunitinib (HR:0.65, 95% CI: 0.49-0.86; p = 0.0028]. Median PFS was 18.0 months in the toripalimab plus axitinib arm, and 9.8 months in the sunitinib arm. Objective response rate was significantly higher in the toripalimab plus axitinib arm compared with the sunitinib arm (56.7% vs. 30.8%;P < 0.0001). Overall survival trend favoroured toripalimab plus axitinib (HR 0.61, 95% CI: 0.40-0.92).This combination is available in China [611].

In the ETER100 trial the combnation of the PD-L1 inhibitor benmelstobart plus the TKI anlotinib was investigated in cc-mRCC patient of all IMDC risk groups. The phase III trial randomized 531 cc-mRCC patient to benmelstobart plus anlotinib (n=266) and sunitinb (n=265). After a median follow-up of 18.7 months the primary endpoint of PFS by BICR was significantly prolonged with benmelstobart plus anlotinib compared to sunitinib (18.9m vs. 9.8m; HR 0.53, CI: 0.42-0.67). Objective response rate was significantly higher with benmelstobart plus anlotinib (71.6% vs. 25.1%, p<0.001). The OS is still immature with a trend favouring benmelstobart plus anlotinib (HR: 0.66, CI: 0.48-0.92). This combination is not available in Europe [612].

In IMDC favourable patients the treatment with axitinib+pembrolizumab (Keynote-426), cabozantinib+nivolumab (CheckMate-9ER) and lenvatinib+pembrolizumab (CLEAR) improved PFS and ORR, but not OS [602, 613, 614]. Given the long-term follow-up with no OS improvement by the respective TKI+IO combination vs. sunitinib, TKI monotherapy becomes a standard of care as an additiional choice in IMDC favourable patients. Although sunitinib was the TKI monotherapy used in theses trials, pazopanib is a valid alternative based on the non-inferiority data of the phase III trial COMPARZ [566].

The COSMIC-313 trial is the first RCT to evaluate a triple combination of cabozantinib (40 mg) plus nivolumab plus ipilimumab vs. nivolumab plus ipilimumab, a current standard of care, in 855 patients with IMDC intermediate- and poor-risk [615]. The primary endpoint of PFS improvement, measured in a PFS ITT of 550 patient was met after 249 events occurred with a HR 0.73 (95% CI: 0.57-0.94, p = 0.013) favouring the triplet therapy. Median PFS was not reached (14.0-NE) vs. 11.3 months (7.7-18.2) in the control arm with a median follow-up of 20.2 months. Overall survival advantage has not been demonstrated yet. the ORR was 43% vs. 36% in the triplet vs. the control arm with a complete response rate of 3% in both arms. Treatment-related adverse events (> grade III) with cabozantinib plus nivolumab plus ipilimumab were 73% vs. 41% in the nivolumab plus ipilimumab control arm. The use of high-dose steroids (> = 40 mg prednisolone or equivalent) was 58% (triplet) vs. 35%. (control). Treatment discontinuation rate of any agent was high in the triplet arm (45%) compared to the doublet (24%), whilst discontinuation of all treatments due to the same adverse events was 12% vs. 5% in the control arm.

Although the primary endpoint of PFS was met, objective RR of the triplet combination are modest as known for TKI + IO doublets. Treatment-related adverse events are high with a high rate of treatment discontinuation. As the OS rate is currently unknown, the additional benefit of this triplet therapy compared to standard immune-based doublet therapy is still uncertain.

Table 7.4: 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 67 months [527, 600-602]	861	PEMBRO 200 mg. IV Q3W plus AXI 5 mg. PO BID vs. SUN 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: 15.7 (13.6-20.2) SUN: 11.1 (8.9-12.5) HR: 0.69 (95% CI: 0.59-0.81) p < 0.0001	(ITT) PEMBRO + AXI: 47.2. (43.6-54.8) SUN: 40.8 (34.3-47.5) HR:, 0.84 (95% CI: 0.71-0.99) p = 0.001

JAVELIN 101 **NCT02684006** Median follow-up 34.1 months [526, 607, 608, 610]	886	AVE 10 mg/kg IV Q2W plus AXI, 5 mg PO BID vs. SUN 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: 13.9 (11.0-17.8) SUN: 8.2 (6.9-9.4) HR: 0.67 (95% CI: 0.57-0.79) p < 0.0001	(PD-L1+) AVE+AXI: 43.2 (36.5-51.7) SUN: 36.2 (29.8-44.2) HR, 0.86 (95% CI: 0.70-1.06) p = 0.0755
IMmotion151 **NCT02420821** Median follow-up 24 months [581, 609]	915	ATEZO 1200 mg fixed dose IV plus BEV 15 mg/kg IV on days 1 and 22 of each 42-day cycle vs. SUN 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: 36.1 (31.5-42.3) SUN: 35.3 (28.6-42.1NE) HR: 0.91 (95% CI: 0.76-1.08) p = 0.27
CheckMate214 **NCT02231749** Median follow-up of 60 months [524, 599]	1096	NIVO 3 mg/kg plus ipilimumab 1 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W vs. SUN 50 mg PO QD 4/2 wk.	PFS and OS in the IMDC inter-mediate and poor risk population by BICR	**IMDC** FAV 23% IMD 61% POOR 17% **MSKCC** Not determined	(IMDC IMD/poor) NIVO + IPI: 11.6 (8.4-16.5) SUN: 8.3 (7.0-10.4) HR: 0.73 (95% CI: 0.61-0.87)	(IMDC IMD/poor) NIVO + IPI: 47.0 (35.4-57.4) SUN: 26.6 (22.1-33.5) HR: 0.68 (0.58-0.81) p = < 0.0001
CheckMate9ER **NCT03141177** Median follow-up of 44 months [603, 604, 614]	651	NIVO 240 mg. fixed dose IV every 2 wk. plus CABO 40 mg PO daily vs. SUN 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 (12.8-19.5) SUN: 8.4 (7.0-9.7) HR: 0.59 (95% CI: 0.49-0.71) p <0.0001	(ITT) NIVO+CABO: 49.5 (40.3-NE) SUN: 35.5 (29.2-42.3) HR: 0.70 (98.9% CI: 0.56-0.87) p = 0.0034
CLEAR **NCT02811861** Median follow-up of 49.8 months [605, 606, 613, 616]	712	PEMBRO 200 mg IV Q3W plus LEN 20 mg PO QD vs. SUN 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: 0.47 (95% CI: 0.38-0.57) p > 0.001	(ITT) PEMBRO+LEN: 23.9 (20.8-27.7) SUN: 9.2 (6.0-11.0) HR: 0.47 (95% CI: 0.38-0.57) p < 0.001
RENOTORCH **NCT04394975** Median follow-up of 14.6 months [611, 612]	421	TORI 240 mg IV Q3W plus AXI 5 mg. PO BID vs. SUN 50 mg PO QD 4/2 wk. or QD 2/1wk.	PFS in the ITT by BIRC	**IMDC** IMD 81% POOR 19%	(ITT) TORI+AXI: 18.0 (15.0-N.E) SUN: 9.8 (8.3-13.8) HR: 0.65 (95% CI: 0.49-0.86) p = 0.0028	(ITT) TORI+AXI: N.E. (N.E.-N.E.) SUN: 26.8 (24.5-N.E.) HR: 0.61 (95% CI: 0.40-0.92)

ETER100 NCT04523272 Median follow-up of 18.7 months [612]	531	BENMEL 1200mg IV Q3W plus ANLO 12mg PO QD 2/1wk Vs SUN 50 mg PO QD 4/2 wk.	PFS in the ITT by BIRC	**IMDC** FAV 14% IMD 71% POOR 15%	(ITT) BENMEL+ANLO: 19.0 (15.3-22.8) SUN: 9.8 (8.4-12.4) HR: 0.53 (95% CI: 0.42-0.67) p < 0.001	(ITT) BENMEL+ANLO: N.E. (38.2-N.E.) SUN: N.E. (30.5-N.E.) HR: 0.66 (95% CI: 0.48-0.92) p=0.0673
COSMIC-313 Median follow-up of 20.2 months [615]	855	NIVO 3 mg/kg plus IPI 1 mg/kg IV Q3W for 4 doses then NIVO 3 mg/kg IV Q2W + CABO 40mg PO QD vs. NIVO 3 mg/kg plus IPI 1 mg/kg IV Q3W for 4 doses then NIVO 3 mg/kg IV Q2W	PFS in the PITT population (first 550 pts. randomised)	**IMDC** IMD 75% POOR 25%	(PITT) NIVO+IPI+CABO: NR (14.0-NE) NIVO+IPI: 11.3 (7.7-18.2) HR: 0.73 (95% CI: 0.57-0.94) p = 0.013	NR

ANLO = anlotininib; ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BENMEL = benmelstobart; BICR = blinded independent central review; BID = twice a day; CABO = cabozantinib; CI = confidence interval; FAV = favourable; HR = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; 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; PITT = PFS intention-to-treat; PO = by mouth; Pts = patients; QD = once a day; Q2W = every 2 weeks; Q3W = every 3 weeks; SUN = sunitinib; TORI = toripalimab; 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 [524, 617] (LE: 1).

Patients who stop TKI and IO due to immune-related toxicity can receive single-agent TKI once the adverse events 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 ICIs 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.

Based on panel consensus, nivolumab plus ipilimumab, pembrolizumab plus axitinib and 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 (LE: 4).

*7.5.4 **Therapeutic strategies***

7.5.4.1 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 7.2). Therefore, the role of VEGFR-TKIs alone in front-line mRCC has been superseded in IMDC intermidiate and poor risk. In IMDC Favorable group, in the absence of OS benefit both options are acceptable. 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 7.2).

7.5.4.1.1 Sequencing systemic therapy in clear-cell metastatic RCC

The sequencing of targeted therapies is established in mRCC and maximises outcomes [575, 589]. Pembrolizumab plus axitinib, nivolumab plus cabozantinib, lenvatinib plus pembrolizumab and nivolumab plus ipilimumab are the new standard of care in front-line therapy in IMDC intermediate/poor. 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 limited. Sequencing immune checkpoint inhibition with atezolizumab did not demonstrate objective response rate, PFS , OS benefit over single agent TKI in the CONTACT 03 [514, 618]. In addition, in the TiNivo trial the combination of tivoazanib plus nicvolumab did not improved PFS, OS and objective response rate over single agent tivozanib [515]. Furthermore, prospective data on cabozantinib, tivozanib [619] 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 [589, 620].

The use of mTOR inhibitors can be considered in VEGF-targeted therapy refractory disease but has been outperformed by other VEGF-targeted therapies in mRCC and belzutifan [585, 621]. 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 [544]. 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 [621]. 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 [575]. As shown in a study which also included patients on ICIs, tivozanib provides PFS superiority over sorafenib in VEGF-refractory disease [622].

7.5.4.1.2 Summary of evidence and recommendations for immunotherapy in cc-mRCC

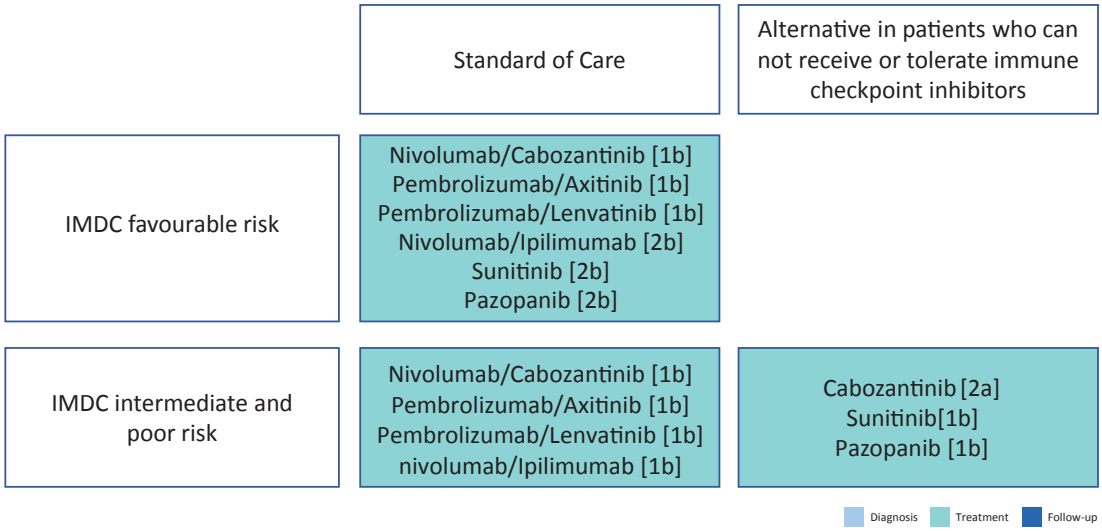
Summary of evidence	**LE**
Treatment-naïve patients	
Currently, PD-L1 expression is not used for patient selection.	2b
The combination of nivolumab and ipilimumab in treatment-naïve patients with cc-mRCC of IMDC, intermediate- and poor risk demonstrated OS and objective response rate benefits compared to sunitinib alone.	1b
The updated OS data for ipilimumab/nivolumab in IMDC favourable risk patients demonstrates the long term benefit for this subgroup of patients.	2b
The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naïve patients with cc-mRCC demonstrated PFS, OS and objective response rate benefits compared to sunitinib in the ITT population.	1b
The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naïve patients with cc-mRCC in IMDC favorable subgroups demonstrated PFS and objective response rate benefits compared to sunitinib, without OS improvememt.	2b
The combination of axitinib plus avelumab did not demonstate significant OS benefit and axitinib plus toripalimab did not demonstrate significant OS benefit yet as did benmelstobart plus anlotinib.	1b
Triplet cabozantinib-nivolumab-ipilimumab demonstrated a PFS benefit over nivolumab-ipilimumab.	1b
Sequencing systemic therapy	
Nivolumab leads to superior OS compared to everolimus in disease progression after one or two lines of VEGF-targeted therapy.	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
Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	4
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	1b
Nivolumab plus ipilimumab was associated with 46% grade III-IV toxicity and 1.5% treatment-related deaths. Tyrosine kinase inhibitor-based IO combination therapies were associated with grade III-V toxicity ranging between 61-72% and 1% of treatment-related deaths.	1b

In the CONTACT 3 study atezolizomab plus cabozantinib offered no benefit compared to cabozantinib alone in patients who's cancers have previously progressed on immune checkpoint inhibition therapy.	1b
Cabozantinib as a single agent has the most robust data after first line PD1 based combination therapy.	3

Recommendations	Strength rating
First line Treatment for metastatic clear cell RCC patients	
Offer nivolumab plus ipilimumab, pembrolizumab plus axitinib, lenvatinib plus pembrolizumab or nivolumab and cabozantinib to patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate- or poor risk-disease.	Strong
Offer pembrolizumab plus axitinib, lenvatinib plus pembrolizumab or nivolumab and cabozantinib or nivolumab plus ipilimumab or sunitinib or pazopanib for IMDC favourable risk disease.	Weak
Offer sunitinib or pazopanib to patients with any IMDC risk who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to patients with IMDC intermediate- and poor-risk clear cell metastatic renal carcinoma (cc-mRCC) who cannot receive or tolerate immune checkpoint inhibition.	Strong*
Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support after discontinuation for toxicity.	Weak
Sequencing systemic therapy for metastatic clear cell RCC	
Sequence systemic therapy in treating metaststic RCC.	Strong
Offer carbozantinib or other vascular endothelial growth factor (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
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer nivolumab or cabozantinib for those patients who received first line VEGF targeted therapy alone.	Strong
Treatment past progression can be justified but requires close scrutiny and the support of an expert multi-disciplinary team.	Weak
Do not re-challenge patients who stopped immune checkpoint inhibitors because of toxicity without expert guidance and support from a multi-disciplinary team.	Strong
Do not offer programmed death-ligand 1 (PD-L1) combination therapy after progression after immune checkpoint inhibition combination.	Weak

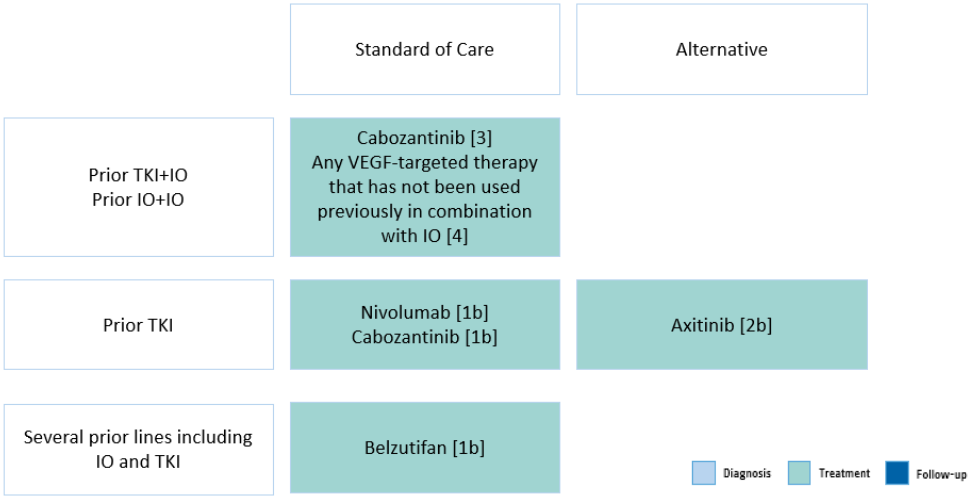
* *While this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib in this population. This justified the same recommendation under exceptional circumstances.*

Figure 7.2: Updated EAU Guidelines recommendations for the first-line treatment of cc- mRCC



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 7.3: EAU Guidelines recommendations for later-line therapy



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.

7.5.4.1.3 Renal tumours with sarcomatoid features

Subset analyses have shown improved results for PD-L1 inhibitors combined with CTLA4 or VEGF-targeted therapy in renal tumours with sarcomatoid features. Ipilimumab/nivolumab, axitinib/pembrolizumab and lenvatinib/pembrolizumab avelumab/axitinib can all be recommended instead of VEFG-targeted therapy alone. These options have OS advantages over sunitinib, sunitinib plus gemicitabine and superseded VEGF-targeted therapy. Nivolumab/Ipilimumab provided *post hoc* analysis demonstrating ORR of 61%, including 23% CR rate, PFS and OS benefit over sunitinb (HR 0.50 and OS HR 0.46 respectively with median OS 48.6 vs. 14.2 month [623, 624].

Table 7.5: Subgroup analysis of first-line immune checkpoint inhibitor combinations in RCC patients with sarcomatoid histology
Cross trial comparison is not recommended and should occur with caution

Study	N (ITT)	Therapy	N (sRCC)	PFS (mo.) Median (95% CI) HR	OS (mo.) Median (95% CI) HR	ORR (%) (95% CI)
KEYNOTE-426 NCT02853331 Median follow-up 12.8 months [600]	861	PEMBRO + AXI SUN	51 54	NR 8.4 HR: 0.54 (0.29-1.00)	NR NR HR: 0.58 (0.21–1.59)	58.8 31.5
JAVELIN 101 NCT02684006 [610, 625, 626]	886	AVE + AXI SUN	47 61	7.0 (5.3-13.8) 4.0 (2.7-5.7) HR 0.57 (0.33-1.00)	NA	46.8 (32.1-61.9) 21.3 (11.9-33.7)
IMmotion151 NCT02420821 Median follow-up 13 to 17 months [627]	915	ATEZO + BEV SUN	68 74	8.3 (5.4, 12.9) 5.3 (3.3, 6.7) HR: 0.52 (0.34-0.79)	21.7 (15.3, NE) 15.4 (10.4, 19.5) HR: 0.64 (0.41, 1.01)	49 (36-1) 14 (7-23)
CheckMate214 NCT02231749 minimum follow-up of 60 months [623]	1096	NIVO + IPI SUN	IMDC Intermediate and poor risk 74 75	26.5 (7.2-NE) 5.5 (4.1-6.9) HR: 0.50 (0.32–0.80)	48.6 (25.2–NE) 14.2 (9.3–22.9) HR: 0.46 (0.29–0.71)	60.8 (48.8-72.0) 23.1 (13.5-35.2)
CheckMate 9ER NCT03141177 Median follow-up 16 months [628]	651	NIVO + CABO SUN	34 41	10.3 (5.6-19.4) 4.2 (2.6-8.3) HR: 0.42 (0.23-0.74)	NR (22.8-NE) 19.7 (8.9-29.5) HR: 0.36 (0.17-0.79)	55.9 (37.9-72.8) 22.0 (10.6-37.6)
CLEAR NCT02811861 Median follow-up 27 months [605, 629]	712	PEMBRO + LEN SUN	28 21	11.1 5.5 HR: 0.39 (0.18-0.84)	NE NE HR: 0.91 (0.32-2.58)	60.7 23.8

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; CABO = cabozantinib; CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; ITT = intention-to-treat; mo = months; NA = not available; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = profession-free survival; sRCC = sarcomatoid RCC; SUN = sunitinib.

7.5.4.1.3.1 Summary of evidence and recommendation for targeted therapy in RCC with sarcomatoid features

Summary of evidence	LE
Immune checkpoint inhibitor combination therapy is superior to sunitinib in terms of PFS and OS in trial subset analysis of clear-cell RCC with sarcomatoid features.	2a

Recommendation	Strength rating
Offer immune checkpoint inhibitor combination therapy for advanced clear cell metastatic renal carcinoma with sarcomatoid features.	Weak

7.5.4.2 Treatment of patients with non-clear-cell metastatic RCC (general considerations)

For the sake of historical purposes, the panel recognizes the use of non-cc-mRCC but will where possible refer to the distinct subtype. This is a heterogenous group including papillary, chromophobe and other rare tumours with a widely differing tumour biology. Patients with non-cc-mRCC should therefore be referred to a clinical trial, where appropriate. While no phase III trials of patients with non-cc-mRCC have been reported it is increasingly recognised to study specific subtypes which have a higher incidence than other non-ccRCC. As pRCC comprise the majority of tumours defined as non-ccRCC, most of the evidence is available for this subtype, either from trials specifically selecting pRCC or having included a high percentage.

7.5.4.2.1 Treatment of patients with papillary metastatic RCC

There are small single-arm trials for sunitinib and everolimus [630-634]. Both these agents have been widely given in pRCC, but more recent data suggests cabozantinib and other combinations may be preferable [635, 636].

For pRCC new evidence is available from the SWOG PAPMET randomised phase II trial which compared sunitinib to cabozantinib, crizotinib and savolitinib in 152 patients with papillary mRCC [635]. Progression- free survival was longer in patients in the cabozantinib group (median 9.0 months, 95% CI: 6-12) than in the sunitinib group (5.6 months, CI: 3-7; HR for progression or death 0.60 [0.37-0.97, one-sided p = 0.019]). Response rate for cabozantinib was 23% vs. 4% for sunitinib (two-sided p = 0.010). Savolitinib and crizotinib did not improve PFS compared with sunitinib. Grade III or IV adverse events occurred in 69% (31/45) of patients receiving sunitinib, 74% (32/43) of patients receiving cabozantinib, 37% (10/27) receiving crizotinib, and 39% (11/28) receiving savolitinib; one grade V thromboembolic event was recorded in the cabozantinib group. These results support adding cabozantinib as an option for patients with papillary mRCC based on superior PFS results compared to sunitinib.

In addition, savolitinib was investigated in the SAVOIR trial [636] as first-line treatment for MET-driven tumours defined as chromosome seven gain, MET amplification, MET kinase domain variations or hepatocyte growth factor amplification by DNA alteration analysis (~30% of screened patients were MET positive). In a limited patient group, savolitinib (n = 27) was compared with sunitinib (n = 33). The trial was stopped early, largely due to poor accrual. The efficacy data appeared to favour savolitinib (median PFS 7.0 months, 95% CI: 2.8 months-NR vs. 5.6 months, 95% CI: 4.1-6.9 months, PFS HR: 0.71, 95% CI: 0.37-1.36, OS HR: 0.51,94% CI: 0.21-1.17, RR: 27% vs. 7%, for savolitinib and sunitinib, respectively). The median OS for savolitinib was not reported, Savolitinib was better tolerated compared with sunitinib with 42% grade > 3 adverse events compared to 81% with sunitinib. There are ongoing trials to confirm these findings. The results on these trials are required before recommendations can be made.

Evidence for TKI + IO based combination is derived from three phase II studies of lenvatinib plus pembrolizumab and cabozantinib and nivolumab. The Keynote-B61 phase II trial investigated lenvatinib plus pembrolizumab administered to non-ccRCC patients of whom 93 patients (59%) with pRCC [637, 638]. The primary endpoint of objective response was 54% in pRCC patients, with a median follow-up of 14.9 months, providing some evidence of good efficacy for TKI + IO based combinations. The cabozantinib and nivolumab study enrolled 40 patients with papillary and unclassified RCC with a response rate of 47% and a PFS of 13 (7-16) months [639]. In this trial chromophobe RCC was excluded and the percentage of pRCC was 68%. The CALYPSO trial investigeated savolitinib and durvalumab in 41 patients with metastatic papllary carcinoma in first or second line plus. The confirmed response rate was was 29% and the the primary endpoint of cRR > 50% was misses. In MET-driven tumours cRR was 53% with a PFS of twelve months while PFS was 4.9 months in the treated population [640]. Indirect comparisons suggest these data compare to an increased efficacy with those of VEGFR-TKI monotherapy alone.

Efficacy for pembrolizumab in the pRCC subset (118/165) was; RR: 29%, PFS: 5.5 months (95% CI: 3.9-6.1 months) and OS: 31.5 months (95% CI: 25.5 months-NR), but these results are based on a single-arm phase II study [641]. Pembrolizumab can be considered in this setting due to the high unmet need; although the VEGFR TKI + IO combination may be preferable.

7.5.4.2.2 Summary of evidence and recommendations for systemic therapy in papillary metastatic RCC

Summary of evidence	LE
Cabozantinib improved PFS over sunitinib in patients with advanced pRCC without additional molecular testing.	2a
Lenvatinib plus pembrolizumab and cabozantinib plus nivolumab demonstrated response rates of 47-54% with median PFS rates > 12 months.	2a
Pembrolizumab resulted in long-term median OS in a single-arm study in the pRCC subgroup.	2a

Recommendations	Strength rating
Offer cabozantinib to patients with papillary RCC (pRCC) based on a positive randomised controlled trial.	Weak
Offer lenvatinib plus pembrolizumab or nivolumab plus cabozantinib to patients with pRCC based on small single-arm trials.	Weak

7.5.4.2.3 Treatment of patients with metastatic non-ccRCC other than papillary RCC

The evidence surrounding systemic therapy for non-ccRCC tumours other than pRCC is especially weak and has relied on subset analysis of randomised phase II trials as well as expanded access programmes. Results consistently demonstrate that the outcome of these patients with targeted therapy is poorer than for ccRCC. Treatment in non-cc-mRCC has focused on temsirolimus, everolimus, sorafenib, sunitinib, cabozantinib and pembrolizumab in the past [630, 639, 642-644]. Recent data of single-arm phase II trials of lenvatinib plus pembrolizumab demonstrated clinical efficacy of this IO+TKI combinations in different non-ccRCC subgroups [637, 638, 645]. Meadian ORR across the different non-ccRCC subgroups of 158 patiens was 49%, and twelve months PFS and OS rates were 63% and 82%.

The academic prospective randomised European trial SUNNIFORECAST in therapy-naïve patients with advanced non-ccRCC entities randomized nivolumab plus ipilimumab (157 pts) or SOC (152 pts; 124 x TKI, 17 x TKI/IO, 2x others). The study included 178 patients (57,6%) with papillary RCCC, 60 patients (19.4%) with chromophobe RCC, twelve patients (3.9%) with MIT RCC, nine (2.9%) patients with collecting duct carcinoma and 50 had other subtypes. Primary endpoint was twelve months OS rate. The trial demonstrated a twelve months OS rate for nivolumab/ipilimumab (Nivo/Ipi) of 86.9% (95%-CI: 80.2%-91.5%) statistically significant superior to the SOC 76.8% (95%-CI: 68.6%-83.1%) (p=0.014). Median OS was 42.4 months for the Ipi/Nivo arm and 33.9 months for the SOC arm (HR:0.83, CI: 0.59-1.17); median PFS was 5.5m for Ipi/Nivo vs.5.7 months for SOC (HR: 0.99, 95% CI: 0.76-1.18). The ORR was respectively 32.8% vs. 19.6%.

7.5.4.2.4 Summary of evidence and recommendation for systemic therapy in chromophobe and unclassified RCC

Summary of evidence	LE
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 and for cabozantinib over sunitinib.	2a
In non-cc-mRCC, sunitinib improved PFS over everolimus in a SR of phase II trials and subgroups of patients.	1a
In non-cc-mRCC lenvatinib plus pembrolizumab demonstrated clinical efficacy in different non-ccRCC subgroups.	2a
In non-cc-mRCC cabozantinib plus nivolumab demonstrated clinical efficacy in different non-ccRCC subgroups except for chromophobe RCC which were excluded from the study.	2a
OS rate at twelve months was significantly higher with nivolumab plus ipilimumab than with SOC in non-ccRCC patients.	1b

Recommendations	Strength rating
Offer sunitinib to patients with other non-clear cell renal cell carcinoma (cc-RCC) subtypes than papillary RCC.	Weak
Offer lenvatinib plus pembrolizumab to patients with non-ccRCC subtypes.	Weak
Offer cabozantinib and nivolumab to patients with non-ccRCC subtypes other than chromophobe RCC.	weak
Offer nivolumab plus ipilimumab in patients with non-ccRCC.	Weak

7.5.4.3 Treatment of patients with rare tumours

7.5.4.3.1 SMARCB1-deficient renal medullary carcinoma

SMARCB1-deficient renal medullary carcinoma (RMC) is one of the most aggressive RCCs [43, 203] and most patients (~67%) will present with metastatic disease [38, 43] and three-year CSM-free survival 35.8 % [646]. Even patients who present with seemingly localised disease may develop macro metastases shortly thereafter, often within a few weeks.

Despite treatment, median OS is thirteen months in the most recent series [49]. Due to the infiltrative nature and medullary epicentre of RMC, 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 [49, 647]. 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 [648, 649]. Renal medullary carcinoma is refractory to monotherapies with targeted anti-angiogenic regimens including TKIs and mTOR inhibitors [49, 179]. The mainstay systemic treatments for RMC are cytotoxic combination regimens which produce partial or complete responses in ~29% of patients [179]. There are no prospective comparisons between different chemotherapy regimens, but most published series used various combinations of platinum agents, taxanes, gemcitabine, and/or anthracyclines [49, 50]. High-dose-intensity combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has also shown efficacy against RMC [650] although a retrospective comparison did not show superiority of MVAC over cisplatin, paclitaxel, and gemcitabine [50]. Single-agent anti-PD-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 [648, 649]. Whenever possible, patients should be enrolled in clinical trials of novel therapeutic approaches, particularly after failing first-line cytotoxic chemotherapy.

In a phase II basket trial, no evidence of clinical activity was showed for pembrolizumab in patients with RMC, irrespective of PD-L1 or tumour-infiltrating lymphocyte levels [651].

7.5.4.3.2 Other rare tumours

Knowledge about the systemic treatment of rare tumours is very limited, mostly based on a set of case reports. For some facts about therapy of renal tumours see chapter 3.5 and table 3.2.

Metastatic collecting duct carcinoma (CDC) has a lowest mortality in concomitant use of cytoreductive nephrectomy and systemic therapy [652]. Systemic therapy was investigated in BONSAI phase II trial. Nivolumab showed cilical benefit in 60 % as a second-line therapy after cabozantinib failure [653].

Anaplastic lymphoma kinase (ALK)-rearranged RCC, there are some reports of the efficacy of ALK inhibitors, e. g. alectinib, crizotinib and entrectinib [654, 655]. *ELOC* (formerly TCEB1)-mutated RCC doesn't exhibit cinically aggressive behaviour [654].

There is no data that indicates a recommendation for one treatment over another.

7.6 Locally-recurrent RCC after treatment of localised disease

Most studies reporting on local recurrent disease after removal of the kidney have not considered the true definition of local recurrence after RN, PN and thermal ablation, which are: local recurrence in the tumour-bearing kidney, tumour growth exclusively confined to the true renal fossa, recurrences within the renal vein, the ipsilateral adrenal gland or the regional LNs. In the existing literature the topic is weakly investigated and often regarded as local recurrent disease.

RECUR is a protocol-based multicentre European registry capturing patient and tumour characteristics, risk of recurrence (RoR), recurrence patterns, and survival of those curatively treated for nonmetastatic RCC from 2006 to 2011. Per-protocol resectable disease (RD) recurrence was defined as (1) solitary metastases, (2)

oligometastases, or (3) renal fossa or renal recurrence after radical or partial nephrectomy, respectively. Within the RECUR consortium, the authors assessed the effectiveness of local treatment of resectable recurrent RCC after surgical treatment of the primary kidney tumour [656]. Of 3039 patients with localised RCC treated with curative intent, 505 presented with recurrence, including 176 with RD. Of these patients, 97 underwent local treatment of recurrence (LTR) and 79 no LTR. The median OS was 70.3 mo versus 27.4 in the LTR versus no-LTR group ($p < 0.001$). The LTR effect on survival was consistent across risk groups. Overall survival HR for high, intermediate, and low risks were 0.36 (0.2-0.64), 0.27 (0.11-0.65), and 0.26 (0.08-0.8), respectively. Local treatment of recurrence was associated with longer survival across groups with a risk of recurrence [656].

*7.6.1 **Locally-recurrent RCC after nephron-sparing approaches***

Locally-recurrent disease can 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, in a minority of the cases to the local spread of the tumour by microvascular embolisation, or true multifocality [217, 657].

The prognosis of recurrent disease not due to multifocality is poor, despite salvage nephrectomy [657]. Recurrent tumour growth in the regional LNs or ipsilateral adrenal gland may reflect metachronous metastatic spread (see Section 7.3). After treatment solely for localised disease, systemic progression is common [658, 659].

There are reports that minimally invasive approaches (laparoscopic and robotic) show atypical reoccurence (e.g. peritoneal, port site, etc) [660, 661]. Therefore, specific maneuvers to prevent tumour-cell contamination should be implemented. Those include the use of extraction bags, minimizing trocar CO_2 leakage, avoiding tumour morcellation, cleansing of instruments before reuse, changing of gloves after tumour extraction, avoiding violation of the tumour's natural capsule, and cleansing of port sites [660, 661].

A retrospective study relying on inverse probability of treatment weighting (IPTW) and comparing percutaneous ablation and surgical resection for an isolated local recurrence (LR) following PN [662]. A total of 81 patients with an isolated LR were included and treated with either ablation (30 RFA and 12 cryoablation) or surgical resection (8 PN and 31 RN). Percutaneous ablation was associated with a significantly lower risk of postoperative complications (5% with PCA vs. 41% with PN; OR=0.22; $p = 0.006$) and a smaller change in eGFR. There were no significant differences in the risk of disease recurrence (HR = 0.72; $p = 0.61$), new LR (HR = 1.51; $p = 0.59$), and distant metastasis (HR = 0.19; $p = 0.09$) [662].

Following thermal ablation or cryotherapy generally intra-renal, but also peri-renal, recurrences have been reported in up to 14% of cases [663]. 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.

*7.6.2 **Locally-recurrent RCC after radical nephrectomy***

Isolated local fossa recurrence is rare and occurs in about 1-3% after radical nephrectomy. More commonly in pT3-4 than pT1-2 and grade III-IV disease. Most patients with local recurrence of RCC are diagnosed by either CT/MRI scans as part of the post-operative follow-up [664]. The median time to recurrence after RN was 19-36 months in isolated local recurrence or 14.5 months in the group including metastatic cases as well [664-666].

Isolated local recurrence is associated with worse survival [217, 667]. 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 [668-670]. Among these alternatives, surgical resection with negative margins remains the only therapeutic option shown to be associated with improved survival [667]. Open surgery has been successfully reported in studies [671, 672]. 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 [668]. Another 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) [673].

The five-year OS with isolated local recurrence was 60% (95% CI: 0.44-0.73) and ten-year OS was 32% (95% CI: 0.15-0.51). Overall survival differed significantly by the time period between primary surgery and occurrence of recurrence (< 2 years vs. > 2 years: ten-year OS rate 31% (95% CI: 10.2-55.0) vs. 45% (95% CI: 21.5-65.8; HR: 0.26; $p = 0.0034$) [664]. Metastatic progression was observed in 60 patients (58.8%) after surgery [665]. Patient survival can be linked to the type of treatment received, as shown in a cohort of 96 patients, 45.8% were metastatic at the time of recurrence; three-year CSS rates after local recurrence were 92.3% ± 7.4%)

for those who were treated with surgery and systemic therapy, 63.2% ± 13.2%) for those who only underwent surgery, 22.7% ± 0.9%) for those who only received systemic therapy and 20.5% ± 10.4%) for those who received no treatment (p < 0.001) [666]. A retrospective multi-center study of patients with local retroperitoneal recurrence after RN with or without surgical treatment from 2008 to 2020. Retroperitoneal recurrence of RCC was defined as an ipsilateral recurrence confined to the renal fossa, adrenal gland or retroperitoneal lymph nodes after prior nephrectomy, which was diagnosed by cross-sectional imaging. Treatment with retroperotineal recurrance surgery resulted in significantly longer CSS than targeted therapy alone (P < 0.001). In multivariable analysis, high Fuhrman grade, size of retroperitoneal recurrence tumour, mixed type of retroperitoneal recurrence, multiple recurrence lesions and the absence of retroperitoneal recurrence surgery were associated with a significantly increased risk of death from RCC, suggesting that an aggressive surgical resection of retroperitoneal recurrence after RN represents a potentially curative treatment for selected RCC patients without synchronous metastases, resulting in significantly longer CSS than targeted therapy alone [674].

Minimally-invasive approaches, including standard and hand-assisted laparoscopic- and robotic approaches for the resection of isolated RCC recurrences have been occasionally reported. A large surgical cohort published of robotic surgery in this setting (n = 35) providing a standardisation of the nomenclature, describing the surgical technique for each scenario and reporting on complications, renal function, and oncologic outcomes [675]. Ablative therapies including cryoablation, radiofrequency and microwave ablation, may also have a role in managing recurrent RCC patients, but further validation will be needed [676, 677].

In summary, the limited available evidence suggests that in selected patients surgical removal of locally-recurrent disease with negative margins can induce durable tumour control, although with expected high risk of complications. A retrospective review 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 [678]. Since local recurrences develop early, with a median time interval of 10-20 months after treatment of the primary tumour [679], a guideline-adapted follow-up scheme for early detection is recommended (see Chapter 9 - Follow-up) even though benefit in terms of cancer control has not yet been demonstrated [680].

Adverse prognostic parameters are a short time interval since treatment of the primary tumour (< 3-12 months) [681], sarcomatoid differentiation of the recurrent lesion and incomplete surgical resection [668]. 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). Following metastasectomy of local recurrence after nephrectomy, adjuvant therapy can be considered (see Section 7.3.5. Neoadjuvant and adjuvant therapy). Local recurrence combined with other metastases is treated as a metastatic RCC.

7.6.3 Summary of evidence and recommendation on locally-recurrent RCC after treatment of localised disease

Summary of evidence	LE
Isolated recurrence after nephron sparing procedures or nephrectomy is a rare entity (< 2%).	3
Surgical or percutaneous treatment of local recurrences in absence of systemic progression should be considered, especially in absence of adverse prognostic parameters and favourable performance status.	3
The most optimal modality of local treatment for locally-recurrent RCC after nephron sparing procedures or nephrectomy is not defined.	3

Recommendation	Strength rating
Offer local treatment of locally-recurrent disease when technically possible and after balancing adverse prognostic features, comorbidities and life expectancy.	Weak

8. HEREDITARY AND SYNDROME SPECIFIC RCC

Five to eight percent of RCCs are hereditary; this proportion could be underestimated due to the limitations of available studies. To date there are more than 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 (age 46 years or younger) of all RCC tumours [178].

Hereditary kidney tumours are found in the following entities: VHL syndrome; hereditary papillary RCC (HPRCC); Birt-Hogg-Dubé syndrome; Fumarate hydratase-deficient RCC (FHD-RCC), previously called hereditary leiomyomatosis and RCC (HLRCC); tuberous sclerosis complex; Hereditary SDH deficient paraganglioma/ pheochromocytoma (HPP) syndrome; Phosphatase and tensin homolog (PTEN) hamartoma syndrome (PHTS); and BRCA-1 associated protein 1 (BAP1) tumour predisposition syndrome).

RCC can also be associated with the following syndromes: Hyperparathyroidism-jaw tumour (HJT) syndrome, Chromosome 3 translocation (Cr3T) syndrome, and MITF-related melanoma and renal cell carcinoma predisposition syndrome. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [65, 682-685].

8.1 Microphthalmia associated transrciption factors (MiTF) associated translocation tumours

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 [686].

Table 8.1: Syndrome-specific RCC hystotypes and extra-renal organ involvement patterns [187, 687, 688].

Syndrome (Inheritance; estimated prevalence)	**Gene**	**Lifetime RCC risk**	**Histology**	**Selected associated extrarenal**
Hereditary RCC				
VHL syndrome (autosomal dominant; estimated prevalence: 1-9 / 100 000)	VHL (3p25.3)	30-40%	ccRCC	Retinal/CNS haemangioblastomas Pancreatic cysts and neuroendocrine tumours Endolymphatic sac tumour Pheochromocytoma Epididymal cystoadenomas Others
Hereditary papillary RCC (HPRCC) (autosomal dominant; prevalence is unknown; estimated at 1/500,000)	MET (7q31)	100%	pRCC	None
Birt-Hogg-Dubé (BHD) syndrome (autosomal dominant; estimated prevalence: 1-9 / 1000 000)	FLCN (17p11.2)	30%	Hybrid oncocytic; chRCC; oncocitoma.	Fibrofolliculomas and other skin findings Renal and lung cysts Parotid gland oncocytomas Pneumothorax
Fumarate hydratase (FH)-deficient RCC (FH-RCC) (autosomal dominant; prevalence is unknown)	FH (1p42.1)	15-32%	FH-deficient RCC	Cutaneous leiomyomas Uterine leiomyomas Leiomyosarcomas Adrenal nodules

Tuberous sclerosis complex (TSC) (autosomal dominant; estimated prevalence: 1-9 / 100 000)	TSC1/TSC2 (9q34/16p13)	<5%	ccRCC; pRCC, chRCC	Renal AMLs; Angiomyofibromas and other dermatological lesions Cortical dysplasia Subependymal giant cell astrocytoma Lymphangioleiomyomatosis Seizures; Others
Hereditary SDH deficient paraganglioma/ pheochromocytoma (HPP) syndrome (autosomal dominant; estimated prevalence: 1-9 / 1000 000)	SDHB/C/D (1p36/ 1q23/ 11q23)	<10%	ccRCC, unclassified	Pheocromocitoma Paraganglioma GI stromal tumour
Phosphatase and tensin homolog (PTEN) hamartoma syndrome (PHTS) (autosomal dominant; prevalence is unknown)	PTEN (10q23)	10-15%	ccRCC, pRCC, chRCC	Macrocephaly Breast cancer and fibrocystic change Thyroid cancer Endometrial cancer Prostate cancer Colonic polyps Facial trichilemmomas
BRCA-1 associated protein 1 (BAP1) tumour predisposition syndrome (autosomal dominant; prevalence is unknown)	BAP-1 (3p21)	<15%	ccRCC	Uveal and cutaneous melanoma Malignant pleural mesothelioma Other cancers (cholangiocarcinoma, basal cell carcinoma, meningioma)
Syndrome-related RCC				
Hyperparathyroidism-jaw tumour (HJT) syndrome (estimated prevalence <1/1000 000)	CDC73 (1q31.2)	<10%	RCC and Wilms	Hyperparathyrodism Parathyroid cancer Jaw fibroma Uterine cancer
Chromosome 3 translocation (Cr3T) syndrome (estimated prevalence <1/1000 000)	- Trans-locations 3:6; 3:8; 3:11	30%	ccRCC	None
Renal medullary carcinoma (prevalence is unknown)	-	-	SMARCB1-deficient renal medullary carcinoma	Hereditary haemoglobinopathies
MITF-related melanoma and renal cell carcinoma predisposition syndrome (estimated prevalence <1/1000 000)	MITF (3p14)	<10%	MiTF family translocation RCC	Pheocromocitoma Melanoma Pancreatic cancer

Data on estimated prevalence/incidence are based on https://www.orpha.net.

Recently published recommendations for the selection of germline genetic testing panels in patients with cancer, including RCC [689] stated that germline genetic testing should be distinguished from biomarker testing (i.e. tumour genomic profiling). To establish whether gene variants identified in a tumour are germline, germline genetic testing must be performed. With advancements in next-generation sequencing technology, genetic panels now encompass an expanding list of available genes. Specific recommendations have been set for the following domains: a) family history collection; b) germline multigene panel testing; c) genes to be included in multigene panels; and d) germline testing in association with somatic genetic tumour testing [689]. For RCC, the

genes recommended for testing and inclusion in multigene panels are: BAP1, FH, FLCN, MET, SDHA, SDHAF2, SDHB, SDHC, SDHD PTEN, VHL (more strongly recommended) and TSC1/TSC2 (less strongly recommended).

8.2 Management of hereditary and syndrome specific RCC

Hereditary RCC often presents with multifocal, de-novo recurring and bilateral tumours, which requires individualized management.

Patients with hereditary kidney cancer syndromes may require repeated surgical intervention [690, 691]. In most hereditary RCCs nephron-sparing approaches are recommended. To avoid multiple repetitive partial nephrectomies, thermal ablation can be considered in the treatment paradigm. A registry based retrospective analysis of 53 patients with inherited RCC syndromes evaluated percutaneous cryoablation for primary mean 2.46 cm tumours demonstrating within mean follow up of 30.4 months estimated five-year local recurrence free survival of 96% (95% CI 75-99), metastases free survival 96.4% (95%CI 77-99%), CSS 90.9% (95% CI 51-99%) and OS 90.9% (95%CI 51-99%). Complication rate was 1.7% and 7.4% had more than 25% reduction in kidney function [692].

The exceptions to nephron-sparing approaches are FHD-RCC and high-grade SDH syndromes for which immediate surgical intervention is recommended due to the aggressive nature of these tumours. For other hereditary syndromes such as VHL, surveillance is recommended until the largest tumour reaches 3 cm in diameter: this to limit the number of repeat interventions [693, 694]. Active surveillance for VHL and other non-aggressive hereditary tumours, should, in individual patients, follow the size, growth rate and location of the tumours, rather than applying a standardised follow-up interval. Regular screening for both renal and extra-renal lesions should follow international guidelines for these syndromes [694]. Multidisciplinary and co-ordinated care should be offered, where appropriate [695]. In FHD-RCC, renal screening in relatives has shown benefit in detecting early-stage RCCs [46], with HLRCCs appearing to have unique molecular profiles.

In the metastatic setting, systemic therapeutic options for fumarate hydratase-deficient RCC with high metastatic potential include ICI monotherapies which offer a better disease control rate than TKI monotherapies. In a phase II trial, ORR of 51 % of combination of erlotinib and bevacizumab was achieved [654]. Another trial expressed a favorable response to ICI/TKI combinational therapy compared to bevacizumab plus erlotinib [92].

Succinate dehydrogenase (SDH)-deficient RCC has a low risk of metastasis (12 %) with exception of high-grade with risk 70 %. Due to rarity of disease, no evidence for systemic therapy [654].

*8.2.1 **von-Hippel-Lindau-disease-associated RCC***

Patients with VHL disease often develop RCC and tumours and cysts in other organs including adrenal glands, CNS, retinal haemangioblastomas, and pancreas, and commonly undergo several surgical resections in their lifetime. In VHL disease, belzutifan, a HIF-2α inhibitor, has been approved by the US Food and Drug Administration [696] for the treatment of ccRCC and other neoplasms associated with VHL for the treatment of tumours that do not require immediate surgery. Approval was based on the results from a phase II, open-label, single-arm trial in 61 patients with tumours not larger than 3 cm [584]. Belzutifan induced partial responses with an RCC ORR of 49%, and a disease control rate of 98.4% after 21.8 months treatment. All patients with pancreatic lesions had an ORR of 77%, and those with CNS haemangioblastoma had a 30% response rate. In total, 33% of patients reported > grade III adverse events, and seven patients (11.5%) discontinued the treatment. In the treatment with pazopanib for VHL only 52% continued with the treatment after 24 weeks [697]. A longer follow-up at 37.8 months, ORR for RCC was increased to 64%, with a median time to response of 11.1 months (range, 2.7 to 30.5). Median duration of response per Kaplan-Meier estimate was not reached (range, 5.4+ to 35.8+ months). Thirty-four of 39 patients with a confirmed response (87%) remain in response as of the data cut-off date (September 2022) [698].

With favourable efficacy results and with relatively low-grade side effects, belzutifan seems to be a valuable contribution to the treatment of patients with the VHL disease. The EMA has not yet considered belzutifan for approval in VHL disease.

*8.2.2 **TFE3-rearranged RCC***

TFE3-rearranged RCC showed objective response rate 25 % with ICI and 0 % with TKI and more prolonged OS (62.4 months with ICI vs. 10.3 with TKI). Cabozantinib may be an exeption with 16.6% objective response. There is discussed future role of ICI-TKI combination (such as nivolumab plus cabozantinib) and cabozantinib plus belzutifan [654].

8.2.3 TFEB-altered RCC

TFEB-rearranged RCC: There is a general lack of information regarding the response to moderm systemic therapy. Combination of ICI and mTOR inhibitors are discussed. TFEB-amplified RCC (it occurs in elderly patients and displays more aggressive behaviour compared to TFEB-rearranged RCC) can be treated with VEGFR targeting agents or with VEGFR-TKI combination [654].

8.2.4 Combined therapy for TFE3- and TFEB-altered RCCs

Some studies combine therapy TFE3- and TFEB-altered RCCs (because of former grouping ob both tumours to MiT family translocation RCCs). Two retrospective studies exhibit efficacy of ICI or ICI-TKI combination [699, 700]. Other study provided evidence of the activity of cabozantinib in MiT TRCC, with more durable responses than those observed historically with other VEGFR-TKIs or ICIs [701].

8.2.5 Summary of evidence and recommendation for hereditary and syndrome-specific RCC

Summary of evidence	LE
Hereditary RCC syndromes are often suggested by family history, age of onset and presence of other lesions typical for the respective syndromes	3
Hereditary RCC tumors are predominantly found in the lowest decile, with 70% occurring in individuals aged 46 years or younger.	3
To establish whether gene variants identified in a tumour are germline, germline genetic testing must be performed.	3
In VHL and non-FHD-RCC tumours can be observed until a diameter of 3 cm.	3
Belzutifan leads to an ORR of VHL lesions of 64% at 37.8 months.	2
There is currently no approved standard first-line treatment for non-VHL hereditary or syndrom specific RCC.	3

Recommendation	Strength rating
Suspect hereditary or syndrome-specific RCC in patients with positive family history, young onset and bilateral or multiple tumours.	Strong
Offer germline testing to patients < 46 years.	Weak
Offer surveillance in VHL until the largest tumour reaches 3 cm in diameter.	Strong
Offer belzutifan to patients with VHL related renal and other tumours who are not surgical candidates.	Weak

9. FOLLOW-UP IN RCC

9.1 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 [680]. 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, ESRD and cardiovascular events [702]. Referral of patients at risk of CKD/renal function deterioration after treatment (surgery/ablation) to a nephrologist may minimise the risk of worsening of renal function; support oncologists in managing treatment-related renal adverse events; assist the choice of optimal follow-up radiological procedures (mainly deciding if, when, and how to use CT contrast media); and

deal with oncological patients on dialysis or with kidney transplant (including if, and when, to start dialysis, or whether to allow a kidney transplant) (expert opinion [703]). Patients with pre-existing or treatment-induced CKD (e.g. patients with new baseline eGFR equal to or less than 45 ml/min [704]), and/or known comorbidities potentially affecting renal function could benefit the most from specialist nephrological assessment during follow-up (expert opinion).

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 [201, 705, 706] (LE: 4). One study has shown a survival benefit in patients who were followed within a structured surveillance protocol vs. patients who were not [707]; patients undergoing follow-up seem to have a longer OS when compared to patients not undergoing routine follow-up [707].

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 [708]. 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. As for pshylogical factors, a SR including fifteen studies revealed that psychological distress (defined as anxiety, depression, or psychological distress at any time during treatment or follow-up) is also prevalent among RCC patients, reaching up to 77% in non-metastatic cases [709].

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 initial 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 continuously exceeded the risk of non-RCC related death [710]. 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 [710, 711].

Recurrence after PN is rare, but early diagnosis is relevant, as the most effective treatment is surgery [671, 712]. Recurrence in the contralateral kidney is rare (1-2%) and can occur late (median 5-6 years) [713] (LE: 3). Follow-up can identify local recurrences or metastases at an early stage. At recurrence, extensive metastatic tumour growth can hinder the opportunity for surgical resection. In addition, early diagnosis of tumour recurrence may enhance the efficacy of systemic treatment if the tumour burden is low.

9.2 Imaging Investigations

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 [714-716]. Therefore, follow-up for recurrence detection with chest radiography and US are less sensitive [717].
- 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 [120, 132].
- Surveillance should also include evaluation of renal function and cardiovascular risk factors [702].
- 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 [718].

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 [256, 258, 719, 720]. These models, of which the most utilised are summarised in Chapter 6 - Prognosis, have been compared and validated [721] (LE: 2). Using prognostic variables, several stage-based follow-up

regimens have been proposed, although, none propose follow-up strategies after ablative therapies [722, 723]. A post-operative nomogram is available to estimate the likelihood of freedom from recurrence at five years [253]. Recently, a pre-operative prognostic model based on age, symptoms and TNM staging has been published and validated [724] (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 [725].

Table 9.1: 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 or2.	-	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 [256]. 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 [257].*

** *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.*

9.3 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 PSM.	3
Patients undergoing follow-up have a better OS than patients not undergoing follow-up.	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
Overall survival is reduced in metastatic RCC patients with symptoms of depression and distress.	2a

Recommendations	Strength rating
Base follow-up after treatment of localised RCC on the risk of recurrence.	Strong
Base risk of recurrence stratification on validated subtype-specific models such as the Leibovich Score for clear cell renal cell carcinoma (ccRCC), or the University of California Los Angeles integrated staging system for non-ccRCC.	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 the RCC recurrence risk.	Weak
Offer psychological evaluation for all patients diagnosed with RCC to provide timely support for distress, depression, or anxiety.	Weak

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11. 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 publicly accessible through the European Association of Urology website: https://uroweb.org/guideline/renalcellcarcinoma/?type=panel/.

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